ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 130 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 130 mg ustekinumab in 26 mL (5 mg/mL).

Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a chinese hamster ovary (CHO) cell line using recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The solution is clear, colourless to light yellow, and its formulated at pH 6.0 ± 0.3. The osmolality of the solution is 290 ± 30 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Crohn's Disease
Pyzchiva is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

4.2 Posology and method of administration

Pyzchiva concentrate for solution for infusion is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of Crohn's disease.
Pyzchiva concentrate for solution for infusion should only be used for the intravenous induction dose.

Posology

Crohn's Disease
Pyzchiva treatment is to be initiated with a single intravenous dose based on body weight. The infusion solution is to be composed of the number of vials of Pyzchiva 130 mg as specified in Table 1 (see section 6.6 for preparation).

Table 1: Initial intravenous dosing of Pyzchiva

Body weight of patient at the time of dosing	Recommended dose[a]	Number of 130 mg Pyzchiva Vials
≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

[a] Approximately 6 mg/kg

The first subcutaneous dose should be given at week 8 following the intravenous dose. For the posology of the subsequent subcutaneous dosing regimen, see section 4.2 of the Pyzchiva solution for injection (vial) and solution for injection in pre-filled syringe SmPC or pre-filled pen SmPC.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

Renal and Hepatic Impairment
Ustekinumab has not been studied in these patient populations. No dose recommendations can be made.

Paediatric Population
The safety and efficacy of ustekinumab for the treatment of Crohn's disease in children less than 18 years have not yet been established. No data are available.

Method of administration
Pyzchiva 130 mg is for intravenous use only. It should be administered over at least one hour. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies and a post-marketing observational study in patients with psoriasis, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab (see section 4.8).

Opportunistic infections including reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis) have been reported in patients treated with ustekinumab.

Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with ustekinumab, patients should be evaluated for tuberculosis infection. Ustekinumab must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering ustekinumab. Anti-tuberculosis therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients

receiving ustekinumab should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and ustekinumab should not be administered until the infection resolves.

Malignancies
Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received ustekinumab in clinical studies and in a post-marketing observational study in patients with psoriasis developed cutaneous and non-cutaneous malignancies (see section 4.8). The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving ustekinumab. Thus, caution should be exercised when considering the use of ustekinumab in these patients.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer (see section 4.8).

Systemic and respiratory hypersensitivity reactions
Systemic
Serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of ustekinumab should be discontinued (see section 4.8).

Infusion-Related Reactions
Infusion-related reactions were observed in clinical trials (see section 4.8). Serious infusion-related reactions including anaphylactic reactions to the infusion have been reported in the post-marketing setting. If a serious or life-threatening reaction is observed, appropriate therapy should be instituted and ustekinumab should be discontinued.

Respiratory
Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section 4.8).

Cardiovascular events
Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to ustekinumab in a post-marketing observational study. Risk factors for cardiovascular disease should be regularly assessed during treatment with ustekinumab.

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with ustekinumab. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving ustekinumab. Before live viral or live bacterial vaccination, treatment with ustekinumab should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the

Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.5 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Patients receiving ustekinumab may receive concurrent inactivated or non-live vaccinations.

Long term treatment with ustekinumab does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1).

Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab. Caution should be exercised when considering concomitant use of other immunosuppressants and ustekinumab or when transitioning from other immunosuppressive biologics (see section 4.5).

Immunotherapy
Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether ustekinumab may affect allergy immunotherapy.

Serious skin conditions
In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. ustekinumab should be discontinued if a drug reaction is suspected.

Lupus-related conditions
Cases of lupus-related conditions have been reported in patients treated with ustekinumab, including cutaneous lupus erythematosus and lupus-like syndrome. If lesions occur, especially in sun exposed areas of the skin or if accompanied by arthralgia, the patient should seek medical attention promptly. If the diagnosis of a lupus-related condition is confirmed, ustekinumab should be discontinued and appropriate treatment initiated.

Special populations
Elderly
No overall differences in efficacy or safety in patients age 65 and older who received ustekinumab were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Sodium content
Ustekinumab contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. ustekinumab is however, diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

Polysorbate 80

Ustekinumab contains 10.4 mg of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.40 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with ustekinumab.

Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

In the population pharmacokinetic analyses of the phase 3 studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an in vitro study and a phase 1 study in subjects with active Crohn's disease do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section 5.2).

In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab. (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.

Pregnancy

Data from a moderate number of prospectively collected pregnancies following exposure to ustekinumab with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3).

However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of ustekinumab in pregnancy.

Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed in utero to ustekinumab may be increased after birth. Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not

recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.5). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Breast-feeding
Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with ustekinumab must be made taking into account the benefit of breast-feeding to the child and the benefit of ustekinumab therapy to the woman.

Fertility
The effect of ustekinumab on human fertility has not been evaluated (see section 5.3).

4.7 Effects on ability to drive and use machines

Ustekinumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies with ustekinumab were nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for ustekinumab is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis.

Tabulated list of adverse reactions
The safety data described below reflect exposure in adults to ustekinumab in 14 phase 2 and phase 3 studies in 6,710 patients (4,135 with psoriasis and/or psoriatic arthritis, 1,749 with Crohn's disease and 826 patients with ulcerative colitis). This includes exposure to ustekinumab in the controlled and non-controlled periods of the clinical studies in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis for at least 6 months (4,577 patients) or at least 1 year (3,648 patients). 2,194 patients with psoriasis, Crohn's disease or ulcerative colitis were exposed for at least 4 years while 1,148 patients with psoriasis or Crohn's disease were exposed for at least 5 years.

Table 2 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness

Table 2: List of adverse reactions

System Organ Class	Frequency: Adverse reaction
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection

System Organ Class	Frequency: Adverse reaction
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis, hypersensitivity vasculitis Very rare: Bullous pemphigoid, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia Very rare: Lupus-like syndrome
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

*See section 4.4, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions Infections
In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,227 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 2.3 years for ulcerative colitis studies. The rate of infection was 0.85 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (289 serious infections in 15,227 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancies
In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of

follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,205 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 2.3 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 76 patients in 15,205 patient-years of follow-up (incidence of 0.50 per 100 patient- years of follow-up for ustekinumab-treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.94 [95% confidence interval: 0.73, 1.18], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma colorectal, and breast cancers. The incidence of non-melanoma skin cancer was 0.46 per 100 patient-years of follow-up for ustekinumab-treated patients (69 patients in 15,165 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (see section 4.4).

Hypersensitivity and infusion reactions
In Crohn's disease and ulcerative colitis intravenous induction studies, no events of anaphylaxis or other serious infusion reactions were reported following the single intravenous dose. In these studies, 2.2% of 785 placebo-treated patients and 1.9% of 790 patients treated with the recommended dose of ustekinumab reported adverse events occurring during or within an hour of the infusion. Serious infusion-related reactions including anaphylactic reactions to the infusion have been reported in the post-marketing setting (see section 4.4).

Paediatric population
Paediatric patients 6 years and older with plaque psoriasis
The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 6 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Pyzchiva is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu.

Mechanism of action

Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis and Crohn's disease.

By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis and Crohn's disease through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with Crohn's disease, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and fecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase. CRP was assessed during the study extension and the reductions observed during maintenance were generally sustained through Week 252.

Immunisation

During the long term extension of Psoriasis Study 2 (PHOENIX 2), adult patients treated with ustekinumab for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titres were similar among ustekinumab-treated and control patients.

Clinical efficacy

Crohn's Disease

The safety and efficacy of ustekinumab was assessed in three randomised, double-blind, placebo-controlled, multicentre studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development program consisted of two 8-week intravenous induction studies (UNITI-1 and UNITI-2) followed by a 44 week subcutaneous randomised withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1,409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analysed through week 8 for both studies. Concomitant doses of oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNFα therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 3). Clinical response and remission were significant as early as week 3 in ustekinumab treated patients and continued to improve through week 8. In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended intravenous induction dose.

Table 3: Induction of Clinical Response and Remission in UNITI-1 and UNITI 2

	UNITI-1*		**UNITI-2****	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
Clinical Remission, week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission

70 point response is defined as reduction in CDAI score by at least 70 points

*Anti-TNFα failures

**Conventional therapy failures

[a] $p < 0.001$

[b] $p < 0.01$

The maintenance study (IM-UNITI) evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomised to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the ustekinumab Solution for injection (vial) and Solution for injection in pre-filled syringe SmPC or pre-filled pen SmPC).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 4).

Table 4: Maintenance of Clinical Response and Remission in IM-UNITI (week 44; 52 weeks from initiation of the induction dose)

	Placebo* **N = 131†**	**90 mg ustekinumab every 8 weeks N = 128†**	**90 mg ustekinumab every 12 weeks N = 129†**
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002‡	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)
who entered from study CRD3001§	26% (16/61)	41% (23/56)	39% (22/57)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

*The placebo group consisted of patients who were in response to ustekinumab and were randomised to receive placebo at the start of maintenance therapy.

†Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy

‡Patients who failed conventional therapy but not anti-TNFα therapy

§Patients who are anti-TNFα refractory/intolerant

[a]$p < 0.01$

[b]$p < 0.05$

[c]nominally significant ($p < 0.05$)

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to receive ustekinumab every 8 weeks. Loss of response was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomized portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority maintained response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomized to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 567 patients who entered on and were treated with ustekinumab in the study extension, clinical remission and response were generally maintained through week 252 for both patients who failed TNF-therapies and those who failed conventional therapies.

The safety analysis including 457 patients (1289.9 person-years) followed up to 220 weeks showed a safety profile between week 44 and 220 that was comparable with that observed up to week 44.

No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with Crohn's Disease.

Endoscopy

Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p = 0.012).

Fistula Response

In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-Related Quality of Life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo. Improvement in health-related quality of life was generally maintained during the extension through week 252.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with increased clearance of ustekinumab in patients with Crohn's disease. No reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in Crohn's Disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following the recommended intravenous induction dose, median peak serum ustekinumab concentration, observed 1 hour after the infusion, was 126.1 µg/mL in patients with Crohn's disease.

Distribution
Median volume of distribution during the terminal phase (V_z) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life (t1/2) of ustekinumab was approximately 3 weeks in patients with Crohn's disease, psoriasis and/or psoriatic arthritis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies.

Dose linearity
The systemic exposure of ustekinumab (Cmax and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg.

Special populations
No pharmacokinetic data are available in patients with impaired renal or hepatic function.
No specific studies have been conducted with intravenous ustekinumab in elderly or paediatric patients.

In patients with Crohn's disease, variability in ustekinumab clearance was affected by body weight, serum albumin level, sex, and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). The impact of these covariates was within ±20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

Regulation of CYP450 enzymes
The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an in vitro study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5).

A phase 1, open-label, drug interaction study, Study CNTO1275CRD1003, was conducted to evaluate the effect of ustekinumab on cytochrome P450 enzyme activities following induction and maintenance dosing in patients with active Crohn's disease (n=18). No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosing in patients with Crohn's disease (see section 4.5).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated-dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed. No adverse effects on female fertility indices were observed using an analogous antibody to IL-12/23 in mice.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Methionine
Disodium edetate
Sucrose
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Pyzchiva should be diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion. Alternatively, a 250 mL infusion bag containing 0.45% Sodium Chloride Injection, USP may be used. Pyzchiva should not be administered concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

Before dilution

3 years
Do not freeze.

Individual vials may be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the vial is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period, the product can be put back in the refrigerator once and kept there until the expiry date. Discard the vial if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier.

After dilution

Chemical and physical in-use stability has been demonstrated for up to 72 hours at 30°C. If necessary, the diluted infusion solution may be kept at 2 °C to 8 °C for up to 1 month and at room temperature up to 30°C for an additional 72 hours after removal from refrigeration including the infusion period.

From a microbiological point of view, the infusion solution should be administered immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

26 mL solution in a type I glass 30 mL vial closed with a chlorobutyl rubber stopper. Pyzchiva is available in packs of 1 or 3 vials or multipack containing 3 (3 packs of 1) vials.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

The solution in the Pyzchiva vial should not be shaken. The solution should be visually inspected for particulate matter or discoloration prior to administration. The solution is clear, colourless to light yellow. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

Dilution
Pyzchiva concentrate for solution for infusion must be diluted and prepared by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of Pyzchiva vials needed based on patient weight (see section 4.2, Table 1). Each 26 mL vial of Pyzchiva contains 130 mg of ustekinumab. Only use complete vials of Pyzchiva.
2. Withdraw and discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 250 mL infusion bag equal to the volume of Pyzchiva to be added. (discard 26 mL sodium chloride for each vial of Pyzchiva needed, for 2 vials-discard 52 mL, for 3 vials-discard 78 mL, for 4 vials- discard 104 mL). Alternatively, a 250 mL infusion bag containing 0.45% Sodium Chloride Injection, USP may be used.
3. Withdraw 26 mL of Pyzchiva from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before administration. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

5. Administer the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within 72 hours at room temperature up to 30°C of the dilution in the infusion bag. If necessary, the diluted infusion solution may be kept at 2°C to 8°C for up to 1 month and at room temperature up to 30°C for an additional 72 hours after removal from refrigeration including the infusion period.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).
7. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.
Olof Palmestraat 10
2616 LR Delft
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1801/003
EU/1/24/1801/006
EU/1/24/1801/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 April 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu/

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 45 mg solution for injection
Pyzchiva 45 mg solution for injection in pre-filled syringe
Pyzchiva 90 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pyzchiva 45 mg solution for injection
Each vial contains 45 mg ustekinumab in 0.5 mL.

Pyzchiva 45 mg solution for injection in pre-filled syringe
Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL.

Pyzchiva 90 mg solution for injection in pre-filled syringe
Each pre-filled syringe contains 90 mg ustekinumab in 1 mL.

Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a CHO cell line using recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pyzchiva 45 mg solution for injection
Solution for injection.

Pyzchiva 45 mg solution for injection in pre-filled syringe
Solution for injection.

Pyzchiva 90 mg solution for injection in pre-filled syringe
Solution for injection.

The solution is clear, colourless to light yellow, and its formulated at pH 6.0 ± 0.3. The osmolality of the solution is 320 ± 32 mOsm/kg..

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis
Pyzchiva is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Paediatric plaque psoriasis
Pyzchiva is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are

intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)
Pyzchiva, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's Disease
Pyzchiva is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

4.2 Posology and method of administration

Pyzchiva is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of conditions for which Pyzchiva is indicated.

Posology

Plaque psoriasis
The recommended posology of Pyzchiva is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Patients with Body Weight > 100 kg
For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy. (see section 5.1, Table 4)

Psoriatic arthritis (PsA)
The recommended posology of Pyzchiva is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

Renal and Hepatic Impairment
Ustekinumab has not been studied in these patient populations. No dose recommendations can be made.

Paediatric Population
The safety and efficacy of ustekinumab in children with psoriasis less than 6 years of age or in children with psoriatic arthritis less than 18 years of age have not yet been established.

Paediatric plaque psoriasis (6 years and older)

The recommended dose of Pyzchiva based on body weight is shown below (Table 1 and Table 2). Pyzchiva should be administered at Weeks 0 and 4, then every 12 weeks thereafter.

Table 1: Recommended dose of ustekinumab for paediatric psoriasis

Body weight at the time of dosing	Recommended Dose
< 60 kg	0.75 mg/kg
≥ 60-≤ 100 kg	45 mg
> 100 kg	90 mg

To calculate the volume of injection (mL) for patients < 60 kg, use the following formula: body weight (kg) x 0.0083 (mL/kg) or see Table 2. The calculated volume should be rounded to the nearest 0.01 mL and administered using a 1 mL graduated syringe. A 45 mg vial is available for paediatric patients who need to receive less than the full 45 mg dose.

Table 2: Injection volumes of Pyzchiva for paediatric psoriasis patients < 60 kg

Body weight at time of dosing (kg)	Dose (mg)	Volume of injection (mL)
15	11.3	0.12
16	12.0	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15.0	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19
24	18.0	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21.0	0.23
29	21.8	0.24
30	22.5	0.25
31	23.3	0.26
32	24.0	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27.0	0.30
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30.0	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33.0	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36.0	0.40
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39.0	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46

56	42.0	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Crohn's Disease
In the treatment regimen, the first dose of Pyzchiva is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the Pyzchiva 130 mg Concentrate for solution for infusion SmPC.

The first subcutaneous administration of 90 mg Pyzchiva should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time (see section 5.1).

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1, section 5.2).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1).

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose.

Immunomodulators and/or corticosteroids may be continued during treatment with Pyzchiva. In patients who have responded to treatment with Pyzchiva, corticosteroids may be reduced or discontinued in accordance with standard of care.

In Crohn's disease, if therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

Renal and Hepatic Impairment
Ustekinumab has not been studied in these patient populations. No dose recommendations can be made.

Paediatric Population
The safety and efficacy of ustekinumab in treatment of Crohn's disease in children less than 18 years have not yet been established. No data are available.

Method of administration
Pyzchiva 45 mg vials or 45 mg and 90 mg pre-filled syringes are for subcutaneous injection only. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients or their caregivers may inject Pyzchiva if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients or their caregivers should be instructed to inject the prescribed amount of Pyzchiva according to the directions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

For further instructions on preparation and special precautions for handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies and a post-marketing observational study in patients with psoriasis, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab (see section 4.8).

Opportunistic infections including reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis) have been reported in patients treated with ustekinumab.

Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with ustekinumab, patients should be evaluated for tuberculosis infection. ustekinumab must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering ustekinumab. Anti-tuberculosis therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving ustekinumab should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and ustekinumab should not be administered until the infection resolves.

Malignancies
Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received ustekinumab in clinical studies and in a post-marketing observational study in patients with psoriasis developed cutaneous and non-cutaneous malignancies (see section 4.8). The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving ustekinumab. Thus, caution should be exercised when considering the use of ustekinumab in these patients.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer (see section 4.8).

Systemic and respiratory hypersensitivity reactions
Systemic

Serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of ustekinumab should be discontinued (see section 4.8).

Respiratory
Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section 4.8).

Cardiovascular events
Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to ustekinumab in a post-marketing observational study. Risk factors for cardiovascular disease should be regularly assessed during treatment with ustekinumab.

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with ustekinumab. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving ustekinumab. Before live viral or live bacterial vaccination, treatment with ustekinumab should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.5 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Patients receiving ustekinumab may receive concurrent inactivated or non-live vaccinations.

Long term treatment with ustekinumab does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1).

Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustakinumab. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab. Caution should be exercised when considering concomitant use of other immunosuppressants and ustekinumab or when transitioning from other immunosuppressive biologics (see section 4.5).

Immunotherapy
Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether ustekinumab may affect allergy immunotherapy.

Serious skin conditions
In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms

that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. ustekinumab should be discontinued if a drug reaction is suspected.

Lupus-related conditions
Cases of lupus-related conditions have been reported in patients treated with ustekinumab, including cutaneous lupus erythematosus and lupus-like syndrome. If lesions occur, especially in sun exposed areas of the skin or if accompanied by arthralgia, the patient should seek medical attention promptly. If the diagnosis of a lupus-related condition is confirmed, ustekinumab should be discontinued and appropriate treatment initiated.

Special populations
Elderly
No overall differences in efficacy or safety in patients age 65 and older who received ustekinumab were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Polysorbate 80
Ustekinumab contains 0.04 mg (90 mg/1.0mL) or 0.02 mg (45 mg/0.5 mL) of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.04 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with ustekinumab.

Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

In the population pharmacokinetic analyses of the phase 3 studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an *in vitro* study and a phase 1 study in subjects with active Crohn's disease do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section 5.2).

In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab. (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.

Pregnancy

Data from a moderate number of prospectively collected pregnancies following exposure to ustekinumab with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3).

However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of ustekinumab in pregnancy.

Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed in utero to ustekinumab may be increased after birth.

Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.5). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable

Breast-feeding
Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with ustekinumab must be made taking into account the benefit of breast-feeding to the child and the benefit of ustekinumab therapy to the woman.

Fertility
The effect of ustekinumab on human fertility has not been evaluated (see section 5.3).

4.7 Effects on ability to drive and use machines

Ustekinumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies with ustekinumab were nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for ustekinumab is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions
The safety data described below reflect exposure in adults to ustekinumab in 14 phase 2 and phase 3 studies in 6,710 patients (4,135 with psoriasis and/or psoriatic arthritis, 1,749 with Crohn's disease and 826 patients with ulcerative colitis). This includes exposure to ustekinumab in the controlled and non-

controlled periods of the clinical studies in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis for at least 6 months (4,577 patients) or at least 1 year (3,648 patients). 2,194 patients with psoriasis, Crohn's disease or ulcerative colitis for at least 4 years while 1,148 patients with psoriasis or Crohn's disease were exposed for at least 5 years.

Table 3 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: List of adverse reactions

System Organ Class	Frequency: Adverse reaction
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis, hypersensitivity vasculitis Very rare: Bullous pemphigoid, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia Very rare: Lupus-like syndrome
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

*See section 4.4, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions Infections

In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in

placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,227 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 2.3 years for ulcerative colitis studies. The rate of infection was 0.85 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (289 serious infections in 15,227 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancies
In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,205 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 2.3 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 76 patients in 15,205 patient-years of follow-up (incidence of 0.50 per 100 patient- years of follow-up for ustekinumab-treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.94 [95% confidence interval: 0.73, 1.18], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma colorectal, and breast cancers. The incidence of non-melanoma skin cancer was 0.46 per 100 patient-years of follow-up for ustekinumab-treated patients (69 patients in 15,165 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (see section 4.4).

Hypersensitivity reactions
During the controlled periods of the psoriasis and psoriatic arthritis clinical studies of ustekinumab, rash and urticaria have each been observed in < 1% of patients (see section 4.4).

Paediatric population
Paediatric patients 6 years and older with plaque psoriasis
The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 6 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Pyzchiva is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu.

Mechanism of action

Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease.

By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with Crohn's disease, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and fecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase. CRP was assessed during the study extension and the reductions observed during maintenance were generally sustained through week 252.

Immunisation

During the long term extension of Psoriasis Study 2 (PHOENIX 2), adult patients treated with ustekinumab for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titers were similar among ustekinumab-treated and control patients.

Clinical efficacy

Plaque psoriasis (Adults)

The safety and efficacy of ustekinumab was assessed in 1,996 patients in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic therapy. In addition, a randomised, blinded assessor, active-controlled study compared ustekinumab and etanercept in patients with moderate to severe plaque psoriasis who had had an inadequate response to, intolerance to, or contraindication to ciclosporin, MTX, or PUVA.

Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. 53% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to

ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 and followed by the same dose every 12 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16 followed by dosing every 12 weeks. Patients originally randomised to ustekinumab who achieved Psoriasis Area and Severity Index 75 response (PASI improvement of at least 75% relative to baseline) at both Weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomised to placebo at week 40 reinitiated ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at week 40. All patients were followed for up to 76 weeks following first administration of study treatment.

Psoriasis Study 2 (PHOENIX 2) evaluated 1,230 patients. 61% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at 16 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (ACCEPT) evaluated 903 patients with moderate to severe psoriasis who inadequately responded to, were intolerant to, or had a contraindication to other systemic therapy and compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept. During the 12-week active-controlled portion of the study, patients were randomised to receive etanercept (50 mg twice a week), ustekinumab 45 mg at Weeks 0 and 4, or ustekinumab 90 mg at Weeks 0 and 4.

Baseline disease characteristics were generally consistent across all treatment groups in Psoriasis Studies 1 and 2 with a median baseline PASI score from 17 to 18, median baseline Body Surface Area (BSA) ≥ 20, and median Dermatology Life Quality Index (DLQI) range from 10 to 12. Approximately one third (Psoriasis Study 1) and one quarter (Psoriasis Study 2) of subjects had Psoriatic Arthritis (PsA). Similar disease severity was also seen in Psoriasis Study 3.

The primary endpoint in these studies was the proportion of patients who achieved PASI 75 response from baseline at week 12 (see Tables 4 and 5).

Table 4: Summary of clinical response in Psoriasis Study 1 (PHOENIX 1) and Psoriasis Study 2 (PHOENIX 2)

	Week 12 2 doses (week 0 and week 4)			Week 28 3 doses (week 0, week 4 and week 16)	
	PBO	45 mg	90 mg	45 mg	90 mg
Psoriasis Study 1					
Number of patients randomised	255	255	256	250	243
PASI 50 response N (%)	26 (10%)	213 (84%)[a]	220 (86%)[a]	228 (91%)	234 (96%)
PASI 75 response N (%)	8 (3%)	171 (67%)[a]	170 (66%)[a]	178 (71%)	191 (79%)
PASI 90 response N (%)	5 (2%)	106 (42%)[a]	94 (37%)[a]	123 (49%)	135 (56%)
PGA[b] of cleared or minimal N (%)	10 (4%)	151 (59%)[a]	156 (61%)[a]	146 (58%)	160 (66%)
Number of patients ≤ 100 kg	166	168	164	164	153
PASI 75 response N (%)	6 (4%)	124 (74%)	107 (65%)	130 (79%)	124 (81%)
Number of patients > 100 kg	89	87	92	86	90
PASI 75 response N (%)	2 (2%)	47 (54%)	63 (68%)	48 (56%)	67 (74%)
Psoriasis Study 2					
Number of patients randomised	410	409	411	397	400
PASI 50 response N (%)	41 (10%)	342 (84%)[a]	367 (89%)[a]	369 (93%)	380 (95%)
PASI 75 response N (%)	15 (4%)	273 (67%)[a]	311 (76%)[a]	276 (70%)	314 (79%)

	Week 12 2 doses (week 0 and week 4)			Week 28 3 doses (week 0, week 4 and week 16)	
	PBO	45 mg	90 mg	45 mg	90 mg
PASI 90 response N (%)	3 (1%)	173 (42%)[a]	209 (51%)[a]	178 (45%)	217 (54%)
PGA[b] of cleared or minimal N (%)	18 (4%)	277 (68%)[a]	300 (73%)[a]	241 (61%)	279 (70%)
Number of patients ≤ 100 kg	290	297	289	287	280
PASI 75 response N (%)	12 (4%)	218 (73%)	225 (78%)	217 (76%)	226 (81%)
Number of patients > 100 kg	120	112	121	110	119
PASI 75 response N (%)	3 (3%)	55 (49%)	86 (71%)	59 (54%)	88 (74%)

[a]$p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with placebo (PBO).
[b]PGA = Physician Global Assessment

Table 5: Summary of clinical response at week 12 in Psoriasis Study 3 (ACCEPT)

	Psoriasis Study 3		
	Etanercept 24 doses (50 mg twice a week)	Ustekinumab 2 doses (week 0 and week 4)	
		45 mg	90 mg
Number of patients randomised	347	209	347
PASI 50 response N (%)	286 (82%)	181 (87%)	320 (92%)[a]
PASI 75 response N (%)	197 (57%)	141 (67%)[b]	256 (74%)[a]
PASI 90 response N (%)	80 (23%)	76 (36%)[a]	155 (45%)[a]
PGA of cleared or minimal N (%)	170 (49%)	136 (65%)[a]	245 (71%)[a]
Number of patients ≤ 100 kg	251	151	244
PASI 75 response N (%)	154 (61%)	109 (72%)	189 (77%)
Number of patients > 100 kg	96	58	103
PASI 75 response N (%)	43 (45%)	32 (55%)	67 (65%)

[a]$p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with etanercept.
[b]$p = 0.012$ for ustekinumab 45 mg in comparison with etanercept.

In Psoriasis Study 1 maintenance of PASI 75 was significantly superior with continuous treatment compared with treatment withdrawal ($p < 0.001$). Similar results were seen with each dose of ustekinumab. At 1 year (week 52), 89% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomised to placebo (treatment withdrawal) ($p < 0.001$). At 18 months (week 76), 84% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomised to placebo (treatment withdrawal). At 3 years (week 148), 82% of patients re-randomised to maintenance treatment were PASI 75 responders. At 5 years (week 244), 80% of patients re-randomised to maintenance treatment were PASI 75 responders.

In patients re-randomised to placebo, and who reinitiated their original ustekinumab treatment regimen after loss of ≥ 50% of PASI improvement 85% regained PASI 75 response within 12 weeks after re-initiating therapy.

In Psoriasis Study 1, at week 2 and week 12, significantly greater improvements from baseline were demonstrated in the DLQI in each ustekinumab treatment group compared with placebo. The improvement was sustained through week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at week 4 and 12, which were sustained through week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the physical and mental component summary scores of the SF-36 and in the Itch Visual Analogue Scale (VAS) were also significant in each ustekinumab treatment group compared with placebo. In Psoriasis Study 2, the Hospital Anxiety and Depression Scale (HADS) and Work Limitations Questionnaire (WLQ) were also significantly improved in each ustekinumab treatment group compared with placebo.

Psoriatic arthritis (PsA) (Adults)
Ustekinumab has been shown to improve signs and symptoms, physical function and health-related quality of life, and reduce the rate of progression of peripheral joint damage in adult patients with active PsA.

The safety and efficacy of ustekinumab was assessed in 927 patients in two randomised, double-blind, placebo-controlled studies in patients with active PsA (≥ 5 swollen joints and ≥ 5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy.
Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients in both studies had enthesitis and dactylitis at baseline, respectively. Patients were randomised to receive treatment with ustekinumab 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤ 25 mg/week).

In PsA Study 1 (PSUMMIT I) and PsA Study 2 (PSUMMIT II), 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In Study 1 previous treatment with anti-tumour necrosis factor (TNF)α agent was not allowed. In Study 2, the majority of patients (58%, n = 180) had been previously treated with one or more anti-TNFα agent(s), of whom over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance at any time.

Signs and Symptoms
Treatment with ustekinumab resulted in significant improvements in the measures of disease activity compared to placebo at week 24. The primary endpoint was the percentage of patients who achieved American College of Rheumatology (ACR) 20 response at week 24. The key efficacy results are shown in Table 6 below.

Table 6: Number of patients who achieved clinical response in Psoriatic arthritis Study 1 (PSUMMIT I) and Study 2 (PSUMMIT II) at week 24

	Psoriatic arthritis Study 1			**Psoriatic arthritis Study 2**		
	PBO	**45 mg**	**90 mg**	**PBO**	**45 mg**	**90 mg**
Number of patients randomised	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)[a]	101 (50%)[a]	21 (20%)	45 (44%)[a]	46 (44%)[a]
ACR 50 response, N (%)	18 (9%)	51 (25%)[a]	57 (28%)[a]	7 (7%)	18 (17%)[b]	24 (23%)[a]
ACR 70 response, N (%)	5 (2%)	25 (12%)[a]	29 (14%)[a]	3 (3%)	7 (7%)[c]	9 (9%)[c]
Number of patients with ≥ 3% BSA[d]	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)[a]	93 (62%)[a]	4 (5%)	41 (51%)[a]	45 (56%)[a]
PASI 90 response, N (%)	4 (3%)	60 (41%)[a]	65 (44%)[a]	3 (4%)	24 (30%)[a]	36 (44%)[a]
Combined PASI 75 and ACR 20 response, N (%)	8 (5%)	40 (28%)[a]	62 (42%)[a]	2 (3%)	24 (30%)[a]	31 (38%)[a]
Number of patients ≤ 100 kg	154	153	154	74	74	73
ACR 20 response, N (%)	39 (25%)	67 (44%)	78 (51%)	17 (23%)	32 (43%)	34 (47%)

	Psoriatic arthritis Study 1			Psoriatic arthritis Study 2		
	PBO	**45 mg**	**90 mg**	**PBO**	**45 mg**	**90 mg**
Number of patients with ≥ 3% BSA[d]	105	105	111	54	58	57
PASI 75 response, N (%)	14 (13%)	64 (61%)	73 (66%)	4 (7%)	31 (53%)	32 (56%)
Number of patients > 100 kg	52	52	50	30	29	31
ACR 20 response, N (%)	8 (15%)	20 (38%)	23 (46%)	4 (13%)	13 (45%)	12 (39%)
Number of patients with ≥ 3% BSA[d]	41	40	38	26	22	24
PASI 75 response, N (%)	2 (5%)	19 (48%)	20 (53%)	0	10 (45%)	13 (54%)

[a]$p < 0.001$

[b]$p < 0.05$

[c]p = NS

[d]Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

ACR 20, 50 and 70 responses continued to improve or were maintained through week 52 (PsA Study 1 and 2) and week 100 (PsA Study 1). In PsA Study 1, ACR 20 responses at week 100 were achieved by 57% and 64%, for 45 mg and 90 mg, respectively. In PsA Study 2, ACR 20 responses at week 52 were achieved by 47% and 48%, for 45 mg and 90 mg, respectively.

The proportion of patients achieving a modified PsA response criteria (PsARC) response was also significantly greater in the ustekinumab groups compared to placebo at week 24. PsARC responses were maintained through weeks 52 and 100. A higher proportion of patients treated with ustekinumab who had spondylitis with peripheral arthritis as their primary presentation, demonstrated 50 and 70 percent improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared with placebo at week 24.

Responses observed in the ustekinumab treated groups were similar in patients receiving and not receiving concomitant MTX, and were maintained through weeks 52 and 100. Patients previously treated with anti-TNFα agents who received ustekinumab achieved a greater response at week 24 than patients receiving placebo (ACR 20 response at week 24 for 45 mg and 90 mg was 37% and 34%, respectively, compared with placebo 15%; $p < 0.05$), and responses were maintained through week 52.

For patients with enthesitis and/or dactylitis at baseline, in PsA Study 1 significant improvement in enthesitis and dactylitis score was observed in the ustekinumab groups compared with placebo at week 24. In PsA Study 2 significant improvement in enthesitis score and numerical improvement (not statistically significant) in dactylitis score was observed in the ustekinumab 90 mg group compared with placebo at week 24. Improvements in enthesitis score and dactylitis score were maintained through weeks 52 and 100.

Radiographic Response

Structural damage in both hands and feet was expressed as change in total van der Heijde-Sharp score (vdH-S score), modified for PsA by addition of hand distal interphalangeal joints, compared to baseline. A pre-specified integrated analysis combining data from 927 subjects in both PsA Study 1 and 2 was performed. Ustekinumab demonstrated a statistically significant decrease in the rate of progression of structural damage compared to placebo, as measured by change from baseline to week 24 in the total modified vdH-S score (mean ± SD score was 0.97 ± 3.85 in the placebo group compared with 0.40 ± 2.11 and 0.39 ± 2.40 in the ustekinumab 45 mg ($p < 0.05$) and 90 mg ($p < 0.001$) groups, respectively). This effect was driven by PsA Study 1. The effect is considered demonstrated irrespective of concomitant MTX use, and was maintained through Weeks 52 (integrated analysis) and 100 (PsA Study 1).

Physical Function and Health-Related Quality of Life

Ustekinumab-treated patients showed significant improvement in physical function as assessed by the

Disability Index of the Health Assessment Questionnaire (HAQ-DI) at week 24. The proportion of patients achieving a clinically meaningful ≥ 0.3 improvement in HAQ-DI score from baseline was also significantly greater in the ustekinumab groups when compared with placebo. Improvement in HAQ-DI score from baseline was maintained through Weeks 52 and 100.

There was significant improvement in DLQI scores in the ustekinumab groups as compared with placebo at week 24, which was maintained through weeks 52 and 100. In PsA Study 2 there was a significant improvement in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores in the ustekinumab groups when compared with placebo at week 24. The proportion of patients achieving a clinically significant improvement in fatigue (4 points in FACIT-F) was also significantly greater in the ustekinumab groups compared with placebo. Improvements in FACIT scores were maintained through week 52.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population with juvenile idiopathic arthritis (see section 4.2 for information on paediatric use).

Paediatric plaque psoriasis

Ustekinumab has been shown to improve signs and symptoms, and health-related quality of life in paediatric patients 6 years and older with plaque psoriasis.

Adolescent patients (12-17 years)

The efficacy of ustekinumab was studied in 110 paediatric patients aged 12 to 17 years with moderate to severe plaque psoriasis in a multicenter, phase 3, randomised, double-blind, placebo-controlled study (CADMUS). Patients were randomised to receive either placebo (n = 37), or the recommended dose of ustekinumab (see section 4.2; n = 36) or half of the recommended dose of ustekinumab (n = 37) by subcutaneous injection at Weeks 0 and 4 followed by every 12 week (q12w) dosing. At week 12, placebo-treated patients crossed over to receive ustekinumab.

Patients with PASI ≥ 12, PGA ≥ 3 and BSA involvement of at least 10%, who were candidates for systemic therapy or phototherapy, were eligible for the study. Approximately 60% of the patients had prior exposure to conventional systemic therapy or phototherapy. Approximately 11% of the patients had prior exposure to biologics.

The primary endpoint was the proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at week 12. Secondary endpoints included PASI 75, PASI 90, change from baseline in Children's Dermatology Life Quality Index (CDLQI), change from baseline in the total scale score of PedsQL (Paediatric Quality of Life Inventory) at week 12. At week 12, subjects treated with ustekinumab showed significantly greater improvement in their psoriasis and health-related quality of life compared with placebo (Table 7).

All patients were followed for efficacy for up to 52 weeks following first administration of study agent. The proportion of patients with a PGA score of cleared (0) or minimal (1) and the proportion achieving PASI 75 showed separation between the ustekinumab treated group and placebo at the first post-baseline visit at week 4, reaching a maximum by week 12. Improvements in PGA, PASI, CDLQI and PedsQL were maintained through week 52 (Table 7).

Table 7: Summary of primary and secondary endpoints at week 12 and week 52

Paediatric psoriasis study (CADMUS) (Age 12-17)			
	Week 12		**Week 52**
	Placebo	Recommended dose of Ustekinumab	Recommended dose of Ustekinumab
	N (%)	N (%)	N (%)
Patients randomised	37	36	35
PGA			
PGA of cleared (0) or minimal (1)	2 (5.4%)	25 (69.4%)[a]	20 (57.1%)
PGA of Cleared (0)	1 (2.7%)	17 (47.2%)[a]	13 (37.1%)
PASI			
PASI 75 responders	4 (10.8%)	29 (80.6%)[a]	28 (80.0%)
PASI 90 responders	2 (5.4%)	22 (61.1%)[a]	23 (65.7%)
PASI 100 responders	1 (2.7%)	14 (38.9%)[a]	13 (37.1%)
CDLQI			
CDLQI of 0 or 1[b]	6 (16.2%)	18 (50.0%)[c]	20 (57.1%)
PedsQL			
Change from baseline Mean (SD)[d]	3.35 (10.04)	8.03 (10.44)[e]	7.26 (10.92)

[a] $p < 0.001$

[b] CDLQI: The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the paediatric population. CDLQI of 0 or 1 indicates no effect on child's quality of life.

[c] $p = 0.002$

[d] PedsQL: The PedsQL Total Scale Score is a general health-related quality of life measure developed for use in children and adolescent populations. For the placebo group at week 12, N = 36

[e] $p = 0.028$

During the placebo-controlled period through week 12, the efficacy of both the recommended and half of the recommended dose groups were generally comparable at the primary endpoint (69.4% and 67.6% respectively) although there was evidence of a dose response for higher level efficacy criteria (e.g. PGA of cleared (0), PASI 90). Beyond week 12, efficacy was generally higher and better sustained in the recommended dose group compared with half of the recommended dosage group in which a modest loss of efficacy was more frequently observed toward the end of each 12 week dosing interval. The safety profiles of the recommended dose and half of the recommended dose were comparable.

Children (6-11 years)

The efficacy of ustekinumab was studied in 44 paediatric patients aged 6 to 11 years with moderate to severe plaque psoriasis in an open label, single-arm, multicenter, phase 3, study (CADMUS Jr.). Patients were treated with the recommended dose of ustekinumab (see section 4.2; n = 44) by subcutaneous injection at weeks 0 and 4 followed by every 12 week (q12w) dosing.

Patients with PASI ≥ 12, PGA ≥ 3 and BSA involvement of at least 10%, who were candidates for systemic therapy or phototherapy, were eligible for the study. Approximately 43% of the patients had prior exposure to conventional systemic therapy or phototherapy. Approximately 5% of the patients had prior exposure to biologics.

The primary endpoint was the proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at week 12. Secondary endpoints included PASI 75, PASI 90, and change from baseline in Children's Dermatology Life Quality Index (CDLQI) at week 12. At week 12, subjects treated with ustekinumab showed clinically meaningful improvements in their psoriasis and health-related quality of life (Table 8).

All patients were followed for efficacy for up to 52 weeks following first administration of study agent. The proportion of patients with a PGA score of cleared (0) or minimal (1) at week 12 was 77.3%. Efficacy (defined as PGA 0 or 1) was observed as early as the first post-baseline visit at week

4 and the proportion of subjects who achieved a PGA score of 0 or 1 increased through week 16 and then remained relatively stable through week 52. Improvements in PGA, PASI, and CDLQI were maintained through week 52 (Table 8).

Table 8: Summary of primary and secondary endpoints at week 12 and week 52

Paediatric psoriasis study (CADMUS Jr.) (Age 6-11)		
	Week 12	**Week 52**
	Recommended dose of Ustekinumab	Recommended dose of Ustekinumab
	N (%)	N (%)
Patients enrolled	44	41
PGA		
PGA of cleared (0) or minimal (1)	34 (77.3%)	31 (75.6%)
PGA of cleared (0)	17 (38.6%)	23 (56.1%)
PASI		
PASI 75 responders	37 (84.1%)	36 (87.8%)
PASI 90 responders	28 (63.6%)	29 (70.7%)
PASI 100 responders	15 (34.1%)	22 (53.7%)
CDLQI[a]		
Patients with a CDLQI > 1 at baseline	(N=39)	(N=36)
CDLQI of 0 or 1	24 (61.5%)	21 (58.3%)

[a] CDLQI: The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the paediatric population. CDLQI of 0 or 1 indicates no effect on child's quality of life.

Crohn's Disease

The safety and efficacy of ustekinumab was assessed in three randomized, double-blind, placebo-controlled, multicenter studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development program consisted of two 8-week intravenous induction studies (UNITI-1 and UNITI-2) followed by a 44 week subcutaneous randomized withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analyzed through week 8 for both studies. Concomitant doses of oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see section 4.2 of the Pyzchiva 130 mg Concentrate for solution for infusion SmPC), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNFα therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 9). Clinical response and

remission were significant as early as week 3 in ustekinumab treated patients and continued to improve through week 8. In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended intravenous induction dose.

Table 9: Induction of Clinical Response and Remission in UNITI-1 and UNITI 2

	UNITI-1*		UNITI-2**	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
Clinical Remission, week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission

70 point response is defined as reduction in CDAI score by at least 70 points

*Anti-TNFα failures

**Conventional therapy failures

[a]$p < 0.001$

[b]$p < 0.01$

The maintenance study (IM-UNITI), evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 9).

Table 10: Maintenance of Clinical Response and Remission in IM-UNITI (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 131†	**90 mg ustekinumab every 8 weeks N = 128†**	**90 mg ustekinumab every 12 weeks N = 129†**
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002‡	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)
who entered from study CRD3001§	26% (16/61)	41% (23/56)	39% (22/57)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

*The placebo group consisted of patients who were in response to ustekinumab and were randomized to receive placebo at the start of maintenance therapy.

†Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy

‡Patients who failed conventional therapy but not anti-TNFα therapy

[§]Patients who are anti-TNFα refractory/intolerant
[a]$p < 0.01$
[b]$p < 0.05$
[c]nominally significant ($p < 0.05$)

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to receive ustekinumab every 8 weeks. Loss of response was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomized portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority maintained response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomized to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 567 patients who entered on and were treated with ustekinumab in the study extension, clinical remission and response were generally maintained through week 252 for both patients who failed TNF-therapies and those who failed conventional therapies.

The safety analysis including 457 patients (1289.9 person-years) followed up to 220 weeks showed a safety profile between week 44 and 220 that was comparable with that observed up to week 44.

No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with Crohn's Disease.

Endoscopy
Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p = 0.012).

Fistula Response
In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-Related Quality of Life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly

greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo. Improvement in health-related quality of life was generally maintained during the extension through week 252.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with both increased clearance and reduced efficacy of ustekinumab, except in patients with Crohn's disease where no reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in Crohn's Disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
The median time to reach the maximum serum concentration (tmax) was 8.5 days after a single 90 mg subcutaneous administration in healthy subjects. The median tmax values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to those observed in healthy subjects.

The absolute bioavailability of ustekinumab following a single subcutaneous administration was estimated to be 57.2% in patients with psoriasis.

Distribution
Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life (t1/2) of ustekinumab was approximately 3 weeks in patients with psoriasis, psoriatic arthritis or, Crohn's disease, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies. In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 l/day and 15.7 l, respectively, in patients with psoriasis. The CL/F of ustekinumab was not impacted by gender. Population pharmacokinetic analysis showed that there was a trend towards a higher clearance of ustekinumab in patients who tested positive for antibodies to ustekinumab.

Dose linearity
The systemic exposure of ustekinumab (Cmax and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg or following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

Single dose versus multiple doses
Serum concentration-time profiles of ustekinumab were generally predictable after single or multiple

subcutaneous dose administrations. In patients with psoriasis, steady-state serum concentrations of ustekinumab were achieved by week 28 after initial subcutaneous doses at Weeks 0 and 4 followed by doses every 12 weeks. The median steady-state trough concentration ranged from 0.21 µg/mL to 0.26 µg/mL (45 mg) and from 0.47 µg/mL to 0.49 µg/mL (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease, following an intravenous dose of ~6 mg/kg, starting at week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. In patients with Crohn's disease, median steady-state trough concentrations ranged from 1.97 µg/mL to 2.24 µg/mL and from 0.61 µg/mL to 0.76 µg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks respectively. The steady-state trough ustekinumab levels resulting from 90 mg ustekinumab every 8 weeks were associated with higher clinical remission rates as compared to the steady-state trough levels following 90 mg every 12 weeks.

Impact of weight on pharmacokinetics
In a population pharmacokinetic analysis using data from patients with psoriasis, body weight was found to be the most significant covariate affecting the clearance of ustekinumab. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared to patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared to patients with weight ≤ 100 kg. The median trough serum concentrations of ustekinumab in patients with higher weight (> 100 kg) in the 90 mg group were comparable to those in patients with lower weight (≤ 100 kg) in the 45 mg group. Similar results were obtained from a confirmatory population pharmacokinetic analysis using data from patients with psoriatic arthritis.

Dosing frequency adjustment
In patients with Crohn's disease, based on observed data and population PK analyses, randomized subjects who lost response to treatment had lower serum ustekinumab concentrations over time compared with subjects who did not lose response. In Crohn's disease, dose adjustment from 90 mg every 12 weeks to 90 mg every 8 weeks was associated with an increase in trough serum ustekinumab concentrations and an accompanying increase in efficacy.

Special populations
No pharmacokinetic data are available in patients with impaired renal or hepatic function. No specific studies have been conducted in elderly patients.

The pharmacokinetics of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis.

In patients with Crohn's disease, variability in ustekinumab clearance was affected by body weight, serum albumin level, sex, and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). The impact of these covariates was within ± 20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

In the population pharmacokinetic analysis, there were no indications of an effect of tobacco or alcohol on the pharmacokinetics of ustekinumab.

The bioavailability of ustekinumab following administration by syringe or pre-filled pen was comparable

Serum ustekinumab concentrations in paediatric psoriasis patients 6 to 17 years of age, treated with the recommended weight-based dose were generally comparable to those in the adult psoriasis population

treated with the adult dose. Serum ustekinumab concentrations in paediatric psoriasis patients 12-17 years of age (CADMUS) treated with half of the recommended weight-based dose were generally lower than those in adults.

Regulation of CYP450 enzymes
The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an in vitro study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5).

A phase 1, open-label, drug interaction study, Study CNTO1275CRD1003, was conducted to evaluate the effect of ustekinumab on cytochrome P450 enzyme activities following induction and maintenance dosing in patients with active Crohn's disease (n=18). No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosing in patients with Crohn's disease (see section 4.5).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated-dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed. No adverse effects on female fertility indices were observed using an analogous antibody to IL-12/23 in mice.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Polysorbate 80 (E 433)
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Pyzchiva 45 mg solution for injection
42 months

Pyzchiva 45 mg solution for injection in pre-filled syringe
42 months

Pyzchiva 90 mg solution for injection in pre-filled syringe
42 months

Individual pre-filled syringes and vials may be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the pre-filled syringe is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period, the product can be put back in the refrigerator once and kept there until the expiry date. Discard the syringe if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial or pre-filled syringe in the outer carton in order to protect from light.
If needed, individual pre-filled syringes may be stored at room temperature up to 30°C (see section 6.3).

6.5 Nature and contents of container

Pyzchiva 45 mg solution for injection
0.5 mL solution in a type I glass 2 mL vial closed with a chlorobutyl rubber stopper.

Pyzchiva 45 mg solution for injection in pre-filled syringe
0.5 mL solution in a type I glass 1 mL syringe with a 29-gauge fixed 1/2 inch stainless steel needle and a needle cover containing rubber and the bromobutyl rubber plunger stopper. The syringe is fitted with a passive safety guard.

Pyzchiva 90 mg solution for injection in pre-filled syringe
1 mL solution in a type I glass 1 mL syringe with a 29-gauge fixed 1/2 inch stainless steel needle and a needle cover containing rubber and the bromobutyl rubber plunger stopper. The syringe is fitted with a passive safety guard.

Pyzchiva is available in a 1 vial pack or a pack of 1 pre-filled syringe.

6.6 Special precautions for disposal and other handling

The solution in the Pyzchiva vial or pre-filled syringe should not be shaken. The solution should be visually inspected for particulate matter or discoloration prior to subcutaneous administration. The solution is clear, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for proteinaceous solutions. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present. Before administration, Pyzchiva should be allowed to reach room temperature (approximately half an hour). Detailed instructions for use are provided in the package leaflet.

Pyzchiva does not contain preservatives; therefore any unused medicinal product remaining in the vial and the syringe should not be used. Pyzchiva is supplied as a sterile, single-use vial or single-use pre-filled syringe. The syringe needle and vial must never be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

When using the single-dose vial, a 1 mL syringe with a 27 gauge, ½ inch (13 mm) needle is recommended.

7. MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.

Olof Palmestraat 10
2616 LR Delft
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Pyzchiva 45 mg solution for injection
EU/1/24/1801/007

Pyzchiva 45 mg solution for injection in pre-filled syringe
EU/1/24/1801/001

Pyzchiva 90 mg solution for injection in pre-filled syringe
EU/1/24/1801/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 April 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu/

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 45 mg solution for injection in pre-filled pen
Pyzchiva 90 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pyzchiva 45 mg solution for injection in pre-filled pen
Each pre-filled pen contains 45 mg ustekinumab in 0.5 mL.

Pyzchiva 90 mg solution for injection in pre-filled pen
Each pre-filled pen contains 90 mg ustekinumab in 1 mL.

Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a CHO cell using recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pyzchiva 45 mg solution for injection in pre-filled pen
Solution for injection.

Pyzchiva 90 mg solution for injection in pre-filled pen
Solution for injection.

The solution is clear, colourless to light yellow, and its formulated at pH 6.0 ± 0.3. The osmolality of the solution is 320 ± 32 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis
Pyzchiva is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Psoriatic arthritis (PsA)
Pyzchiva, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's Disease
Pyzchiva is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

4.2 Posology and method of administration

Pyzchiva is intended for use under the guidance and supervision of physicians experienced in the

diagnosis and treatment of conditions for which Pyzchiva is indicated.

Posology

Plaque psoriasis
The recommended posology of Pyzchiva is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Patients with body weight > 100 kg
For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy. (see section 5.1, Table 4).

Psoriatic arthritis (PsA)
The recommended posology of Pyzchiva is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

Renal and hepatic impairment
Ustekinumab has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of ustekinumab in children with psoriasis less than 6 years of age or in children with psoriatic arthritis less than 18 years of age have not yet been established. The pre-filled pen has not been studied in the paediatric population and is not recommended for use in paediatric patients. See section 4.2 of the pre-filled syringe SmPC for posology and method of administration in paediatric patients 6 years and older with psoriasis.

Crohn's Disease
In the treatment regimen, the first dose of Pyzchiva is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the Pyzchiva 130 mg Concentrate for solution for infusion SmPC.

The first subcutaneous administration of 90 mg Pyzchiva should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time (see section 5.1).

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1, section 5.2).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1).

Consideration should be given to discontinuing treatment in patients who show no evidence of

therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose.

Immunomodulators and/or corticosteroids may be continued during treatment with Pyzchiva. In patients who have responded to treatment with Pyzchiva, corticosteroids may be reduced or discontinued in accordance with standard of care.

In Crohn's disease, if therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

Renal and hepatic impairment
Ustekinumab has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of ustekinumab in treatment of Crohn's disease in children less than 18 years have not yet been established. No data are available.

Method of administration
Pyzchiva 45 mg and 90 mg pre-filled pens are for subcutaneous injection only. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients or their caregivers may inject Pyzchiva if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients or their caregivers should be instructed to inject the prescribed amount of Pyzchiva according to the directions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

For further instructions on preparation and special precautions for handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies and a post-marketing observational study in patients with psoriasis, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab (see section 4.8).

Opportunistic infections including reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis) have been reported in patients treated with ustekinumab.

Caution should be exercised when considering the use of ustekinumab in patients with a chronic

infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with ustekinumab, patients should be evaluated for tuberculosis infection. ustekinumab must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering ustekinumab. Anti-tuberculosis therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving ustekinumab should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and ustekinumab should not be administered until the infection resolves.

Malignancies
Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received ustekinumab in clinical studies and in a post-marketing observational study in patients with psoriasis developed cutaneous and non-cutaneous malignancies (see section 4.8). The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving ustekinumab. Thus, caution should be exercised when considering the use of ustekinumab in these patients.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer (see section 4.8).

Systemic and respiratory hypersensitivity reactions
Systemic
Serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of ustekinumab should be discontinued (see section 4.8).

Respiratory
Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section 4.8).

Cardiovascular events
Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to ustekinumab in a post-marketing observational study. Risk factors for cardiovascular disease should be regularly assessed during treatment with ustekinumab.

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with ustekinumab. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving ustekinumab. Before live viral or live bacterial vaccination, treatment with ustekinumab should be withheld for at least 15 weeks

after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.5 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Patients receiving ustekinumab may receive concurrent inactivated or non-live vaccinations.

Long term treatment with ustekinumab does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1).

Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab. Caution should be exercised when considering concomitant use of other immunosuppressants and ustekinumab or when transitioning from other immunosuppressive biologics (see section 4.5).

Immunotherapy
Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether ustekinumab may affect allergy immunotherapy.

Serious skin conditions
In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. Ustekinumab should be discontinued if a drug reaction is suspected.

Lupus-related conditions
Cases of lupus-related conditions have been reported in patients treated with ustekinumab, including cutaneous lupus erythematosus and lupus-like syndrome. If lesions occur, especially in sun exposed areas of the skin or if accompanied by arthralgia, the patient should seek medical attention promptly. If the diagnosis of a lupus-related condition is confirmed, ustekinumab should be discontinued and appropriate treatment initiated.

Special populations
Elderly
No overall differences in efficacy or safety in patients age 65 and older who received ustekinumab were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Polysorbate 80
Ustekinumab contains 0.04 mg (90 mg/1.0mL) or 0.02 mg (45 mg/0.5 mL) of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.04 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with ustekinumab.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

In the population pharmacokinetic analyses of the phase 3 studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an *in vitro* study and a phase 1 study in subjects with active Crohn's disease do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section 5.2).

In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.

Pregnancy

Data from a moderate number of prospectively collected pregnancies following exposure to ustekinumab with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3).

However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of ustekinumab in pregnancy.

Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed *in utero* to ustekinumab may be increased after birth.
Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.5). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Breast-feeding
Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with ustekinumab must be made taking into account the benefit of breast-feeding to the child and the benefit of ustekinumab therapy to the woman.

Fertility
The effect of ustekinumab on human fertility has not been evaluated (see section 5.3).

4.7 Effects on ability to drive and use machines

Ustekinumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies with ustekinumab were nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for ustekinumab is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions
The safety data described below reflect exposure in adults to ustekinumab in 14 phase 2 and phase 3 studies in 6,710 patients (4,135 with psoriasis and/or psoriatic arthritis, 1,749 with Crohn's disease and 826 patients with ulcerative colitis). This includes exposure to ustekinumab in the controlled and non-controlled periods of the clinical studies in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis for at least 6 months (4,577 patients) or at least 1 year (3,648 patients). 2,194 patients with psoriasis, Crohn's disease or ulcerative colitis were exposed for at least 4 years while 1,148 patients with psoriasis or Crohn's disease were exposed for at least 5 years.

Table 1 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions

System Organ Class	Frequency: Adverse reaction
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression

Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis, hypersensitivity vasculitis Very rare: Bullous pemphigoid, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia Very rare: Lupus-like syndrome
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

* See section 4.4, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions

Infections
In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,227 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 2.3 years for ulcerative colitis studies. The rate of infection was 0.85 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (289 serious infections in 15,227 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancies
In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and

ulcerative colitis clinical studies, representing 15,205 patient-years of exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 2.3 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 76 patients in 15,205 patient-years of follow-up (incidence of 0.50 per 100 patient-years of follow-up for ustekinumab-treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.94 [95% confidence interval: 0.73, 1.18], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal, and breast cancers. The incidence of non-melanoma skin cancer was 0.46 per 100 patient-years of follow-up for ustekinumab-treated patients (69 patients in 15,165 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (see section 4.4).

Hypersensitivity reactions
During the controlled periods of the psoriasis and psoriatic arthritis clinical studies of ustekinumab, rash and urticaria have each been observed in <1% of patients (see section 4.4).

Paediatric population
Paediatric patients 6 years and older with plaque psoriasis
The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 6 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, and Crohn's

disease.

By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, and Crohn's disease and through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with Crohn's disease, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and fecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase. CRP was assessed during the study extension and the reductions observed during maintenance were generally sustained through week 252.

Immunisation
During the long term extension of Psoriasis Study 2 (PHOENIX 2), adult patients treated with ustekinumab for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titres were similar among ustekinumab -treated and control patients.

Clinical efficacy

Plaque psoriasis (Adults)
The safety and efficacy of ustekinumab was assessed in 1,996 patients in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic therapy. In addition, a randomised, blinded assessor, active-controlled study compared ustekinumab and etanercept in patients with moderate to severe plaque psoriasis who had had an inadequate response to, intolerance to, or contraindication to ciclosporin, MTX, or PUVA.

Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. 53% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 and followed by the same dose every 12 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16 followed by dosing every 12 weeks. Patients originally randomised to ustekinumab who achieved Psoriasis Area and Severity Index 75 response (PASI improvement of at least 75% relative to baseline) at both Weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomised to placebo at week 40 reinitiated ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at week 40. All patients were followed for up to 76 weeks following first administration of study treatment.

Psoriasis Study 2 (PHOENIX 2) evaluated 1,230 patients. 61% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at 16 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (ACCEPT) evaluated 903 patients with moderate to severe psoriasis who inadequately responded to, were intolerant to, or had a contraindication to other systemic therapy and compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept. During the 12-week active-controlled portion of the study, patients were randomised to receive etanercept (50 mg twice a week), ustekinumab 45 mg at Weeks 0 and 4, or ustekinumab 90 mg at Weeks 0 and 4.

Baseline disease characteristics were generally consistent across all treatment groups in Psoriasis Studies 1 and 2 with a median baseline PASI score from 17 to 18, median baseline Body Surface Area (BSA) ≥ 20, and median Dermatology Life Quality Index (DLQI) range from 10 to 12. Approximately

one third (Psoriasis Study 1) and one quarter (Psoriasis Study 2) of subjects had Psoriatic Arthritis (PsA). Similar disease severity was also seen in Psoriasis Study 3.

The primary endpoint in these studies was the proportion of patients who achieved PASI 75 response from baseline at week 12 (see Tables 2 and 3).

Table 2: Summary of clinical response in Psoriasis Study 1 (PHOENIX 1) and Psoriasis Study 2 (PHOENIX 2)

	Week 12 2 doses (week 0 and week 4)			Week 28 3 doses (week 0, week 4 and week 16)	
	PBO	45 mg	90 mg	45 mg	90 mg
Psoriasis Study 1					
Number of patients randomised	255	255	256	250	243
PASI 50 response N (%)	26 (10%)	213 (84%)[a]	220 (86%)[a]	228 (91%)	234 (96%)
PASI 75 response N (%)	8 (3%)	171 (67%)[a]	170 (66%)[a]	178 (71%)	191 (79%)
PASI 90 response N (%)	5 (2%)	106 (42%)[a]	94 (37%)[a]	123 (49%)	135 (56%)
PGA[b] of cleared or minimal N (%)	10 (4%)	151 (59%)[a]	156 (61%)[a]	146 (58%)	160 (66%)
Number of patients ≤ 100 kg	166	168	164	164	153
PASI 75 response N (%)	6 (4%)	124 (74%)	107 (65%)	130 (79%)	124 (81%)
Number of patients > 100 kg	89	87	92	86	90
PASI 75 response N (%)	2 (2%)	47 (54%)	63 (68%)	48 (56%)	67 (74%)
Psoriasis Study 2					
Number of patients randomised	410	409	411	397	400
PASI 50 response N (%)	41 (10%)	342 (84%)[a]	367 (89%)[a]	369 (93%)	380 (95%)
PASI 75 response N (%)	15 (4%)	273 (67%)[a]	311 (76%)[a]	276 (70%)	314 (79%)
PASI 90 response N (%)	3 (1%)	173 (42%)[a]	209 (51%)[a]	178 (45%)	217 (54%)
PGA[b] of cleared or minimal N (%)	18 (4%)	277 (68%)[a]	300 (73%)[a]	241 (61%)	279 (70%)
Number of patients ≤ 100 kg	290	297	289	287	280
PASI 75 response N (%)	12 (4%)	218 (73%)	225 (78%)	217 (76%)	226 (81%)
Number of patients > 100 kg	120	112	121	110	119
PASI 75 response N (%)	3 (3%)	55 (49%)	86 (71%)	59 (54%)	88 (74%)

[a] $p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with placebo (PBO).
[b] PGA = Physician Global Assessment

Table 3: Summary of clinical response at week 12 in Psoriasis Study 3 (ACCEPT)

	Psoriasis Study 3		
	Etanercept 24 doses (50 mg twice a week)	Ustekinumab 2 doses (week 0 and week 4)	
		45 mg	90 mg
Number of patients randomised	347	209	347
PASI 50 response N (%)	286 (82%)	181 (87%)	320 (92%)[a]
PASI 75 response N (%)	197 (57%)	141 (67%)[b]	256 (74%)[a]
PASI 90 response N (%)	80 (23%)	76 (36%)[a]	155 (45%)[a]
PGA of cleared or minimal N (%)	170 (49%)	136 (65%)[a]	245 (71%)[a]
Number of patients ≤ 100 kg	251	151	244
PASI 75 response N (%)	154 (61%)	109 (72%)	189 (77%)
Number of patients > 100 kg	96	58	103
PASI 75 response N (%)	43 (45%)	32 (55%)	67 (65%)

[a] $p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with etanercept.

[b] $p = 0.012$ for ustekinumab 45 mg in comparison with etanercept.

In Psoriasis Study 1 maintenance of PASI 75 was significantly superior with continuous treatment compared with treatment withdrawal ($p < 0.001$). Similar results were seen with each dose of ustekinumab. At 1 year (week 52), 89% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomised to placebo (treatment withdrawal) ($p < 0.001$). At 18 months (week 76), 84% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomised to placebo (treatment withdrawal). At 3 years (week 148), 82% of patients re-randomised to maintenance treatment were PASI 75 responders. At 5 years (week 244), 80% of patients re-randomised to maintenance treatment were PASI 75 responders.

In patients re-randomised to placebo, and who reinitiated their original ustekinumab treatment regimen after loss of ≥ 50% of PASI improvement 85% regained PASI 75 response within 12 weeks after re-initiating therapy.

In Psoriasis Study 1, at week 2 and week 12, significantly greater improvements from baseline were demonstrated in the DLQI in each ustekinumab treatment group compared with placebo. The improvement was sustained through week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at week 4 and 12, which were sustained through week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the physical and mental component summary scores of the SF-36 and in the Itch Visual Analogue Scale (VAS) were also significant in each ustekinumab treatment group compared with placebo. In Psoriasis Study 2, the Hospital Anxiety and Depression Scale (HADS) and Work Limitations Questionnaire (WLQ) were also significantly improved in each ustekinumab treatment group compared with placebo.

Psoriatic arthritis (PsA) (Adults)

Ustekinumab has been shown to improve signs and symptoms, physical function and health-related quality of life, and reduce the rate of progression of peripheral joint damage in adult patients with active PsA.

The safety and efficacy of ustekinumab was assessed in 927 patients in two randomised, double-blind, placebo-controlled studies in patients with active PsA (≥ 5 swollen joints and ≥ 5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients in both studies had enthesitis and dactylitis at baseline, respectively. Patients were randomised to receive treatment with ustekinumab 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤ 25 mg/week).

In PsA Study 1 (PSUMMIT I) and PsA Study 2 (PSUMMIT II), 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In Study 1 previous treatment with anti-tumour necrosis factor (TNF)α agent was not allowed. In Study 2, the majority of patients (58%, n = 180) had been previously treated with one or more anti-TNFα agent(s), of whom over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance at any time.

Signs and symptoms

Treatment with ustekinumab resulted in significant improvements in the measures of disease activity compared to placebo at week 24. The primary endpoint was the percentage of patients who achieved American College of Rheumatology (ACR) 20 response at week 24. The key efficacy results are shown in Table 4 below.

Table 4: Number of patients who achieved clinical response in Psoriatic arthritis Study 1 (PSUMMIT I) and Study 2 (PSUMMIT II) at week 24

	Psoriatic arthritis Study 1			Psoriatic arthritis Study 2		
	PBO	**45 mg**	**90 mg**	**PBO**	**45 mg**	**90 mg**
Number of patients randomised	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)[a]	101 (50%)[a]	21 (20%)	45 (44%)[a]	46 (44%)[a]
ACR 50 response, N (%)	18 (9%)	51 (25%)[a]	57 (28%)[a]	7 (7%)	18 (17%)[b]	24 (23%)[a]
ACR 70 response, N (%)	5 (2%)	25 (12%)[a]	29 (14%)[a]	3 (3%)	7 (7%)[c]	9 (9%)[c]
Number of patients with ≥ 3% BSA[d]	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)[a]	93 (62%)[a]	4 (5%)	41 (51%)[a]	45 (56%)[a]
PASI 90 response, N (%)	4 (3%)	60 (41%)[a]	65 (44%)[a]	3 (4%)	24 (30%)[a]	36 (44%)[a]
Combined PASI 75 and ACR 20 response, N (%)	8 (5%)	40 (28%)[a]	62 (42%)[a]	2 (3%)	24 (30%)[a]	31 (38%)[a]
Number of patients ≤ 100 kg	154	153	154	74	74	73
ACR 20 response, N (%)	39 (25%)	67 (44%)	78 (51%)	17 (23%)	32 (43%)	34 (47%)
Number of patients with ≥ 3% BSA[d]	105	105	111	54	58	57
PASI 75 response, N (%)	14 (13%)	64 (61%)	73 (66%)	4 (7%)	31 (53%)	32 (56%)
Number of patients > 100 kg	52	52	50	30	29	31
ACR 20 response, N (%)	8 (15%)	20 (38%)	23 (46%)	4 (13%)	13 (45%)	12 (39%)
Number of patients with ≥ 3% BSA[d]	41	40	38	26	22	24
PASI 75 response, N (%)	2 (5%)	19 (48%)	20 (53%)	0	10 (45%)	13 (54%)

[a] $p < 0.001$

[b] $p < 0.05$

[c] p = NS

[d] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

ACR 20, 50 and 70 responses continued to improve or were maintained through week 52 (PsA Study 1 and 2) and week 100 (PsA Study 1). In PsA Study 1, ACR 20 responses at week 100 were achieved by 57% and 64%, for 45 mg and 90 mg, respectively. In PsA Study 2, ACR 20 responses at week 52 were achieved by 47% and 48%, for 45 mg and 90 mg, respectively.

The proportion of patients achieving a modified PsA response criteria (PsARC) response was also significantly greater in the ustekinumab groups compared to placebo at week 24. PsARC responses were maintained through weeks 52 and 100. A higher proportion of patients treated with ustekinumab who had spondylitis with peripheral arthritis as their primary presentation, demonstrated 50 and 70 percent improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared with placebo at week 24.

Responses observed in the ustekinumab treated groups were similar in patients receiving and not receiving concomitant MTX, and were maintained through weeks 52 and 100. Patients previously treated with anti-TNFα agents who received ustekinumab achieved a greater response at week 24 than

patients receiving placebo (ACR 20 response at week 24 for 45 mg and 90 mg was 37% and 34%, respectively, compared with placebo 15%; $p < 0.05$), and responses were maintained through week 52.

For patients with enthesitis and/or dactylitis at baseline, in PsA Study 1 significant improvement in enthesitis and dactylitis score was observed in the ustekinumab groups compared with placebo at week 24. In PsA Study 2 significant improvement in enthesitis score and numerical improvement (not statistically significant) in dactylitis score was observed in the ustekinumab 90 mg group compared with placebo at week 24. Improvements in enthesitis score and dactylitis score were maintained through weeks 52 and 100.

Radiographic Response
Structural damage in both hands and feet was expressed as change in total van der Heijde-Sharp score (vdH-S score), modified for PsA by addition of hand distal interphalangeal joints, compared to baseline. A pre-specified integrated analysis combining data from 927 subjects in both PsA Study 1 and 2 was performed. Ustekinumab demonstrated a statistically significant decrease in the rate of progression of structural damage compared to placebo, as measured by change from baseline to week 24 in the total modified vdH-S score (mean ± SD score was 0.97 ± 3.85 in the placebo group compared with 0.40 ± 2.11 and 0.39 ± 2.40 in the ustekinumab 45 mg ($p < 0.05$) and 90 mg ($p < 0.001$) groups, respectively). This effect was driven by PsA Study 1. The effect is considered demonstrated irrespective of concomitant MTX use, and was maintained through Weeks 52 (integrated analysis) and 100 (PsA Study 1).

Physical function and health-related quality of life
Ustekinumab-treated patients showed significant improvement in physical function as assessed by the Disability Index of the Health Assessment Questionnaire (HAQ-DI) at week 24. The proportion of patients achieving a clinically meaningful ≥ 0.3 improvement in HAQ-DI score from baseline was also significantly greater in the ustekinumab groups when compared with placebo. Improvement in HAQ-DI score from baseline was maintained through Weeks 52 and 100.

There was significant improvement in DLQI scores in the ustekinumab groups as compared with placebo at week 24, which was maintained through weeks 52 and 100. In PsA Study 2 there was a significant improvement in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores in the ustekinumab groups when compared with placebo at week 24. The proportion of patients achieving a clinically significant improvement in fatigue (4 points in FACIT-F) was also significantly greater in the ustekinumab groups compared with placebo. Improvements in FACIT scores were maintained through week 52.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population with juvenile idiopathic arthritis. The pre-filled pen has not been studied in the paediatric psoriasis population and is not recommended for use by paediatric patients.

Crohn's Disease
The safety and efficacy of ustekinumab was assessed in three randomised, double-blind, placebo-controlled, multicentre studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development program consisted of two 8-week intravenous induction studies (UNITI-1 and UNITI-2) followed by a 44 week subcutaneous randomised withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1,409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analysed through week 8 for both studies. Concomitant doses of oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous

administration of either the recommended tiered dose of approximately 6 mg/kg (see section 4.2 of the ustekinumab 130 mg Concentrate for solution for infusion SmPC), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNFα therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 5). Clinical response and remission were significant as early as week 3 in ustekinumab treated patients and continued to improve through week 8. In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended intravenous induction dose.

Table 5: Induction of Clinical Response and Remission in UNITI-1 and UNITI 2

	UNITI-1*		**UNITI-2****	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
Clinical Remission, week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission

70 point response is defined as reduction in CDAI score by at least 70 points

* Anti-TNFα failures

** Conventional therapy failures

[a] $p < 0.001$

[b] $p < 0.01$

The maintenance study (IM-UNITI), evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomised to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 6).

Table 6: Maintenance of Clinical Response and Remission in IM-UNITI (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 131†	**90 mg ustekinumab every 8 weeks N = 128†**	**90 mg ustekinumab every 12 weeks N = 129†**
Clinical Remission	36%	53%[a]	49%[b]

Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002‡	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)
who entered from study CRD3001§	26% (16/61)	41% (23/56)	39% (22/57)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to ustekinumab and were randomised to receive placebo at the start of maintenance therapy.

† Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy.

‡ Patients who failed conventional therapy but not anti-TNFα therapy.

§ Patients who are anti-TNFα refractory/intolerant.

[a] $p < 0.01$

[b] $p < 0.05$

[c] nominally significant ($p < 0.05$)

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to receive ustekinumab every 8 weeks. Loss of response was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomised portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority maintained response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomised to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 567 patients who entered on and were treated with ustekinumab in the study extension, clinical remission and response were generally maintained through week 252 for both patients who failed TNF-therapies and those who failed conventional therapies.

The safety analysis including 457 patients (1289.9 person-years) followed up to 220 weeks showed a safety profile between week 44 and 220 that was comparable with that observed up to week 44.

No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with Crohn's Disease.

Endoscopy

Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean

change = -0.7, p = 0.012).

Fistula Response
In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo. Improvement in health-related quality of life was generally maintained during the extension through week 252.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with both increased clearance and reduced efficacy of ustekinumab, except in patients with Crohn's disease where no reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in Crohn's Disease. The pre-filled pen has not been studied in the paediatric population and is not recommended for use by paediatric patients.

5.2 Pharmacokinetic properties

Absorption
The median time to reach the maximum serum concentration (t_{max}) was 8.5 days after a single 90 mg subcutaneous administration in healthy subjects. The median t_{max} values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to those observed in healthy subjects.

The absolute bioavailability of ustekinumab following a single subcutaneous administration was estimated to be 57.2% in patients with psoriasis.

Distribution
Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with psoriasis, psoriatic arthritis, or Crohn's disease, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies. In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 l/day and 15.7 l, respectively, in patients with psoriasis. The CL/F of ustekinumab was not impacted by gender. Population pharmacokinetic analysis showed that there was a trend towards a higher clearance

of ustekinumab in patients who tested positive for antibodies to ustekinumab.

Dose linearity
The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg or following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

Single dose versus multiple doses
Serum concentration-time profiles of ustekinumab were generally predictable after single or multiple subcutaneous dose administrations. In patients with psoriasis, steady-state serum concentrations of ustekinumab were achieved by week 28 after initial subcutaneous doses at Weeks 0 and 4 followed by doses every 12 weeks. The median steady-state trough concentration ranged from 0.21 μg/mL to 0.26 μg/mL (45 mg) and from 0.47 μg/mL to 0.49 μg/mL (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease, following an intravenous dose of ~6 mg/kg, starting at week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. In patients with Crohn's disease, median steady-state trough concentrations ranged from 1.97 μg/mL to 2.24 μg/mL and from 0.61 μg/mL to 0.76 μg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks respectively. The steady-state trough ustekinumab levels resulting from 90 mg ustekinumab every 8 weeks were associated with higher clinical remission rates as compared to the steady-state trough levels following 90 mg every 12 weeks.

Impact of weight on pharmacokinetics
In a population pharmacokinetic analysis using data from patients with psoriasis, body weight was found to be the most significant covariate affecting the clearance of ustekinumab. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared to patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared to patients with weight ≤ 100 kg. The median trough serum concentrations of ustekinumab in patients with higher weight (> 100 kg) in the 90 mg group were comparable to those in patients with lower weight (≤ 100 kg) in the 45 mg group. Similar results were obtained from a confirmatory population pharmacokinetic analysis using data from patients with psoriatic arthritis.

Dosing frequency adjustment
In patients with Crohn's disease, based on observed data and population PK analyses, randomised subjects who lost response to treatment had lower serum ustekinumab concentrations over time compared with subjects who did not lose response. In Crohn's disease, dose adjustment from 90 mg every 12 weeks to 90 mg every 8 weeks was associated with an increase in trough serum ustekinumab concentrations and an accompanying increase in efficacy.

Special populations
No pharmacokinetic data are available in patients with impaired renal or hepatic function.
No specific studies have been conducted in elderly patients.

The pharmacokinetics of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis.

In patients with Crohn's disease, variability in ustekinumab clearance was affected by body weight, serum albumin level, sex, and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). The impact of these covariates was within ± 20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

In the population pharmacokinetic analysis, there were no indications of an effect of tobacco or alcohol on the pharmacokinetics of ustekinumab.

The bioavailability of ustekinumab following administration by syringe or pre-filled pen was comparable.

The pre-filled pen has not been studied in the paediatric population and is not recommended for use by paediatric patients.

Regulation of CYP450 enzymes
The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5).

A phase 1, open-label, drug interaction study, Study CNTO1275CRD1003, was conducted to evaluate the effect of ustekinumab on cytochrome P450 enzyme activities following induction and maintenance dosing in patients with active Crohn's disease (n=18). No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosing in patients with Crohn's disease (see section 4.5).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated-dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed. No adverse effects on female fertility indices were observed using an analogous antibody to IL-12/23 in mice.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Polysorbate 80 (E 433)
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Pyzchiva 45 mg solution for injection in pre-filled pen
42 months

Pyzchiva 90 mg solution for injection in pre-filled pen
42 months

Individual pre-filled pens may be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the pre-filled pen is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period, the product can be put back in the refrigerator once and kept there until the expiry date. Discard the pre-filled pen if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.
If needed, individual pre-filled pens may be stored at room temperature up to 30°C (see section 6.3).

6.5 Nature and contents of container

Pyzchiva 45 mg solution for injection in pre-filled pen
0.5 mL solution in a type I glass 1 mL syringe with a 29-gauge fixed 1/2 inch stainless steel needle assembled in a pre-filled pen with a passive needle guard.

Pyzchiva 90 mg solution for injection in pre-filled pen
1 mL solution in a type I glass 1 mL syringe with a 29-gauge fixed 1/2 inch stainless steel needle assembled in a pre-filled pen with a passive needle guard.

Pyzchiva is available in a pack of 1 pre-filled pen.

6.6 Special precautions for disposal and other handling

The solution in the Pyzchiva pre-filled pen should not be shaken. The solution should be visually inspected for particulate matter or discolouration prior to subcutaneous administration. The solution is clear, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for proteinaceous solutions. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present. Before administration, Pyzchiva should be allowed to reach room temperature (approximately half an hour). Detailed instructions for use are provided in the package leaflet.

Pyzchiva does not contain preservatives; therefore any unused medicinal product remaining in pre-filled pen should not be used. Pyzchiva is supplied as a sterile, single-use pre-filled pen. The pre-filled pen must never be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.
Olof Palmestraat 10
2616 LR Delft
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Pyzchiva 45 mg solution for injection in pre-filled pen
EU/1/24/1801/004

Pyzchiva 90 mg solution for injection in pre-filled pen
EU/1/24/1801/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 April 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

AGC Biologics A/S
Vandtårnsvej 83B
Søborg, 2860
Denmark

Name and address of the manufacturer responsible for batch release

Samsung Bioepis NL B.V.
Olof Palmestraat 10,
2616 LR Delft
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency:
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (130 mg)

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 130 mg concentrate for solution for infusion
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 130 mg of ustekinumab in 26 mL

3. LIST OF EXCIPIENTS

Excipients: Histidine, Histidine hydrochloride monohydrate, Methionine, Disodium edetate, Sucrose, Polysorbate 80 (E 433), Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for Solution for infusion
130 mg/26 mL
1 vial
3 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.
For single use only.
Intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Write the date removed from the refrigerator

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 35 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.
Olof Palmestraat 10
2616 LR Delft
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1801/003
EU/1/24/1801/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACKS OF 3 VIALS (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 130 mg concentrate for solution for infusion
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 130 mg of ustekinumab in 26 mL

3. LIST OF EXCIPIENTS

Excipients: Histidine, Histidine hydrochloride monohydrate, Methionine, Disodium edetate, Sucrose, Polysorbate 80 (E 433), Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for Solution for infusion
130 mg/26 mL

Multipack: 3 (3 packs of 1) vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.
For single use only.
Intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Write the date removed from the refrigerator

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 35 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.
Olof Palmestraat 10
2616 LR Delft
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1801/006 multipack of 3 vials (3 packs of 1 vial)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 VIAL AS INTERMEDIATE PACK, COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 130 mg concentrate for solution for infusion
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 130 mg of ustekinumab in 26 mL

3. LIST OF EXCIPIENTS

Excipients: Histidine, Histidine hydrochloride monohydrate, Methionine, Disodium edetate, Sucrose, Polysorbate 80 (E 433), Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for Solution for infusion
130 mg/26 mL
1 vial

Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.
For single use only.
Intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Write the date removed from the refrigerator

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 35 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.
Olof Palmestraat 10
2616 LR Delft
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1801/006 multipack of 3 vials (3 packs of 1 vial)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL TEXT (130 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pyzchiva 130 mg concentrate for solution for infusion
ustekinumab

2. METHOD OF ADMINISTRATION

For IV use after dilution.
Do not shake.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

130 mg/26 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 45 mg solution for injection
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 45 mg of ustekinumab in 0.5 mL.

3. LIST OF EXCIPIENTS

Excipients: Histidine, Histidine hydrochloride monohydrate, E 433, Sucrose, Water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
45 mg/0.5 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Write the date removed from the refrigerator

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 35 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.
Olof Palmestraat 10
2616 LR Delft
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1801/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pyzchiva 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pyzchiva 45 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 45 mg solution for injection in pre-filled syringe
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 45 mg of ustekinumab in 0.5 mL.

3. LIST OF EXCIPIENTS

Excipients: Histidine, Histidine hydrochloride monohydrate, Polysorbate 80 (E 433), Sucrose, Water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
45 mg/0.5 mL
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Write the date removed from the refrigerator

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

Can be stored at room temperature (up to 30°C) for a single period up to 35 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.
Olof Palmestraat 10
2616 LR Delft
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1801/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pyzchiva 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pyzchiva 45 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 90 mg solution for injection in pre-filled syringe
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 90 mg of ustekinumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: Histidine, Histidine hydrochloride monohydrate, Polysorbate 80 (E 433), Sucrose, Water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
90 mg/1 mL
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Write the date removed from the refrigerator

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 35 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.
Olof Palmestraat 10
2616 LR Delft
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1801/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pyzchiva 90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pyzchiva 90 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

90 mg/1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 45 mg solution for injection in pre-filled pen
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 45 mg of ustekinumab in 0.5 mL.

3. LIST OF EXCIPIENTS

Excipients: Histidine, Histidine hydrochloride monohydrate, Polysorbate 80 (E 433), Sucrose, Water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen
45 mg/0.5 mL
1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Write the date removed from the refrigerator

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

Can be stored at room temperature (up to 30°C) for a single period up to 35 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.
Olof Palmestraat 10
2616 LR Delft
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1801/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pyzchiva 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pyzchiva 45 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT

Pyzchiva 90 mg solution for injection in pre-filled pen
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 90 mg of ustekinumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: Histidine, Histidine hydrochloride monohydrate, Polysorbate 80 (E 433), Sucrose, Water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen
90 mg/1 mL
1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Write the date removed from the refrigerator

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 35 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Samsung Bioepis NL B.V.
Olof Palmestraat 10
2616 LR Delft
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1801/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pyzchiva 90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pyzchiva 90 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

90 mg/1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Pyzchiva 130 mg concentrate for solution for infusion
ustekinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pyzchiva is and what it is used for
2. What you need to know before you use Pyzchiva
3. How Pyzchiva will be given
4. Possible side effects
5. How to store Pyzchiva
6. Contents of the pack and other information

1. What Pyzchiva is and what it is used for

What Pyzchiva is
Pyzchiva contains the active substance 'ustekinumab', a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Pyzchiva belongs to a group of medicines called 'immunosuppressants'. These medicines work by weakening part of the immune system.

What Pyzchiva is used for
Pyzchiva is used to treat the following inflammatory diseases:
- Moderate to severe Crohn's disease - in adults

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Pyzchiva to reduce the signs and symptoms of your disease.

2. What you need to know before you use Pyzchiva

Do not use Pyzchiva
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Warnings and precautions
Talk to your doctor or pharmacist before using Pyzchiva. Your doctor will check how well you are before treatment. Make sure you tell your doctor about any illness you have before treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Pyzchiva. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Pyzchiva can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Pyzchiva. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Pyzchiva tell your doctor:
- **If you ever had an allergic reaction to ustekinumab.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like ustekinumab weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher
- **If you have or have had a recent infection or if you have any abnormal skin openings (fistulae).**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with ustekinumab has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if ustekinumab may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with ustekinumab. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Ustekinumab is not recommended for use in children under 18 years of age with Crohn's disease because it has not been studied in this age group.

Other medicines, vaccines and Pyzchiva
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Pyzchiva.

- If you received Pyzchiva while pregnant, tell your baby's doctor about your Pyzchiva treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to ustekinumab in the womb. However, there is limited experience with ustekinumab in pregnant women. It is therefore preferable to avoid the use of ustekinumab in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using ustekinumab and for at least 15 weeks after the last ustekinumab treatment.
- Ustekinumab can pass across the placenta to the unborn baby. If you received Pyzchiva during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Pyzchiva during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use ustekinumab - do not do both.

Driving and using machines
Ustekinumab has no or negligible influence on the ability to drive and use machines.

Pyzchiva contains sodium
Pyzchiva contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. However, before Pyzchiva is given to you, it is mixed with a solution that contains sodium. Talk to your doctor if you are on a low salt diet.

Pyzchiva contains polysorbate 80 (E433)
This medicine contains 10.4 mg of polysorbate 80 (E433) in each vial (30 ml) which is equivalent to 10.4 mg/26 ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Pyzchiva will be given

Pyzchiva is intended for use under the guidance and supervision of a doctor experienced in the diagnosis and treatment of Crohn's disease.

Pyzchiva 130 mg concentrate for solution for infusion will be given to you by your doctor, through a drip in the vein of your arm (intravenous infusion) over at least one hour. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Pyzchiva is given
Your doctor will decide how much Pyzchiva you need to receive and for how long.

Adults aged 18 years or older
- The doctor will work out the recommended intravenous infusion dose for you based on your body weight.

Your body weight	Dose
≤ 55 kg	260 mg
> 55 kg to ≤ 85 kg	390 mg
> 85 kg	520 mg

- After the starting intravenous dose, you will have the next dose of 90 mg Pyzchiva by an injection under your skin (subcutaneous injection) 8 weeks later, and then every 12 weeks thereafter.

How Pyzchiva is given
- The first dose of Pyzchiva for treatment of Crohn's disease is given by a doctor as a drip in the vein of an arm (intravenous infusion).

Talk to your doctor if you have any questions about receiving Pyzchiva.

If you forget to use Pyzchiva
If you forget or miss the appointment for receiving the dose, contact your doctor to reschedule your appointment.

If you stop using Pyzchiva
It is not dangerous to stop using ustekinumab. However, if you stop, your symptoms may come back. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking ustekinumab (may affect up to 1 in 1,000 people). Signs include:
    - difficulty breathing or swallowing
    - low blood pressure, which can cause dizziness or light-headedness
    - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

Infusion-related reactions – If you are being treated for Crohn's disease, the first dose of ustekinumab is given through a drip into a vein (intravenous infusion). Some patients have experienced serious allergic reactions during the infusion.

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Pyzchiva again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.
- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)

- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Ustekinumab may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using ustekinumab. These include:
- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea.
- Visual disturbance or vision loss
- Headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use ustekinumab until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching (‘pruritus’)
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people):
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face (‘facial palsy’ or ‘Bell’s palsy’), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pyzchiva

- Pyzchiva 130 mg concentrate for solution for infusion is given in a hospital or clinic and patients should not need to store or handle it.
- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- If needed, individual Pyzchiva vials may also be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the vial is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period, the product can be put back in the refrigerator once and kept there until the expiry date. Discard the vial if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake the Pyzchiva vials. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Pyzchiva looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.
- If the seal is broken.

Pyzchiva is for single use only. Any diluted infusion solution or unused product remaining in the vial and the syringe should be thrown away in accordance with local requirements.

6. Contents of the pack and other information

What Pyzchiva contains
- The active substance is ustekinumab. Each vial contains 130 mg ustekinumab in 26 mL.
- The other ingredients are Histidine, Histidine hydrochloride monohydrate, Methionine, Disodium edetate, Sucrose, Polysorbate 80 (E 433), Water for injections.

What Pyzchiva looks like and contents of the pack
Pyzchiva is a clear, colourless to light yellow concentrate for solution for infusion. It is supplied as a carton pack containing 1 or 3 single-dose, glass 30 mL vials and a multipack comprising 3 cartons, each containing 1 vial. Each vial contains 130 mg ustekinumab in 26 mL of concentrate for solution for infusion.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Traceability:

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Instructions for dilution:

Pyzchiva concentrate for solution for infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of Pyzchiva vials needed based on patient weight (see section 3, Table 1). Each 26 mL vial of Pyzchiva contains 130 mg of ustekinumab.
2. Withdraw and then discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 250 mL infusion bag equal to the volume of Pyzchiva to be added (discard 26 mL sodium chloride for each vial of Pyzchiva needed, for 2 vials- discard 52 mL, for 3 vials discard 78 mL, for 4 vials- discard 104 mL). Alternatively, a 250 mL infusion bag containing 0.45% Sodium Chloride Injection, USP may be used.
3. Withdraw 26 mL of Pyzchiva from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before infusion. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within 72 hours of the dilution in the infusion bag. If necessary, the diluted

infusion solution may be kept at 2 °C to 8 °C for up to 1 month and at room temperature up to 30°C for an additional 72 hours after removal from refrigeration including the infusion period.

6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).
7. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

Storage

If needed, individual Pyzchiva vials may also be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the vial is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period, the product can be put back in the refrigerator once and kept there until the expiry date. Discard the vial if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier.

The diluted infusion solution may be kept at room temperature up to 30°C for up to 72 hours including infusion period. If necessary, the diluted infusion solution may be kept at 2 °C to 8 °C for up to 1 month and at room temperature up to 30°C for an additional 72 hours after removal from refrigeration including the infusion period. Do not freeze.

Package leaflet: Information for the user

Pyzchiva 45 mg solution for injection
ustekinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Pyzchiva to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pyzchiva is and what it is used for
2. What you need to know before you use Pyzchiva
3. How to use Pyzchiva
4. Possible side effects
5. How to store Pyzchiva
6. Contents of the pack and other information

1. What Pyzchiva is and what it is used for

What Pyzchiva is
Pyzchiva contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Pyzchiva belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Pyzchiva is used for
Pyzchiva is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Pyzchiva will reduce the inflammation and other signs of the disease.

Pyzchiva is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Pyzchiva is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Pyzchiva to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Pyzchiva to reduce the signs and symptoms of your disease.

2. What you need to know before you use Pyzchiva

Do not use Pyzchiva
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Warnings and precautions
Talk to your doctor or pharmacist before using Pyzchiva. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Pyzchiva. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Pyzchiva can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Pyzchiva. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Pyzchiva tell your doctor:
- **If you ever had an allergic reaction to ustekinumab**. Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like ustekinumab weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher.
- **If you have or have had a recent infection**.
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with ustekinumab has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if ustekinumab may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with ustekinumab. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Ustekinumab is not recommended for use in children with psoriasis under 6 years of age, or for use in children under 18 years of age with psoriatic arthritis, or Crohn's disease because it has not been studied in this age group.

Other medicines, vaccines and Pyzchiva
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Pyzchiva.
- If you received Pyzchiva while pregnant, tell your baby's doctor about your Pyzchiva treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to ustekinumab in the womb. However, there is limited experience with ustekinumab in pregnant women. It is therefore preferable to avoid the use of ustekinumab in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using ustekinumab and for at least 15 weeks after the last ustekinumab treatment.
- Pyzchiva can pass across the placenta to the unborn baby. If you received Pyzchiva during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Pyzchiva during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use ustekinumab - do not do both.

Driving and using machines
Ustekinumab has no or negligible influence on the ability to drive and use machines.

Pyzchiva contains polysorbate 80 (E433)
This medicine contains 0.02 mg of polysorbate 80 (E433) in each vial (2 ml) which is equivalent to 0.02 mg/0.5 ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Pyzchiva

Pyzchiva is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Pyzchiva is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Pyzchiva is given
Your doctor will decide how much Pyzchiva you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Pyzchiva. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease
- During treatment, the first dose of approximately 6 mg/kg Pyzchiva will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Pyzchiva after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Pyzchiva may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older
Psoriasis
- The doctor will work out the right dose for you, including the amount (volume) of Pyzchiva to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- If you weigh less than 60 kg, the recommended dose is 0.75 mg of Pyzchiva per kg body weight.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Pyzchiva.
- If you weigh more than 100 kg, the recommended dose is 90 mg Pyzchiva.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks.

How Pyzchiva is given
- Pyzchiva is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Pyzchiva.
- However, you and your doctor may decide that you may inject Pyzchiva yourself. In this case you will get training on how to inject Pyzchiva yourself.
- For instructions on how to inject Pyzchiva, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Pyzchiva than you should
If you have used or been given too much Pyzchiva, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Pyzchiva
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Pyzchiva
It is not dangerous to stop using ustekinumab. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking ustekinumab (may affect up to 1 in 1,000 people). Signs include:
    - difficulty breathing or swallowing
    - low blood pressure, which can cause dizziness or light-headedness
    - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Pyzchiva again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.
- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Ustekinumab may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using ustekinumab. These include:
- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use ustekinumab until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people):
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1,000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pyzchiva

- Keep this medicine out of the sight and reach of children.

- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- If needed, individual Pyzchiva vials may also be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the vial is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period, the product can be put back in the refrigerator once and kept there until the expiry date. Discard the vial if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake the Pyzchiva vials. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Pyzchiva looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.
- If the seal is broken.

Pyzchiva is for single use only. Any unused product remaining in the vial and the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pyzchiva contains
- The active substance is ustekinumab. Each vial contains 45 mg ustekinumab in 0.5 mL.
- The other ingredients are Histidine, Histidine hydrochloride monohydrate, Polysorbate 80 (E 433), Sucrose, Water for injections.

What Pyzchiva looks like and contents of the pack
Pyzchiva is a clear, colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 2 mL vial. Each vial contains 45 mg ustekinumab in 0.5 mL of solution for injection.

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Traceability:

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

This leaflet was last revised in MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Pyzchiva yourself. If this happens, you will get training on how to inject Pyzchiva. Talk to your doctor if you have any questions about giving yourself an injection.

- Do not mix Pyzchiva with other liquids for injection
- Do not shake Pyzchiva vials. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

1. Check the number of vials and prepare the materials:

Take the vial(s) out of the refrigerator. Let the vial stand for about half an hour. This will let the liquid come to a comfortable temperature for injection (room temperature).

Check the vial(s) to make sure:

- the number of vials and strength is correct
    - If your dose is 45 mg or less, you will get one 45 mg vial of Pyzchiva
    - If your dose is 90 mg you will get two 45 mg vials of Pyzchiva and you will need to give yourself two injections. Choose two different sites for these injections (for example one injection in the right thigh and the other injection in the left thigh), and give the injections one right after the other. Use a new needle and syringe for each injection.
- it is the right medicine
- it has not passed its expiry date
- the vial is not damaged and the seal is not broken
- the solution in the vial is clear and colourless to light yellow
- the solution is not discoloured or cloudy and does not contain any foreign particles
- the solution is not frozen.

Children weighing less than 60 kg need a dose lower than 45 mg. Make sure you know the proper amount (volume) to remove from the vial and type of syringe needed for dosing. If you don't know the amount or type of syringe needed, contact your healthcare provider for further instruction.

Get everything together that you need and lay out on a clean surface. This includes a syringe, needle, antiseptic wipes, a cotton ball or gauze, and a sharps container (see Figure 1).

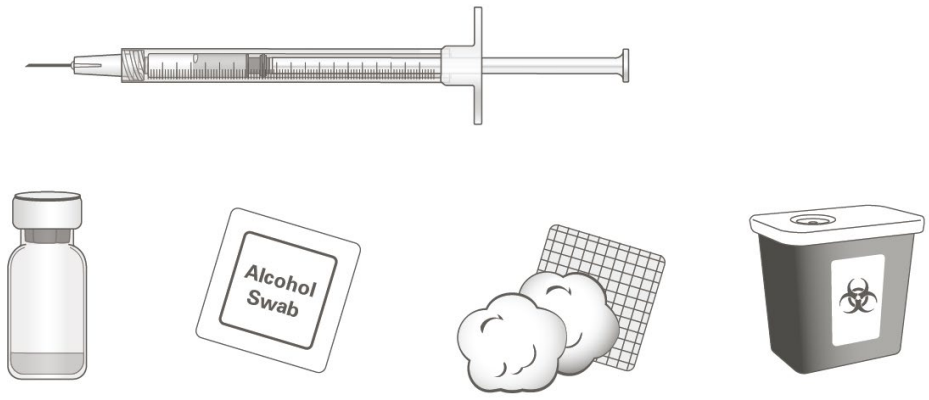


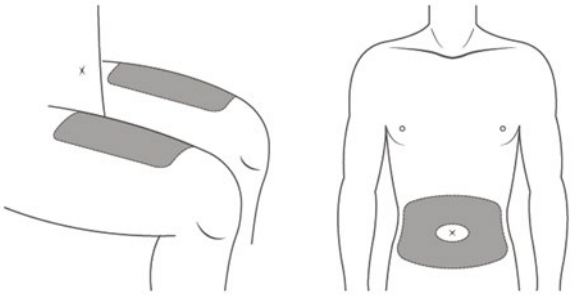
Figure 1

2. Choose and prepare the injection site:

Choose an injection site (see Figure 2)

- Pyzchiva is given by injection under the skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis

- If someone will assist in giving you the injection, then he or she may also choose the upper arms as an injection site



*Areas in gray are recommended injection sites.

Figure 2

Prepare the injection site
- Wash your hands very well with soap and warm water
- Wipe the injection site on the skin with an antiseptic wipe
- Do not touch this area again before giving the injection

3. Prepare the dose:
- Take the cap off the top of the vial (see Figure 3)

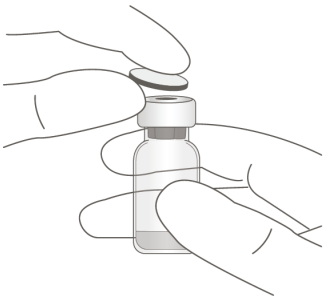


Figure 3

- Do not remove the stopper
- Clean the stopper with an antiseptic swab
- Put the vial on a flat surface.
- Pick up the syringe and remove the needle cover
- Do not touch the needle or let the needle touch anything
- Push the needle through the rubber stopper
- Turn the vial and the syringe upside down
- Pull on the syringe plunger to fill the syringe with the amount of liquid prescribed by your doctor
- It is important that the needle is always in the liquid. This stops air bubbles forming in the syringe (see Figure 4)

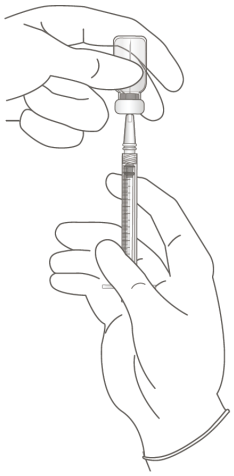


Figure 4

- Remove the needle from the vial
- Hold the syringe with the needle pointing up to see if it has any air bubbles inside
- If there are air bubbles, tap the side gently until the air bubbles go to the top of the syringe (see Figure 5)

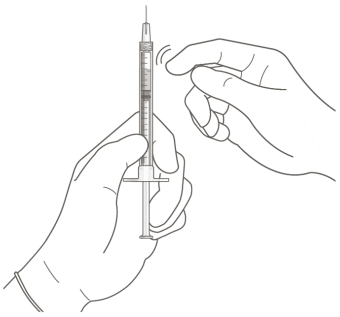


Figure 5

- Then press the plunger until all of the air (but none of the liquid) has been removed
- Do not lay the syringe down or allow the needle to touch anything.

4. Inject the dose:

- Gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Push the needle into the pinched skin
- Push the plunger with your thumb as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skin gently pinched
- When the plunger is pushed as far as it will go, take out the needle and let go of the skin

5. After the injection:

- Press an antiseptic wipe over the injection site for a few seconds after the injection
- There may be a small amount of blood or liquid at the injection site. This is normal
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds
- Do not rub the skin at the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

6. Disposal:

- Used syringes and needles should be placed in a puncture-resistant container, like a sharps container. Never re-use needles and syringes, for your safety and health, and for the safety of others. Dispose of your sharps container according to your local regulations
- Empty vials, antiseptic wipes, and other supplies can be disposed of in your garbage.

Package leaflet: Information for the user

Pyzchiva 45 mg solution for injection in pre-filled syringe
ustekinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Pyzchiva to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pyzchiva is and what it is used for
2. What you need to know before you use Pyzchiva
3. How to use Pyzchiva
4. Possible side effects
5. How to store Pyzchiva
6. Contents of the pack and other information

1. What Pyzchiva is and what it is used for

What Pyzchiva is
Pyzchiva contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Pyzchiva belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Pyzchiva is used for
Pyzchiva is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Pyzchiva will reduce the inflammation and other signs of the disease.

Pyzchiva is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Pyzchiva is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments

did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Pyzchiva to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Pyzchiva to reduce the signs and symptoms of your disease.

2. What you need to know before you use Pyzchiva

Do not use Pyzchiva
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Warnings and precautions
Talk to your doctor or pharmacist before using Pyzchiva. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Pyzchiva. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Pyzchiva can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Pyzchiva. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Pyzchiva tell your doctor:
- **If you ever had an allergic reaction to ustekinumab.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like ustekinumab weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with ustekinumab has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies –** it is not known if ustekinumab may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with ustekinumab. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Ustekinumab is not recommended for use in children with psoriasis under 6 years of age, or for use in children under 18 years of age with psoriatic arthritis, or Crohn's disease because it has not been studied in this age group.

Other medicines, vaccines and Pyzchiva
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Pyzchiva.
- If you received Pyzchiva while pregnant, tell your baby's doctor about your Pyzchiva treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to ustekinumab in the womb. However, there is limited experience with ustekinumab in pregnant women. It is therefore preferable to avoid the use of ustekinumab in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using ustekinumab and for at least 15 weeks after the last ustekinumab treatment.
- Pyzchiva can pass across the placenta to the unborn baby. If you received Pyzchiva during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Pyzchiva during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use ustekinumab - do not do both.

Driving and using machines
Ustekinumab has no or negligible influence on the ability to drive and use machines.

Pyzchiva contains polysorbate 80 (E433)
This medicine contains 0.02 mg of polysorbate 80 (E433) in each pre-filled syringe (1 ml) which is equivalent to 0.02 mg/0.5 ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Pyzchiva

Pyzchiva is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Pyzchiva is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Pyzchiva is given
Your doctor will decide how much Pyzchiva you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Pyzchiva. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease
- During treatment, the first dose of approximately 6 mg/kg Pyzchiva will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Pyzchiva after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Pyzchiva may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older
Psoriasis
- The doctor will work out the right dose for you, including the amount (volume) of Pyzchiva to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- A 45 mg vial is available for children who need to receive less than the full 45 mg dose.
- If you weigh less than 60 kg, the recommended dose is 0.75 mg of Pyzchiva per kg body weight.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Pyzchiva.
- If you weigh more than 100 kg, the recommended dose is 90 mg Pyzchiva
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks

How Pyzchiva is given
- Pyzchiva is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Pyzchiva.
- However, you and your doctor may decide that you may inject Pyzchiva yourself. In this case you will get training on how to inject Pyzchiva yourself.
- For instructions on how to inject Pyzchiva, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Pyzchiva than you should
If you have used or been given too much Pyzchiva, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Pyzchiva
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Pyzchiva
It is not dangerous to stop using ustekinumab. However, if you stop, your symptoms may come back. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking ustekinumab (may affect up to 1 in 1,000 people). Signs include:
    - difficulty breathing or swallowing
    - low blood pressure, which can cause dizziness or light-headedness
    - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Pyzchiva again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Ustekinumab may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using ustekinumab. These include:
- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea.
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use ustekinumab until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people):
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pyzchiva

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the pre-filled syringe in the outer carton in order to protect from light.
- If needed, individual Pyzchiva pre-filled syringes may also be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the pre-filled syringe is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period, the product can be put back in the refrigerator once and kept there until the expiry date. Discard the syringe if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake Pyzchiva pre-filled syringes. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Pyzchiva looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Pyzchiva is for single use only. Any unused product remaining in the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pyzchiva contains
- The active substance is ustekinumab. Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL.
- The other ingredients are Histidine, Histidine hydrochloride monohydrate, Polysorbate 80 (E 433), Sucrose, Water for injections.

What Pyzchiva looks like and contents of the pack
Pyzchiva is a clear, colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled syringe. Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL of solution for injection.

Marketing Authorisation Holder and Manufacturer
Samsung Bioepis NL. B.V.
Olof Palmestraat 10
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The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Traceability:

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

This leaflet was last revised in MM/YYYY

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Pyzchiva yourself. If this happens, you will get training on how to inject Pyzchiva. Talk to your doctor if you have any questions about giving yourself an injection.

- Do not mix Pyzchiva with other liquids for injection
- Do not shake Pyzchiva pre-filled syringes. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

Figure 1 shows what the pre-filled syringe looks like.

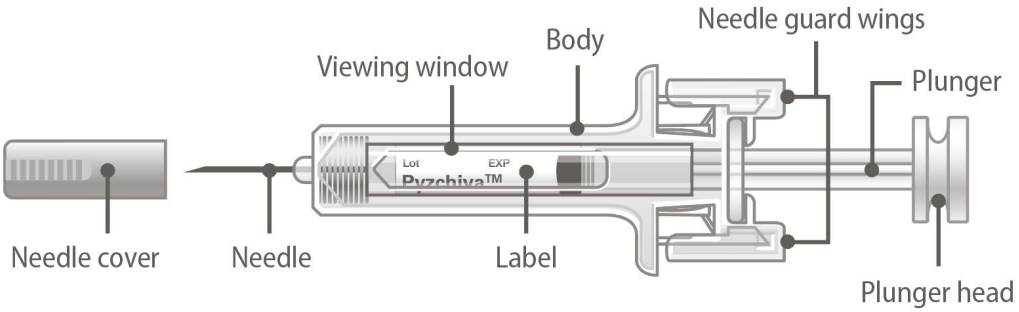


Figure 1

1. Check the number of pre-filled syringes and prepare the materials:

Preparing for use of the pre-filled syringe

- Take the pre-filled syringe(s) out of the refrigerator. Let the pre-filled syringe stand outside the box for about half an hour. This will let the liquid come to a comfortable temperature for injection (room temperature). Do not warm the pre-filled syringe in any other way (for example, do not warm it in a microwave or in hot water.). Do not remove the syringe's needle cover while allowing it to reach room temperature
- Hold the pre-filled syringe by the body of the syringe with the covered needle pointing upward
- Do not hold by the plunger head, plunger, needle guard wings, or needle cover
- Do not pull back on the plunger at any time
- Do not remove the needle cover from the pre-filled syringe until instructed to do so

Check the pre-filled syringe(s) to make sure

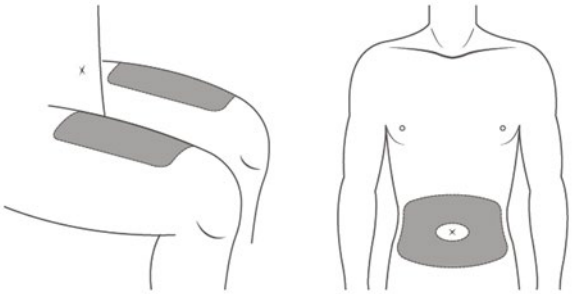
- the number of pre-filled syringes and strength is correct
    - If your dose is 45 mg you will get one 45 mg pre-filled syringe of Pyzchiva
    - If your dose is 90 mg you will get two 45 mg pre-filled syringes of Pyzchiva and you will need to give yourself two injections. Choose two different sites for these injections (e.g. one injection in the right thigh and the other injection in the left thigh), and give the injections one right after the other.
- it is the right medicine
- it has not passed its expiry date
- the pre-filled syringe is not damaged
- the solution in the pre-filled syringe is clear and colourless to light yellow
- the solution in the pre-filled syringe is not discoloured or cloudy and does not contain any foreign particles
- the solution in the pre-filled syringe is not frozen.

Get everything together that you need and lay out on a clean surface. This includes antiseptic wipes, a cotton ball or gauze, and a sharps container.

2. Choose and prepare the injection site:

Choose an injection site (see Figure 2)

- Pyzchiva is given by injection under the skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis
- If someone will assist in giving you the injection, then he or she may also choose the upper arms as an injection site



*Areas in gray are recommended injection sites.

Figure 2

Prepare the injection site

- Wash your hands very well with soap and warm water
- Wipe the injection site on the skin with an antiseptic wipe
- **Do not** touch this area again before giving the injection
- **Do not** fan or blow on the clean area

3. Remove the needle cover (see Figure 3):

- The needle cover should **not** be removed until you are ready to inject the dose
- Pick up the pre-filled syringe, hold the body of the syringe with one hand
- Pull the needle cover straight off and throw it away. Do not touch the plunger while you do this

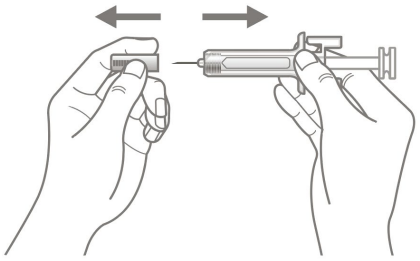


Figure 3

- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the end of the needle. These are both normal and do not need to be removed
- Do not touch the needle or allow it to touch any surface
- Do not use the pre-filled syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist
- Inject the dose promptly after removing the needle cover.

4. Inject the dose:

- Hold the pre-filled syringe with one hand between the middle and index fingers and place the thumb on top of the plunger head and use the other hand to gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Do not pull back on the plunger at any time
- In a single and swift motion, insert the needle through the skin as far as it will go (see Figure 4)



Figure 4

- Inject all of the medication by pushing in the plunger until the plunger head is completely between the needle guard wings (see Figure 5)

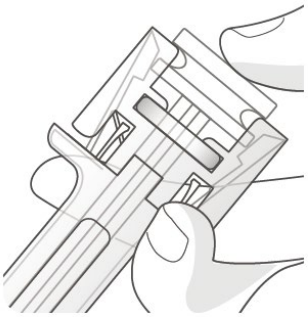


Figure 5

- When the plunger is pushed as far as it will go, continue to keep the pressure on the plunger head, take out the needle and let go of the skin (see Figure 6)

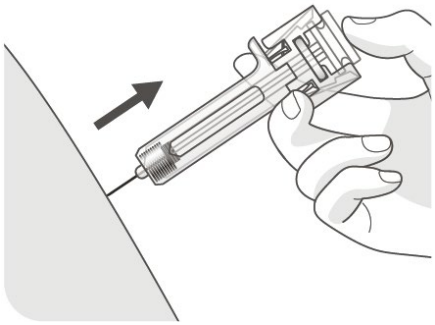


Figure 6

- Slowly take your thumb off the plunger head to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by Figure 7:

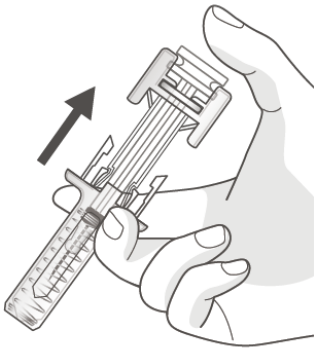


Figure 7

5. After the injection:

- Press an antiseptic wipe over the injection site for a few seconds after the injection.
- There may be a small amount of blood or liquid at the injection site. This is normal.
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds.
- Do not rub the skin at the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

6. Disposal:

- Used syringes should be placed in a puncture-resistant container, like a sharps container (see Figure 8). Never re-use a syringe, for your safety and health and for the safety of others. Dispose of your sharps container according to your local regulations
- Antiseptic wipes and other supplies can be disposed of in your garbage.



Figure 8

Package leaflet: Information for the user

Pyzchiva 90 mg solution for injection in pre-filled syringe
ustekinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Pyzchiva to a child, please read this information carefully.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pyzchiva is and what it is used for
2. What you need to know before you use Pyzchiva
3. How to use Pyzchiva
4. Possible side effects
5. How to store Pyzchiva
6. Contents of the pack and other information

1. What Pyzchiva is and what it is used for

What Pyzchiva is
Pyzchiva contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Pyzchiva belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Pyzchiva is used for
Pyzchiva is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Pyzchiva will reduce the inflammation and other signs of the disease.

Pyzchiva is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Pyzchiva is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Pyzchiva to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Pyzchiva to reduce the signs and symptoms of your disease.

2. What you need to know before you use Pyzchiva

Do not use Pyzchiva
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Warnings and precautions
Talk to your doctor or pharmacist before using Pyzchiva. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Pyzchiva. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Pyzchiva can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Pyzchiva. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Pyzchiva tell your doctor:
- **If you ever had an allergic reaction to ustekinumab.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like ustekinumab weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis –** such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with ustekinumab has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if ustekinumab may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with ustekinumab. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Ustekinumab is not recommended for use in children with psoriasis under 6 years of age, or for use in children under 18 years of age with psoriatic arthritis, or Crohn's disease because it has not been studied in this age group.

Other medicines, vaccines and Pyzchiva
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Pyzchiva.
- If you received Pyzchiva while pregnant, tell your baby's doctor about your Pyzchiva treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to ustekinumab in the womb. However, there is limited experience with ustekinumab in pregnant women. It is therefore preferable to avoid the use of ustekinumab in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using ustekinumab and for at least 15 weeks after the last ustekinumab treatment.
- Pyzchiva can pass across the placenta to the unborn baby. If you received Pyzchiva during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Pyzchiva during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use ustekinumab -do not do both.

Driving and using machines
Ustekinumab has no or negligible influence on the ability to drive and use machines.

Pyzchiva contains polysorbate 80 (E433)
This medicine contains 0.04 mg of polysorbate 80 (E433) in each pre-filled syringe (1 ml) which is equivalent to 0.04 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Pyzchiva

Pyzchiva is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Pyzchiva is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Pyzchiva is given
Your doctor will decide how much Pyzchiva you need to use and for how long.

Adults aged 18 years or older Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Pyzchiva. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease
- During treatment, the first dose of approximately 6 mg/kg Pyzchiva will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Pyzchiva after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Pyzchiva may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older
Psoriasis
- The doctor will work out the right dose for you, including the amount (volume) of Pyzchiva to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- A 45 mg vial is available for children who need to receive less than the full 45 mg dose.
- If you weigh less than 60 kg, the recommended dose is 0.75 mg of Pyzchiva per kg body weight.

- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Pyzchiva.
- If you weigh more than 100 kg, the recommended dose is 90 mg Pyzchiva.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks

How Pyzchiva is given
- Pyzchiva is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Pyzchiva.
- However, you and your doctor may decide that you may inject Pyzchiva yourself. In this case you will get training on how to inject Pyzchiva yourself.
- For instructions on how to inject Pyzchiva, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Pyzchiva than you should
If you have used or been given too much Pyzchiva, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Pyzchiva
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Pyzchiva
It is not dangerous to stop using ustekinumab. However, if you stop, your symptoms may come back. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking ustekinumab (may affect up to 1 in 1,000 people). Signs include:
    - difficulty breathing or swallowing
    - low blood pressure, which can cause dizziness or light-headedness
    - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Pyzchiva again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.
- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Ustekinumab may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.
You must look out for signs of infection while you are using ustekinumab. These include:
- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea.
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use ustekinumab until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people):
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pyzchiva

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the pre-filled syringe in the outer carton in order to protect from light.
- If needed, individual Pyzchiva pre-filled syringes may also be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the pre-filled syringe is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period, the product can be put back in the refrigerator once and kept there until the expiry date. Discard the syringe if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake Pyzchiva pre-filled syringes. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Pyzchiva looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Pyzchiva is for single use only. Any unused product remaining in the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pyzchiva contains
- The active substance is ustekinumab. Each pre-filled syringe contains 90 mg ustekinumab in 1 mL.
- The other ingredients are Histidine, Histidine hydrochloride monohydrate, Polysorbate 80 (E 433), Sucrose, Water for injections.

What Pyzchiva looks like and contents of the pack
Pyzchiva is a clear, colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled syringe. Each pre-filled syringe contains 90 mg ustekinumab in 1 mL of solution for injection.

Marketing Authorisation Holder and Manufacturer
Samsung Bioepis NL. B.V.
Olof Palmestraat 10
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The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Traceability:

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

This leaflet was last revised in MM/YYYY
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Pyzchiva yourself. If this happens, you will get training on how to inject Pyzchiva. Talk to your doctor if you have any questions about giving yourself an injection.

- Do not mix Pyzchiva with other liquids for injection
- Do not shake Pyzchiva pre-filled syringes. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

Figure 1 shows what the pre-filled syringe looks like.

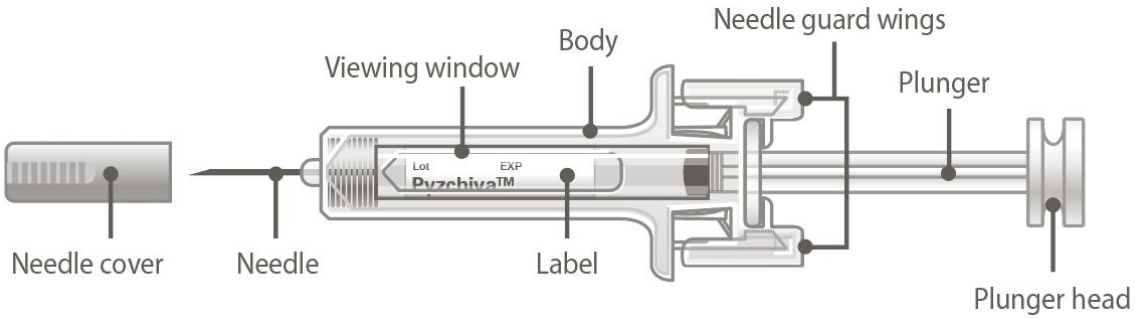


Figure 1

1. Check the number of pre-filled syringes and prepare the materials:

Preparing for use of the pre-filled syringe

- Take the pre-filled syringe(s) out of the refrigerator. Let the pre-filled syringe stand outside the box for about half an hour. This will let the liquid come to a comfortable temperature for injection (room temperature). Do not warm the pre-filled syringe in any other way (for example, do not warm it in a microwave or in hot water.). Do not remove the syringe's needle cover while allowing it to reach room temperature
- Hold the pre-filled syringe by the body of the syringe with the covered needle pointing upward
- Do not hold by the plunger head, plunger, needle guard wings, or needle cover
- Do not pull back on the plunger at any time
- Do not remove the needle cover from the pre-filled syringe until instructed to do so.

Check the pre-filled syringe(s) to make sure

- the number of pre-filled syringes and strength is correct
    - If your dose is 90 mg you will get one 90 mg pre-filled syringe of Pyzchiva.
- it is the right medicine
- it has not passed its expiry date
- the pre-filled syringe is not damaged
- the solution in the pre-filled syringe is clear and colourless to light yellow
- the solution in the pre-filled syringe is not discoloured or cloudy and does not contain any foreign particles
- the solution in the pre-filled syringe is not frozen.

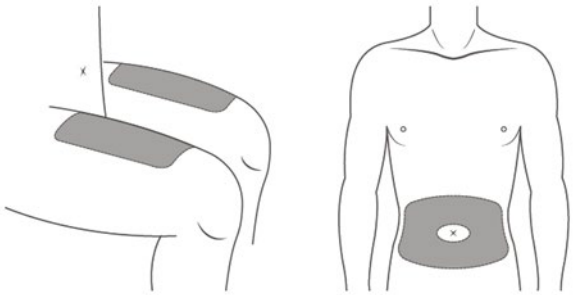
Get everything together that you need and lay out on a clean surface. This includes antiseptic wipes, a cotton ball or gauze, and a sharps container.

2. Choose and prepare the injection site:

Choose an injection site (see Figure 2)

- Pyzchiva is given by injection under the skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis

- If someone will assist in giving you the injection, then he or she may also choose the upper arms as an injection site.



*Areas in gray are recommended injection sites.

Figure 2

Prepare the injection site

- Wash your hands very well with soap and warm water
- Wipe the injection site on the skin with an antiseptic wipe
- **Do not** touch this area again before giving the injection.
- **Do not** fan or blow on the clean area

3. Remove the needle cover (see Figure 3):

- The needle cover should **not** be removed until you are ready to inject the dose
- Pick up the pre-filled syringe, hold the body of the syringe with one hand
- Pull the needle cover straight off and throw it away. Do not touch the plunger while you do this

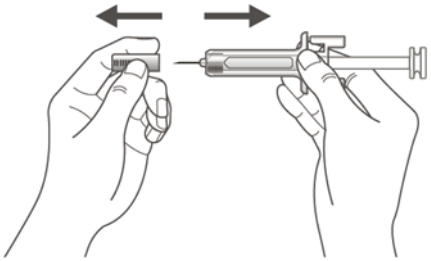


Figure 3

- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the end of the needle. These are both normal and do not need to be removed
- Do not touch the needle or allow it to touch any surface
- Do not use the pre-filled syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist
- Inject the dose promptly after removing the needle cover.

4. Inject the dose:

- Hold the pre-filled syringe with one hand between the middle and index fingers and place the thumb on top of the plunger head and use the other hand to gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Do not pull back on the plunger at any time
- In a single and swift motion, insert the needle through the skin as far as it will go (see Figure 4)



Figure 4

- Inject all of the medication by pushing in the plunger until the plunger head is completely between the needle guard wings (see Figure 5)

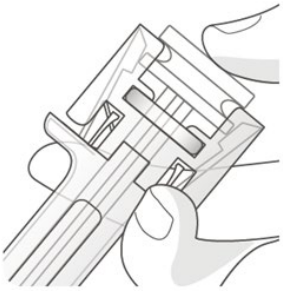


Figure 5

- When the plunger is pushed as far as it will go, continue to keep the pressure on the plunger head, take out the needle and let go of the skin (see Figure 6)

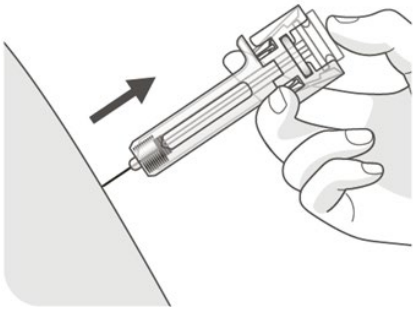


Figure 6

- Slowly take your thumb off the plunger head to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by Figure 7:

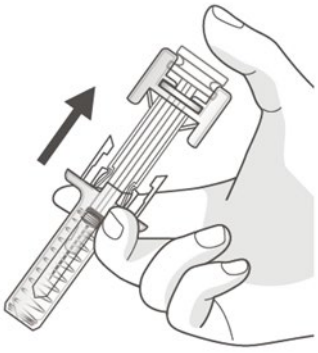


Figure 7

5. After the injection:

- Press an antiseptic wipe over the injection site for a few seconds after the injection.
- There may be a small amount of blood or liquid at the injection site. This is normal.
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds.
- Do not rub the skin at the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

6. Disposal:

- Used syringes should be placed in a puncture-resistant container, like a sharps container (see Figure 8). Never re-use a syringe, for your safety and health and for the safety of others. Dispose of your sharps container according to your local regulations
- Antiseptic wipes and other supplies can be disposed of in your garbage.



Figure 8

Package leaflet: Information for the user

Pyzchiva 45 mg solution for injection in pre-filled pen
ustekinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pyzchiva is and what it is used for
2. What you need to know before you use Pyzchiva
3. How to use Pyzchiva
4. Possible side effects
5. How to store Pyzchiva
6. Contents of the pack and other information

1. What Pyzchiva is and what it is used for

What Pyzchiva is
Pyzchiva contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Pyzchiva belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Pyzchiva is used for
Pyzchiva administered using the pre-filled pen is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Pyzchiva will reduce the inflammation and other signs of the disease.

Pyzchiva administered using the pre-filled pen is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well

enough to these medicines, you may be given Pyzchiva to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Pyzchiva to reduce the signs and symptoms of your disease.

2. What you need to know before you use Pyzchiva

Do not use Pyzchiva
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Warnings and precautions
Talk to your doctor or pharmacist before using Pyzchiva. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Pyzchiva. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Pyzchiva can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Pyzchiva. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Pyzchiva tell your doctor:
- **If you ever had an allergic reaction to ustekinumab.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like ustekinumab weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with ustekinumab has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies –** it is not known if ustekinumab may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised,

scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with ustekinumab. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Ustekinumab pre-filled pen is not recommended for use in children and adolescents under 18 years of age with psoriasis because it has not been studied in this age group. The pre-filled syringe or vial should be used instead for children 6 years of age and older and adolescents with psoriasis.

Ustekinumab is not recommended for use in children and adolescents under 18 years of age with psoriatic arthritis, Crohn's disease because it has not been studied in this age group.

Other medicines, vaccines and Pyzchiva
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Pyzchiva.
- If you received Pyzchiva while pregnant, tell your baby's doctor about your Pyzchiva treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to ustekinumab in the womb. However, there is limited experience with ustekinumab in pregnant women. It is therefore preferable to avoid the use of ustekinumab in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using ustekinumab and for at least 15 weeks after the last ustekinumab treatment.
- Pyzchiva can pass across the placenta to the unborn baby. If you received Pyzchiva during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Pyzchiva during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use ustekinumab - do not do both.

Driving and using machines
Ustekinumab has no or negligible influence on the ability to drive and use machines.

Pyzchiva contains polysorbate 80 (E433)
This medicine contains 0.02 mg of polysorbate 80 (E433) in each pre-filled pen (1 ml) which is equivalent to 0.02 mg/0.5 ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Pyzchiva

Pyzchiva is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Pyzchiva is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Pyzchiva is given
Your doctor will decide how much Pyzchiva you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Pyzchiva. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease
- During treatment, the first dose of approximately 6 mg/kg Pyzchiva will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Pyzchiva after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Pyzchiva may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

How Pyzchiva is given
- Pyzchiva is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Pyzchiva.
- However, you and your doctor may decide that you may inject Pyzchiva yourself. In this case you will get training on how to inject Pyzchiva yourself.
- For instructions on how to inject Pyzchiva, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Pyzchiva than you should
If you have used or been given too much Pyzchiva, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Pyzchiva
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Pyzchiva
It is not dangerous to stop using ustekinumab. However, if you stop, your symptoms may come back. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking ustekinumab (may affect up to 1 in 1,000 people). Signs include:
    - difficulty breathing or swallowing
    - low blood pressure, which can cause dizziness or light-headedness
    - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Pyzchiva again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Ustekinumab may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using ustekinumab. These include:
- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea.
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use ustekinumab until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people):
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pyzchiva

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the pre-filled pen in the outer carton in order to protect from light.

- If needed, individual Pyzchiva pre-filled pens may also be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the pre-filled pen is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period, the product can be put back in the refrigerator once and kept there until the expiry date. Discard the pen if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake Pyzchiva pre-filled pens. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Pyzchiva looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Pyzchiva is for single use only. Any unused product remaining in the pre-filled pen should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pyzchiva contains
- The active substance is ustekinumab. Each pre-filled pen contains 45 mg ustekinumab in 0.5 mL.
- The other ingredients are Histidine, Histidine hydrochloride monohydrate, Polysorbate 80, Sucrose, Water for injections.

What Pyzchiva looks like and contents of the pack
Pyzchiva is a clear, colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled pen. Each pre-filled pen contains 45 mg ustekinumab in 0.5 mL of solution for injection.

Marketing Authorisation Holder and Manufacturer
Samsung Bioepis NL. B.V.
Olof Palmestraat 10
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Traceability:

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

This leaflet was last revised in MM/YYYY

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

INSTRUCTIONS FOR USE
Pyzchiva
(ustekinumab)
injection, for subcutaneous use
Pre-filled pen

Instructions for injecting Pyzchiva using a pre-filled pen.

Read this Instructions for Use before you start using Pyzchiva. Your healthcare professional should show you how to prepare and give your injection of Pyzchiva the right way.

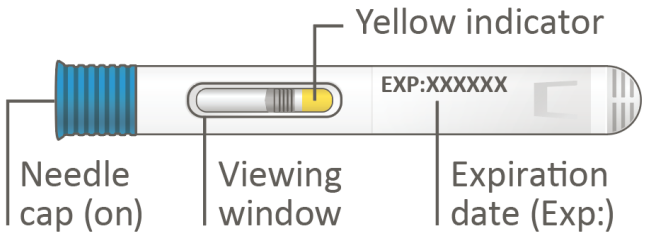
If you cannot give yourself the injection:

- ask your healthcare professional to help you, or
- ask someone who has been trained by a healthcare professional to give your injections.

Do not try to inject Pyzchiva yourself until you have been shown how to inject Pyzchiva by your health professional.

Need help?
Call your doctor to talk about any questions you may have. For additional assistance or to share your feedback refer to the Package Leaflet for your local representative contact information.

Guide to parts:
Before use



After use

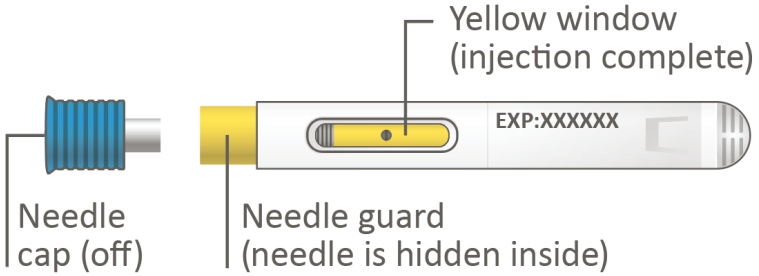


Figure A

Important information You Need to Know Before Injecting Pyzchiva

- **For subcutaneous injection only** (inject directly under the skin)
- **Do not** remove the needle cap before you are ready to inject.
- **Do not shake the pre-filled pen at any time.** Shaking your pre-filled pen may damage your Pyzchiva medicine.

Storing Pyzchiva pre-filled pen:
- Store Pyzchiva in the refrigerator between 2°C to 8°C.
- Store Pyzchiva in the original carton to protect from light or physical damage.

- If needed, individual Pyzchiva pre-filled pens may also be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the pre-filled pen is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period, the product can be put back in the refrigerator once and kept there until the expiry date. Discard the pen if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier. **Do not** store Pyzchiva in extreme heat or cold.
- **Do not** freeze.

Preparing to Inject Pyzchiva pre-filled pen

Step 1 Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.
- If your dose is 45 mg, you will receive one 45 mg pre-filled pen.
- If your dose is 90 mg, you will receive either one 90 mg pre-filled pen or two 45 mg pre-filled pens. If you receive two 45 mg pre-filled pens for a 90 mg dose, you will need to give yourself two injections, one right after the other.

Step 2 Gather supplies
- **Step 2.1:** Choose a well-lit, clean, flat work surface.
- **Step 2.2:** Gather the supplies you will need to prepare and to give your injection **(Figure B)**.
- You will need the following supplies.
  - Included in the carton:

-Pyzchiva pre-filled pen
  - Not included in the carton:
    - Alcohol swab
    - Cotton balls or gauze pads
    - Adhesive bandage
    - Sharps disposal container **(See "Disposing of Pyzchiva pre-filled pen.")**

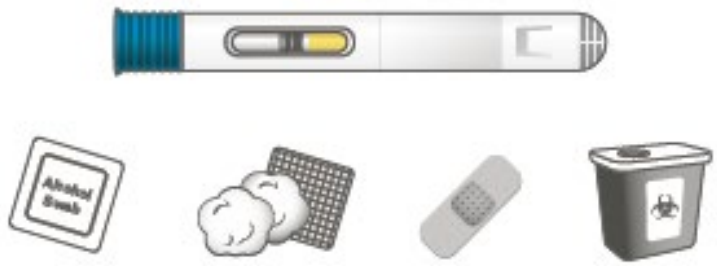


Figure B

Step 3 Inspect the pre-filled pen (Figure C)
- **Step 3.1:** Check the expiration date on the pre-filled pen or carton.
- **Step 3.2:** Check the medicine in the window for any particles or discoloration. The medicine should look clear and colorless to light yellow with few white particles.
- **Step 3.3:** Make sure the pen is not damaged.
- **Do not** use Pyzchiva if:
  - the expiration date has passed or if the pre-filled pen has been kept at room temperature up to 30ºC for longer than a maximum single period of 35 days or if the pre-filled pen has been stored above 30ºC.
  - it is frozen, discolored, cloudy or has large particles.
  - it is damaged.
  - it is dropped and appears cracked or broken.
- It is normal to see 1 or more bubbles in the window.

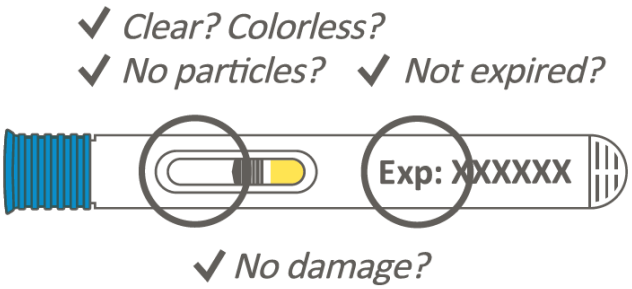


Figure C

Step 4 Allow the medicine to reach room temperature



- For a more comfortable injection, leave Pyzchiva pre-filled pen at room temperature for about 30 minutes before injecting, after removing it from the refrigerator.
- **Do not** warm the pre-filled pen in any other way (for example, do not warm it in a microwave or in hot water).

Step 5 Wash your hands

- Wash your hands well with soap and warm water **(Figure D).**

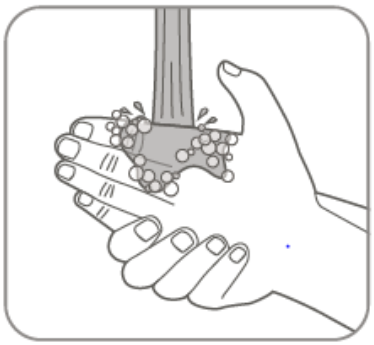


Figure D

Step 6 Choose the injection site

- Choose an injection site around your upper legs (thighs) or lower stomach area (lower abdomen) except for a 5-centimetre area right around your navel (belly-button). If a caregiver is giving you the injection, the outer area of the upper arms may also be used. **(Figure E)**
- **Use a different injection site for each injection.**
- **Do not** give an injection in an area of the skin that is tender, bruised, red, or hard or shows signs of psoriasis.

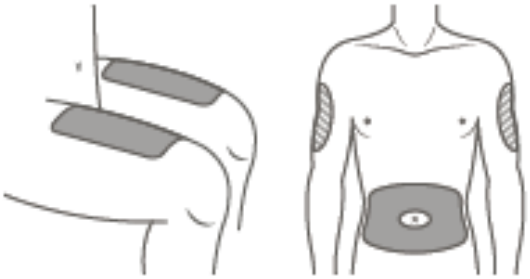


Figure E

Step 7 Clean the skin at the injection site

- Clean the skin with a new alcohol swab where you plan to give your injection. **(Figure F)**
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.

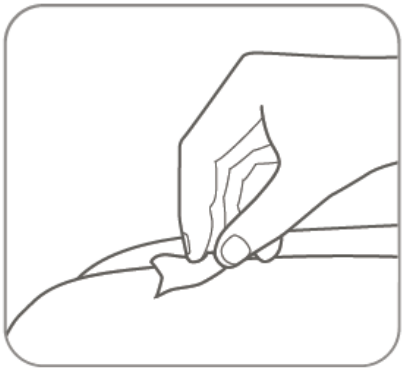


Figure F

Injecting Pyzchiva pre-filled pen

Step 8 Pull the needle cap straight off when you are ready to inject your Pyzchiva (Figure G).

- Throw away the needle cap.
- It is normal to see a few drops of liquid come out of the needle.
- **Do not** twist or bend the needle cap while removing it, as this may damage the needle.
- **Do not** use the pre-filled pen if it is dropped after removing the needle cap. Call your health professional for instructions.

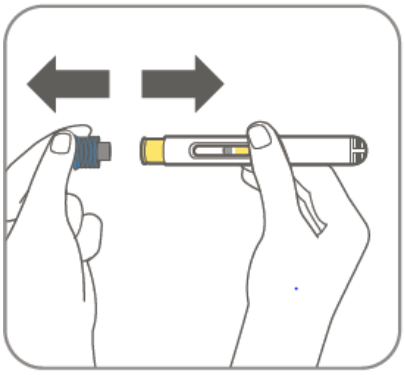


Figure G

Step 9 Position the pre-filled pen straight on your skin at 90 degrees (Figure H).

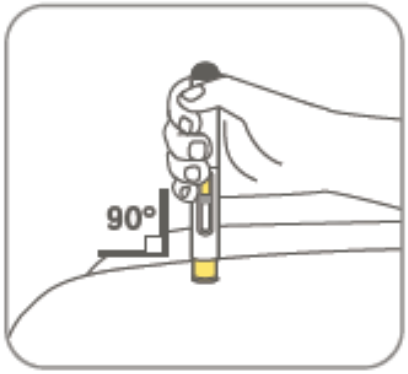


Figure H

Step 10 Firmly push the pre-filled pen down onto the skin to start the injection (Figure I).

- You may hear a first click when the injection begins.

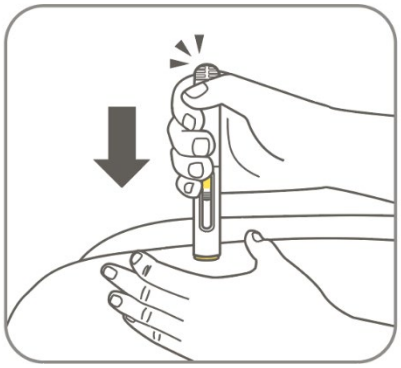


Figure I

Step 11 Continue to press down onto the skin until the yellow indicator stops moving. (Figure J). Your injection could take up to **10 seconds.**

- You may hear a second click. This means the injection is finished.
- **Do not** release pressure against the injection site before the injection is complete.
- **Do not** move the pre-filled pen during the injection.

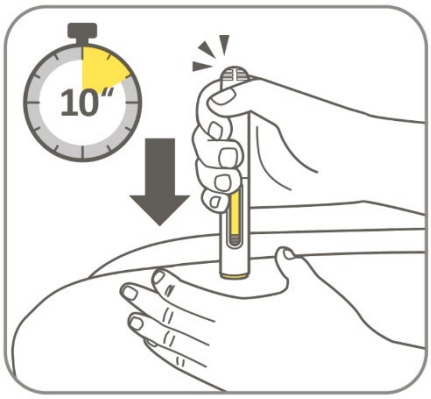


Figure J

Step 12 Check that the viewing window has turned yellow to make sure the full dose has been delivered and remove the empty pen from your skin (Figure K).

- The needle guard will completely cover the needle.
- As in **Figure K**, a small gray band may still be visible in the viewing window.
- When the needle is pulled out of your skin, there may be a little bleeding or a few drops at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

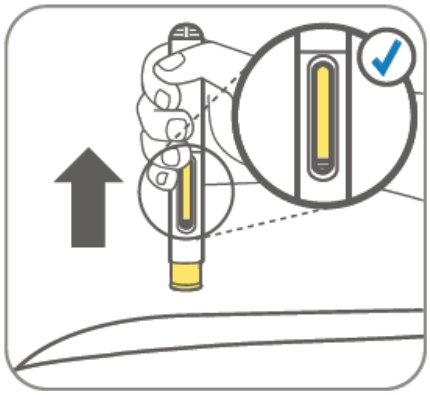


Figure K

If your dose is 90 mg, you will receive either one 90 mg pre-filled pen or two 45 mg pre-filled pens. If you receive two 45 mg pre-filled pens for a 90 mg dose, you will need to give yourself a

second injection right after the first. Repeat Steps 1–12 for the second injection using a new pen. Choose a different site for the second injection.

Disposing of Pyzchiva pre-filled pen

Step 13 Put the used pen in a sharps disposal container right away after use (Figure L).

- **Do not** throw away (dispose of) loose pens in your household trash.
- **Do not** recycle your used sharps disposal container.



Figure L

Keep Pyzchiva and all medicines out of the reach of children.

Package leaflet: Information for the user

Pyzchiva 90 mg solution for injection in pre-filled pen
ustekinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pyzchiva is and what it is used for
2. What you need to know before you use Pyzchiva
3. How to use Pyzchiva
4. Possible side effects
5. How to store Pyzchiva
6. Contents of the pack and other information

1. What Pyzchiva is and what it is used for

What Pyzchiva is
Pyzchiva administered using the pre-filled pen contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Pyzchiva belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Pyzchiva is used for
Pyzchiva is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Pyzchiva will reduce the inflammation and other signs of the disease.

Pyzchiva administered using the pre-filled pen is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Pyzchiva to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Pyzchiva to reduce the signs and symptoms of your disease.

2. What you need to know before you use Pyzchiva

Do not use Pyzchiva
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Warnings and precautions
Talk to your doctor or pharmacist before using Pyzchiva. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Pyzchiva. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Pyzchiva can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Pyzchiva. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Pyzchiva tell your doctor:
- **If you ever had an allergic reaction to ustekinumab.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like ustekinumab weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis –** such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with ustekinumab has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if ustekinumab may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Pyzchiva.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with ustekinumab. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Ustekinumab pre-filled pen is not recommended for use in children and adolescents under 18 years of age with psoriasis because it has not been studied in this age group. The pre-filled syringe or vial should be used instead for children 6 years of age and older and adolescents with psoriasis.

Ustekinumab is not recommended for use in children and adolescents under 18 years of age with psoriatic arthritis, Crohn's disease because it has not been studied in this age group.

Other medicines, vaccines and Pyzchiva
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Pyzchiva.
- If you received Pyzchiva while pregnant, tell your baby's doctor about your Pyzchiva treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to ustekinumab in the womb. However, there is limited experience with ustekinumab in pregnant women. It is therefore preferable to avoid the use of ustekinumab in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using ustekinumab and for at least 15 weeks after the last ustekinumab treatment.
- Pyzchiva can pass across the placenta to the unborn baby. If you received Pyzchiva during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Pyzchiva during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Pyzchiva during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use ustekinumab -do not do both.

Driving and using machines
Ustekinumab has no or negligible influence on the ability to drive and use machines.

Pyzchiva contains polysorbate 80 (E433)
This medicine contains 0.04 mg of polysorbate 80 (E433) in each pre-filled pen (1 ml) which is equivalent to 0.04 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Pyzchiva

Pyzchiva is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Pyzchiva is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Pyzchiva is given
Your doctor will decide how much Pyzchiva you need to use and for how long.

Adults aged 18 years or older Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Pyzchiva. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease
- During treatment, the first dose of approximately 6 mg/kg Pyzchiva will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Pyzchiva after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Pyzchiva may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

How Pyzchiva is given
- Pyzchiva is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Pyzchiva.
- However, you and your doctor may decide that you may inject Pyzchiva yourself. In this case you will get training on how to inject Pyzchiva yourself.
- For instructions on how to inject Pyzchiva, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Pyzchiva than you should
If you have used or been given too much Pyzchiva, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Pyzchiva
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Pyzchiva
It is not dangerous to stop using ustekinumab. However, if you stop, your symptoms may come back. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking ustekinumab (may affect up to 1 in 1,000 people). Signs include:
    - difficulty breathing or swallowing
    - low blood pressure, which can cause dizziness or light-headedness
    - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Pyzchiva again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.
- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Ustekinumab may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.
You must look out for signs of infection while you are using ustekinumab. These include:
- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea.
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use ustekinumab until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people):
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pyzchiva

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the pre-filled pen in the outer carton in order to protect from light.
- If needed, individual Pyzchiva pre-filled pens may also be stored at room temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light.

Record the date when the pre-filled pen is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period the product can be put back in the refrigerator once and kept there until the expiry date. Discard the pen if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake Pyzchiva pre-filled pens. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Pyzchiva looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Pyzchiva is for single use only. Any unused product remaining in the pre-filled pen should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pyzchiva contains
- The active substance is ustekinumab. Each pre-filled pen contains 90 mg ustekinumab in 1 mL.
- The other ingredients are Histidine, Histidine hydrochloride monohydrate, Polysorbate 80, Sucrose, Water for injections.

What Pyzchiva looks like and contents of the pack
Pyzchiva is a clear, colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled pen. Each pre-filled pen contains 90 mg ustekinumab in 1 mL of solution for injection.

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Traceability:

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

This leaflet was last revised in MM/YYYY
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

INSTRUCTIONS FOR USE
Pyzchiva
(ustekinumab)
injection, for subcutaneous use
Pre-filled pen

Instructions for injecting Pyzchiva using a pre-filled pen.

Read this Instructions for Use before you start using Pyzchiva. Your healthcare professional should show you how to prepare and give your injection of Pyzchiva the right way.

If you cannot give yourself the injection:

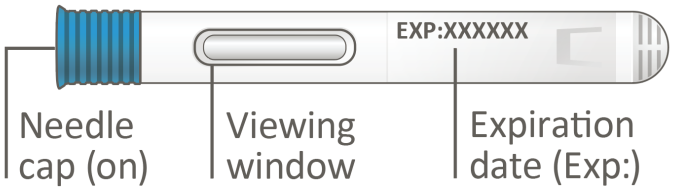
- ask your healthcare professional to help you, or
- ask someone who has been trained by a healthcare professional to give your injections.

Do not try to inject Pyzchiva yourself until you have been shown how to inject Pyzchiva by your health professional.

Need help?
Call your doctor to talk about any questions you may have. For additional assistance or to share your feedback refer to the Package Leaflet for your local representative contact information.

Guide to parts:

Before use



After use

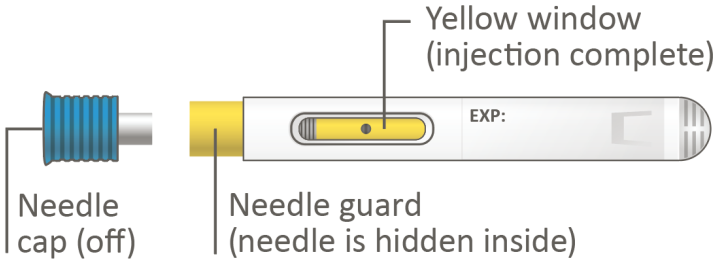


Figure A

Important information You Need to Know Before Injecting Pyzchiva

- **For subcutaneous injection only** (inject directly under the skin)
- **Do not** remove the needle cap before you are ready to inject.
- **Do not shake the pre-filled pen at any time.** Shaking your pre-filled pen may damage your Pyzchiva medicine.

Storing Pyzchiva pre-filled pen:
- Store Pyzchiva in the refrigerator between 2°C to 8°C.
- Store Pyzchiva in the original carton to protect from light or physical damage.
- If needed, individual Pyzchiva pre-filled pens may also be stored at room

temperature up to 30°C for a maximum single period of up to 35 days in the original carton in order to protect from light. Record the date when the pre-filled pen is first removed from the refrigerator in the space provided on the outer carton. At any time before the end of this period the product can be put back in the refrigerator once and kept there until the expiry date. Discard the pen if not used after the maximum period of 35 days at room temperature storage or by the original expiry date, whichever is earlier. **Do not** store Pyzchiva in extreme heat or cold.

- **Do not** freeze.

Preparing to Inject Pyzchiva pre-filled pen

Step 1 Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.

- If your dose is 45 mg, you will receive one 45 mg pre-filled pen.
- If your dose is 90 mg, you will receive either one 90 mg pre-filled pen or two 45 mg pre-filled pens. If you receive two 45 mg pre-filled pens for a 90 mg dose, you will need to give yourself two injections, one right after the other.

Step 2 Gather supplies

- **Step 2.1:** Choose a well-lit, clean, flat work surface.
- **Step 2.2:** Gather the supplies you will need to prepare and to give your injection **(Figure B)**.
- You will need the following supplies.
  - Included in the carton:

  - Pyzchiva pre-filled pen
  - Not included in the carton:
    - Alcohol swab
    - Cotton balls or gauze pads
    - Adhesive bandage
    - Sharps disposal container **(See "Disposing of Pyzchiva pre-filled pen.")**

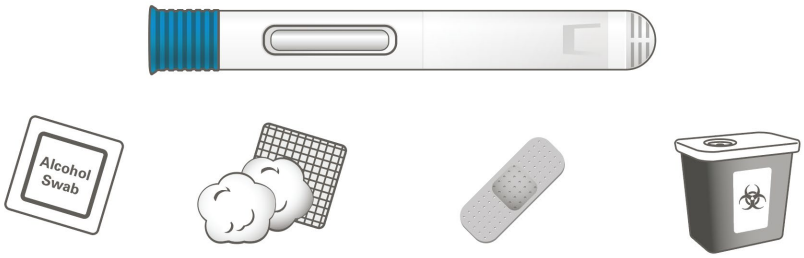


Figure B

Step 3 Inspect the pre-filled pen (Figure C)

- **Step 3.1:** Check the expiration date on the pre-filled pen or carton.
- **Step 3.2:** Check the medicine in the window for any particles or discoloration. The medicine should look clear and colorless to light yellow with few white particles.
- **Step 3.3:** Make sure the pen is not damaged.
- **Do not** use Pyzchiva if:
  - the expiration date has passed or if the pre-filled pen has been kept at room temperature up to 30ºC for longer than a maximum single period of 35 days or if the pre-filled pen has been stored above 30ºC.
  - it is frozen, discolored, cloudy or has large particles.
  - it is damaged.
  - it is dropped and appears cracked or broken.
- It is normal to see 1 or more bubbles in the window.

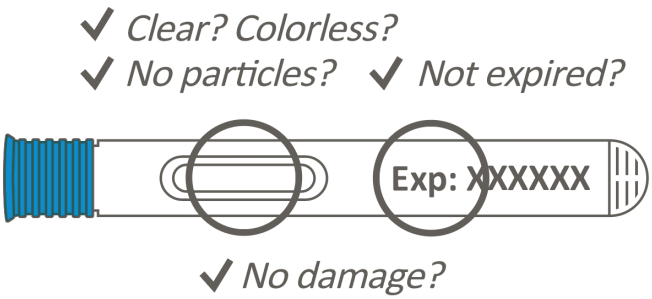


Figure C

Step 4 Allow the medicine to reach room temperature



- For a more comfortable injection, leave Pyzchiva pre-filled pen at room temperature for about 30 minutes before injecting, after removing it from the refrigerator.
- **Do not** warm the pre-filled pen in any other way (for example, do not warm it in a microwave or in hot water).

Step 5 Wash your hands

- Wash your hands well with soap and warm water **(Figure D).**

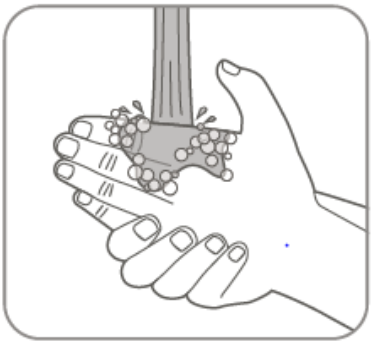


Figure D

Step 6 Choose the injection site

- Choose an injection site around your upper legs (thighs) or lower stomach area (lower abdomen) except for a 5-centimetre area right around your navel (belly-button). If a caregiver is giving you the injection, the outer area of the upper arms may also be used. **(Figure E)**
- **Use a different injection site for each injection.**
- **Do not** give an injection in an area of the skin that is tender, bruised, red, or hard or shows signs of psoriasis.

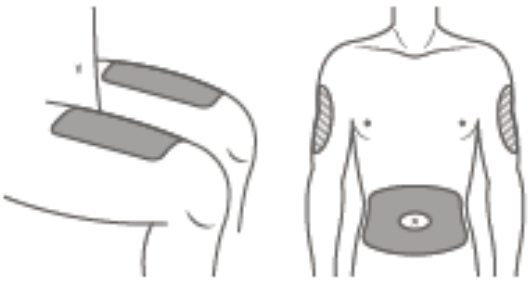


Figure E

Step 7 Clean the skin at the injection site

- Clean the skin with a new alcohol swab where you plan to give your injection. **(Figure F)**
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.

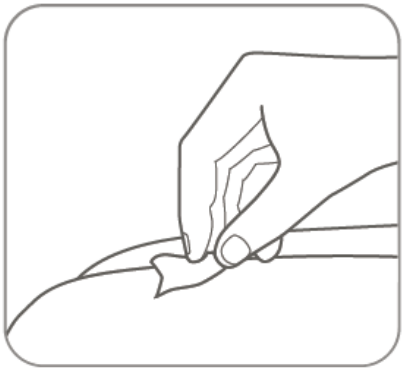


Figure F

Injecting Pyzchiva pre-filled pen

Step 8 Pull the needle cap straight off when you are ready to inject your Pyzchiva (Figure G).

- Throw away the needle cap.
- It is normal to see a few drops of liquid come out of the needle.
- **Do not** twist or bend the needle cap while removing it, as this may damage the needle.
- **Do not** use the pre-filled pen if it is dropped after removing the needle cap. Call your health professional for instructions.

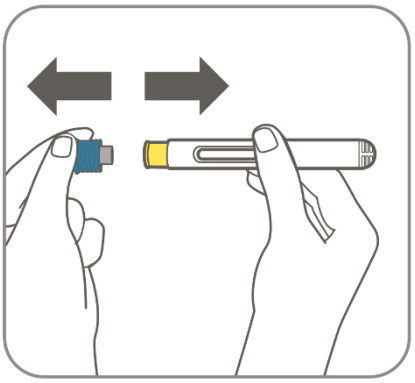


Figure G

Step 9 Position the pre-filled pen straight on your skin at 90 degrees (Figure H).

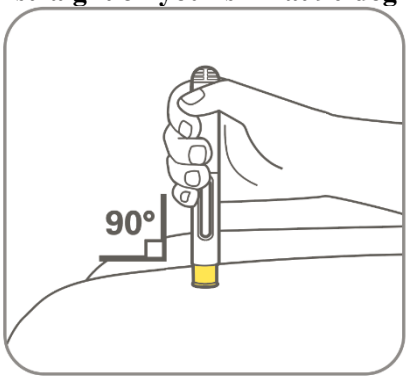


Figure H

Step 10 Firmly push the pre-filled pen down onto the skin to start the injection (Figure I).

- You may hear a first click when the injection begins.

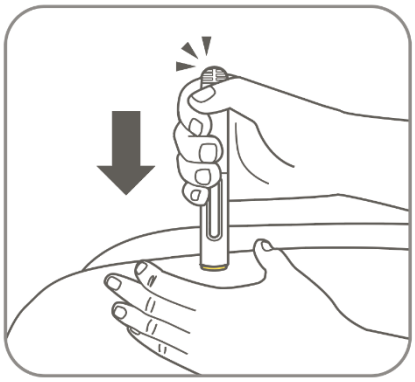


Figure I

Step 11 Continue to press down onto the skin until the yellow indicator stops moving. (Figure J). Your injection could take up to **10 seconds.**

- You may hear a second click. This means the injection is finished.
- **Do not** release pressure against the injection site before the injection is complete.
- **Do not** move the pre-filled pen during the injection.

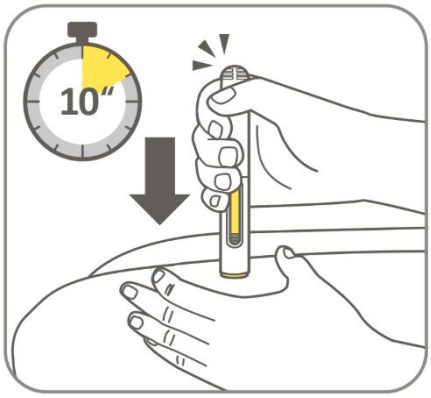


Figure J

Step 12 Check that the viewing window has turned yellow to make sure the full dose has been delivered and remove the empty pen from your skin (Figure K).

- The needle guard will completely cover the needle.
- As in **Figure K**, a small gray band may still be visible in the viewing window.
- When the needle is pulled out of your skin, there may be a little bleeding or a few drops at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

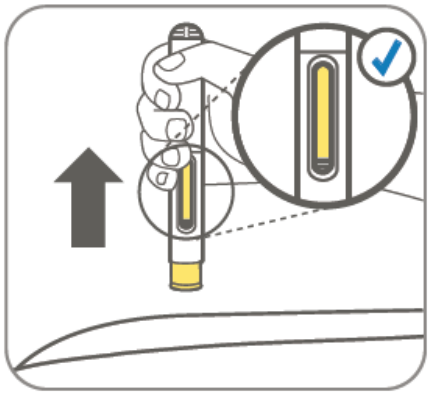


Figure K

If your dose is 90 mg, you will receive either one 90 mg pre-filled pen or two 45 mg pre-filled pens. If you receive two 45 mg pre-filled pens for a 90 mg dose, you will need to give yourself a

second injection right after the first. Repeat Steps 1–12 for the second injection using a new pen. Choose a different site for the second injection.

Disposing of Pyzchiva pre-filled pen

Step 13 Put the used pen in a sharps disposal container right away after use (Figure L).

- **Do not** throw away (dispose of) loose pens in your household trash.
- **Do not** recycle your used sharps disposal container.



Figure L

Keep Pyzchiva and all medicines out of the reach of children.