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

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen

Each single-use pre-filled pen contains 30 mg of nemolizumab per 0.49 ml dose following reconstitution.

Nemolizumab, a humanised monoclonal modified immunoglobulin G (IgG) antibody, is produced by recombinant DNA technology in Chinese Hamster Ovary cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Powder for solution for injection: lyophilised white powder.
Solvent for solution for injection: A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atopic dermatitis (AD)

Nemluvio is indicated for the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older who are candidates for systemic therapy.

Prurigo nodularis (PN)

Nemluvio is indicated for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.

4.2 Posology and method of administration

Treatment with nemolizumab should be initiated and supervised by healthcare professionals experienced in the diagnosis and treatment of conditions for which nemolizumab is indicated.

Posology

Atopic dermatitis (AD)

The recommended dose is:
- An initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (Q4W)

- After 16 weeks of treatment, for patients who achieve clinical response, the recommended maintenance dose is 30 mg every 8 weeks (Q8W)

Nemolizumab can be used with or without topical corticosteroids (TCS). Topical calcineurin inhibitors (TCI) may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas. Any use of topical therapies should be tapered and subsequently discontinued when the disease has sufficiently improved.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for atopic dermatitis. Some patients with initial partial response may further improve with continued treatment beyond 16 weeks.
Once clinical response is achieved, the recommended maintenance dose of nemolizumab is 30 mg every 8 weeks.

Prurigo nodularis (PN)

The recommended dose for patients weighing < 90 kg is an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (Q4W).

The recommended dose for patients weighing ≥ 90 kg is an initial dose of 60 mg dose (two 30 mg injections), followed by 60 mg given every 4 weeks (Q4W).

Consideration should be given to discontinuing treatment in patients who have shown no response on pruritus after 16 weeks of treatment for prurigo nodularis.

Missed dose

If a dose is missed, it should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly (≥ 65 years)
No dose adjustment is recommended for elderly patients (see section 5.2).

Hepatic and renal impairment
No dose adjustment is needed in patients with hepatic or renal impairment (see section 5.2).

Paediatric population

Atopic dermatitis
The safety and efficacy of nemolizumab in children less than 12 years of age and body weight < 30 kg have not yet been established. No data are available.

Prurigo nodularis
The safety and efficacy of nemolizumab in children less than 18 years of age have not been established. No data are available.

Method of administration

Subcutaneous use.

The subcutaneous injection should be administered into the front upper thighs or abdomen avoiding the 5 cm area around the navel. Injection into the upper arm should only be performed by a caregiver or healthcare professional.

For subsequent doses, it is recommended to rotate the injection site with each dose. Nemolizumab should not be injected into skin that is tender, inflamed, swollen, damaged or has bruises, scars or open wounds.

Nemolizumab is intended for use under the guidance of a healthcare professional. A patient may self-inject nemolizumab or the patient's caregiver may administer nemolizumab if their healthcare professional determines that this is appropriate. Prior to first injection, patients and/or caregivers should be given proper training on the preparation and administration of nemolizumab according to the instructions for use at the end of the package leaflet.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Hypersensitivity

Cases of type 1 hypersensitivity, including angioedema, have been reported. If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of nemolizumab should be discontinued immediately and appropriate therapy initiated (see section 4.8).

Worsening of asthma (including PEF decrease)

In the population of PN subjects with pre-existing asthma, a mild to moderate worsening of asthma (WOA) has been reported after initiation of nemolizumab. This was observed more frequently in patients weighing > 90 kg who received 60 mg nemolizumab every 4 weeks compared to patients weighing < 90 kg who received 30 mg nemolizumab every 4 weeks (see section 4.8).

Patients with an exacerbation of asthma requiring hospitalization in the preceding 12 months, patients with uncontrolled asthma during the preceding 3 months and patients with a current medical history of COPD and/or chronic bronchitis were excluded from clinical studies. No information on the efficacy or safety of nemolizumab in those patients is available.

Vaccinations

It is recommended that patients complete all age-appropriate vaccinations in agreement with current immunisation guidelines prior to initiating treatment. Concurrent use of live vaccines in patients treated with nemolizumab should be avoided. It is unknown if administration of live vaccines during treatment will impact the safety or efficacy of these vaccines. No data are available on the response to non-live vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines

The safety and efficacy of concurrent use of nemolizumab with live attenuated vaccines has not been studied. Live vaccines should not be given concurrently with nemolizumab (see section 4.4).

Non-live vaccines

The safety and efficacy of concurrent use of nemolizumab with non-live vaccines has not been studied (see section 4.4)

Interactions with cytochrome P450

The effects of nemolizumab on the pharmacokinetics of midazolam (CYP3A4/5 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate), and caffeine (CYP1A2 substrate) were evaluated in a study in subjects with moderate to severe AD. No clinically significant changes in the exposure of CYP450 substrates were observed compared to prior to nemolizumab treatment. No dose adjustment is necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data on the use of nemolizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of nemolizumab during pregnancy.

Breast-feeding

No data are present on the excretion of nemolizumab in human milk. In humans, excretion of IgG antibodies in milk occurs during the first few days after birth, which is decreasing to low concentrations soon afterwards. Consequently, transfer of IgG antibodies to the newborns through milk, may happen during the first few days. In this short period, a risk to the breastfed child cannot be excluded. Afterwards, nemolizumab could be used during breast-feeding if clinically needed.

Fertility

Animal studies showed no impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Nemluvio 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 in atopic dermatitis and prurigo nodularis are type I hypersensitivity (1.1%; includes urticaria 1.0% and angioedema 0.1%) and injection site reactions (1.2%) (see section 4.4). Additional adverse reactions such as headache (7.0%), atopic dermatitis (4.6%), eczema (3.8%), eczema nummular (3.5%), superficial fungal infections (3.0%) and worsening of asthma (2.2%) were reported in prurigo nodularis.

Tabulated list of adverse reactions

Table 1 includes all adverse reactions observed in clinical studies presented by system organ class and frequency, using the following categories: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions

MedDRA System Organ Class	Frequency	Adverse reactions
Infections and infestations	Common	Superficial fungal infections*[#]
Blood and lymphatic system disorders	Uncommon	Eosinophilia[†]
Immune system disorders	Common	Type I hypersensitivity (incl. urticaria[†] and angioedema*)
Nervous system disorders	Common	Headache* (incl. tension headache)
Respiratory, thoracic and mediastinal disorders	Common	Worsening of asthma* (incl. asthma, wheezing, peak expiratory flow rate decreased)
Skin and subcutaneous tissue disorders	Common Uncommon	Atopic dermatitis* Eczema* Eczema nummular* Bullous pemphigoid[§]
General disorders and administration site conditions	Common	Injection site reactions (incl. erythema, pruritus, haematoma[†], pain[†], irritation[†], bruising*, and injection site oedema[†])

[†]Occurred in atopic dermatitis studies
*Occurred in prurigo nodularis studies
[#]Superficial fungal infections include: body tinea, tinea pedis, onychomycosis, fungal infection, tinea versicolor, tinea cruris, fungal skin infection and fungal foot infection
[§]From post-marketing reporting

Description of selected adverse reactions

Hypersensitivity
Type 1 hypersensitivity reactions (Ig-E mediated reactions), including mild urticaria and mild facial (peri-ocular) angioedema, were commonly observed in subjects treated with nemolizumab during the clinical studies. These reactions did not lead to treatment discontinuation (see section 4.4).

Headache
In patients with prurigo nodularis, headache was more frequently reported in patients treated with nemolizumab (7.0%) compared to patients treated with placebo. Headache was more frequently observed in female patients in both groups. In the nemolizumab group, headache was mostly mild or moderate in severity and did not lead to discontinuation of treatment.

Worsening of asthma
In the PN patients with pre-existing asthma (n=51), 8 (15.7%) patients experienced a worsening of asthma (WOA) after initiation of nemolizumab, 5 of whom had a body weight > 90 kg and received 60 mg nemolizumab every 4 weeks. In the population of PN patients with pre-existing asthma, WOA was 3 times more frequent in patients with a body weight > 90 kg who received 60 mg nemolizumab every 4 weeks than in patients with a body weight < 90 kg who received 30 mg nemolizumab every 4 weeks.

The majority of WOA events occurred within the first two months of treatment initiation and all were reported as mild or moderate in severity. Most patients experienced a single event of WOA during treatment and the event resolved with standard of care asthma medications (inhalers) without the use of systemic steroids. None led to permanent discontinuation of treatment. The incidence of WOA did not increase with longer term exposure to nemolizumab (up to Week 52) in the PN open-label long-term extension study.

Eczematous reactions
In patients with prurigo nodularis, eczematous reactions such as atopic dermatitis, eczema nummular or eczema were more frequently reported in nemolizumab-treated patients compared to patients treated with placebo: Atopic dermatitis (4.6%), eczema (3.8%) and eczema nummular (3.5%). These eczematous reactions were mild or moderate in severity. Atopic dermatitis led to nemolizumab discontinuation in 2 (0.5%) patients. Patients > 65 years of age had a higher rate of eczematous reactions.

Eosinophilia
Proportion of patients with clinically significant elevated eosinophils (> 700 cells/mcL) was 10,2% in the AD population (in the initial period) and 5,5% in the PN population. Severe eosinophilia (> 5000 cells/mcL) was not observed in AD nemolizumab-treated patients in the initial treatment period. Adverse reactions of eosinophilia were reported in 0.2% of AD patients treated with nemolizumab during the initial treatment period up to Week 16. All events in AD subjects were mild in intensity and not associated with clinical symptoms. No TEAE of eosinophilia led to discontinuation of treatment. Apart from one case of eosinophilic colitis in an AD subject with other atopic comorbidities, there were no other reports of eosinophilic disorders.

Paediatric population

Atopic dermatitis

Adolescents (12 to 17 years of age)
The safety of nemolizumab was assessed in 176 paediatric subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis enrolled in the ARCADIA 1 and ARCADIA 2 studies. The safety profile of nemolizumab in these subjects through Week 16 was similar to the safety profile seen in adults with atopic dermatitis.

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

There is no specific treatment for nemolizumab overdose. In the event of overdose, the patient should be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH12

Mechanism of action

Nemolizumab is a humanised IgG2 monoclonal antibody that inhibits interleukin-31 (IL-31) signalling by binding selectively to interleukin-31 receptor alpha (IL-31 RA). IL-31 is a naturally occurring cytokine that is involved in pruritus, inflammation, epidermal dysregulation, and fibrosis. Nemolizumab inhibited IL-31-induced responses including the release of proinflammatory cytokines and chemokines.

In atopic dermatitis clinical studies, nemolizumab was found to modulate gene expression related to the pathophysiology of atopic dermatitis, with a primary impact on immune system processes, by decreasing the inflammatory and proliferative profile of specific immune cells (T-cells and monocytes/macrophages) without leading to immunosuppression.

In prurigo nodularis clinical studies, nemolizumab was found to modulate molecular processes related to the pathophysiology of prurigo nodularis, with impact on pruritus, inflammation, epidermal differentiation and fibrosis.

Pharmacodynamic effect

Immunogenicity
Anti-drug antibodies (ADA) were very commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

Clinical efficacy and safety in atopic dermatitis

Adults and adolescents with atopic dermatitis

The efficacy and safety of nemolizumab with concomitant topical background therapy was evaluated in two randomised, double-blind, placebo-controlled pivotal studies (ARCADIA 1 and ARCADIA 2) that enrolled a total of 1728 subjects 12 years of age and older with moderate-to-severe atopic dermatitis not adequately controlled by topical treatments. Disease severity was defined by an Investigator's Global Assessment (IGA) score of 3 (moderate) and 4 (severe) in the overall assessment of atopic dermatitis, an Eczema Area and Severity Index (EASI) score of ≥ 16, a minimum body surface area (BSA) involvement of ≥ 10%, and a Peak Pruritus Numeric Rating Scale (PP NRS) score of ≥ 4.

Subjects in the studies received initial subcutaneous injections of either nemolizumab 60 mg, followed by 30 mg injections every 4 weeks (Q4W), or matching placebo. Concomitant low and/ or medium potency TCS and/or TCI were administered both in nemolizumab and placebo groups for at least 14 days prior to baseline and continued during the study. Based on disease activity, these concomitant therapies could be tapered and/or discontinued at investigator discretion.

After 16 weeks, subjects achieving either EASI-75 or IGA success continued into the study maintenance period for another 32 weeks to evaluate the maintenance of response achieved at Week 16. Nemolizumab responders were re-randomised to either nemolizumab 30 mg every 4 weeks, nemolizumab 30 mg every 8 weeks or placebo every 4 weeks (all groups continued background TCS/TCI). Subjects randomised to placebo in the initial treatment period who achieved the same clinical response at Week 16 continued to receive placebo every 4 weeks. Non-responders at Week 16, subjects who lost clinical response during the maintenance period and subjects who completed maintenance period had the opportunity to enrol into the open-label study (ARCADIA LTE) and receive treatment with nemolizumab 30 mg every 4 weeks up to 200 weeks.

Endpoints

Both ARCADIA 1 and ARCADIA 2 assessed the primary endpoints of:
- Proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from baseline) at Week 16
- Proportion of subjects with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16

Key secondary endpoints included PP NRS improvement ≥4 from baseline at Weeks 1, 2, 4 and 16, PP NRS < 2 at Week 4 and Week 16, Sleep Disturbance Numeric Rating Scale (SD NRS) improvement ≥ 4 from baseline at Week 16, subjects with both EASI-75 and PP NRS

improvement ≥ 4 from baseline at Week 16, and subjects with both IGA success and PP NRS improvement ≥ 4 from baseline at Week 16.

Baseline characteristics

In these studies, at baseline, 51.0% of subjects were male, 79.9% were White, and the mean weight was 75.0 kg. The mean age was 34.1 years, 15.4% of subjects were adolescents (12-17 years) and 5.3% were 65 years of age or older. 70% of subjects had a baseline IGA score of 3 (moderate AD), and 30% of subjects had a baseline IGA score of 4 (severe AD). The mean (SD) baseline EASI score was 27.5 (10.5), the baseline weekly average (SD) PP NRS was 7.1 (1.5) (severe itch) and baseline weekly average (SD) SD NRS was 5.8 (2.2). Overall, 63.3% of subjects received other previous systemic treatments for atopic dermatitis.

Clinical response

ARCADIA 1 and ARCADIA 2 – Adults and Adolescents - induction period, Week 0 to Week 16

Nemolizumab was statistically significantly superior to placebo with respect to skin-related co-primary endpoints IGA success and EASI-75 over 16 weeks (Table 2). Results for both co-primary endpoints were consistent in the severe pruritus population (baseline PP NRS ≥ 7).

Table 2 – Efficacy Results of nemolizumab (30 mg Q4W) with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 at Week 16

	ARCADIA 1		ARCADIA 2	
	Nemolizumab + TCS/ TCI	**Placebo + TCS/ TCI**	**Nemolizumab + TCS/ TCI**	**Placebo + TCS/ TCI**
Number of subjects randomised and dosed (Baseline PP NRS ≥ 4)	620	321	522	265
% of subjects with IGA 0 or 1[a]	35.6[#]	24.6	37.7[#]	26.0
% of subjects with EASI-75[a]	43.5*	29.0	42.1[#]	30.2

[a] Subjects who received rescue treatment or with missing data were considered as non-responders
*p-value < 0.0001, [#]p-value < 0.001
Strata adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline

Figure 1 – Proportion of subjects with IGA success and EASI-75 from baseline to Week 16 in ARCADIA 1 and ARCADIA 2

Figure 1a. IGA Success

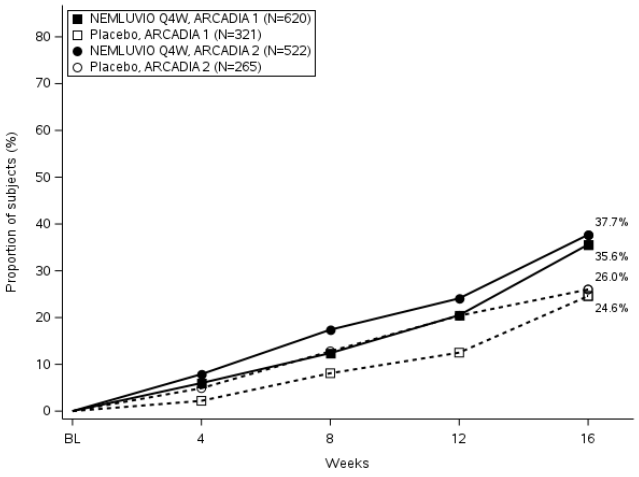
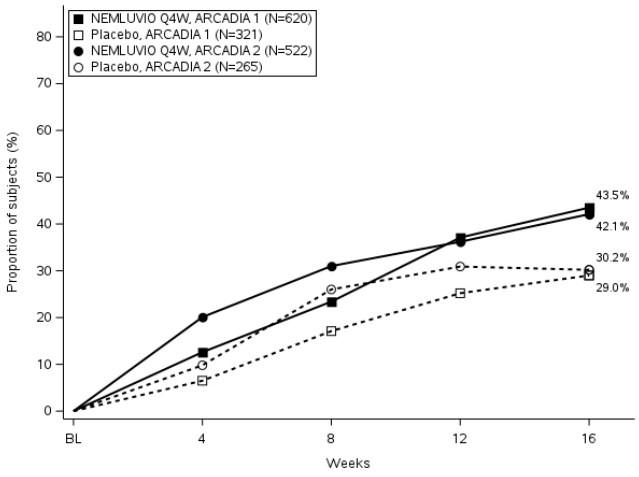


Figure 1b. EASI-75



Significant improvement in pruritus for subjects treated with nemolizumab in ARCADIA 1 and ARCADIA 2 compared to placebo based on PP NRS improvements ≥ 4 and PP NRS percent change

from baseline was observed starting at Week 1 and was maintained up to Week 16 (Table 3 and Figure 2). Results were consistent in the severe pruritus population (baseline PP NRS ≥ 7).

Table 3 – Efficacy results on itch for nemolizumab with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 up to Week 16

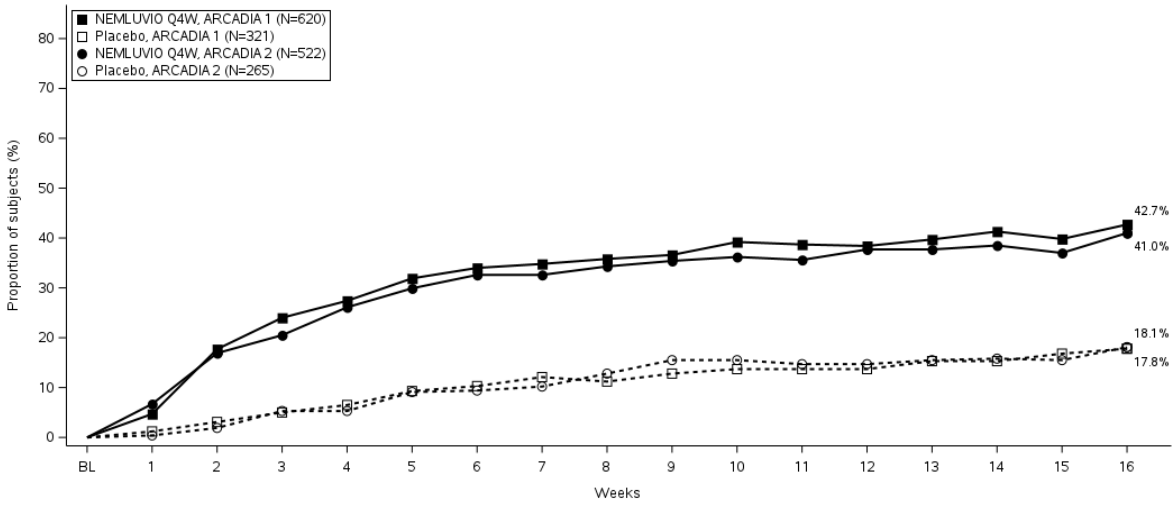
	ARCADIA 1		ARCADIA 2	
	Nemolizumab + TCS/TCI	**Placebo + TCS/TCI**	**Nemolizumab + TCS/ TCI**	**Placebo + TCS/ TCI**
Number of subjects randomised and dosed (Baseline PP NRS ≥ 4)[a]	620	321	522	265
% of subjects with PP NRS improvement ≥ 4[a]				
At Week 1	4.7[§]	1.2	6.7*	0.4
At Week 2	17.7*	3.1	16.9*	1.9
At Week 4	27.4*	6.5	26.1*	5.3
At Week 16	42.7*	17.8	41.0*	18.1
% of subjects with PP NRS < 2[a]				
At Week 4	16.0*	3.7	15.9*	2.6
At Week 16	30.6*	11.2	28.4*	11.3
Mean change from baseline (%)				
At Week 16	-56.1*	-30.6	-55.6*	-30.3

[a] Subjects who received rescue treatment or with missing data were considered as non-responders

*p-value < 0.0001, [§]p-value < 0.05

Strata adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline

Figure 2 –Proportion of subject with PP NRS improvement of ≥4 from baseline up to Week 16 in ARCADIA 1 and ARCADIA 2



In patients with a body weight ≥ 90kg, in a post-hoc analysis in each of the pivotal studies there was no difference in anti-inflammatory response (IGA 0 or 1 and EASI 75) at Week 16 between nemolizumab and placebo arms, though the effect was observed in reducing pruritus (PP NRS).

The Sleep Disturbance Numeric Rating Scale (SD NRS) is a daily scale used by the subjects to report the degree of their sleep loss related to atopic dermatitis. A significant improvement in sleep disturbance was observed at Week 16 when compared to placebo (Table 4). Results were consistent in the severe pruritus population (baseline PP NRS ≥ 7).

Table 4 – Efficacy on Sleep Disturbance for nemolizumab with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 at Week 16

	ARCADIA 1		ARCADIA 2	
	Nemolizumab + TCS/TCI	**Placebo + TCS/TCI**	**Nemolizumab + TCS/ TCI**	**Placebo + TCS/ TCI**
Number of subjects randomised and dosed (Baseline PP NRS ≥ 4)[a]	620	321	522	265
% of subjects with SD NRS improvement ≥ 4[a]	37.9*	19.9	33.5*	16.2
Mean change from baseline (%)	-64.6	-38.1	-59.7	-35.4

[a] Subjects who received rescue treatment or with missing data were considered as non-responders
*p-value <0.0001
Strata adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline

Adolescents with atopic dermatitis (12 to 17 years of age)

The efficacy results of the ARCADIA 1, ARCADIA 2 studies at Week 16 for paediatric subjects 12 to 17 years of age are presented in Table 5. The results in the paediatric subject population were generally consistent with the results in the adult subject population. Results in co-primary and key secondary endpoints were consistent in the severe pruritus population (baseline PP NRS ≥ 7).

Table 5 – Efficacy Results for nemolizumab (30 mg Q4W) with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 at Week 16 in paediatric subjects 12 to 17 years of age

	ARCADIA 1 AND ARCADIA 2	
	Nemolizumab + TCS/TCI	**Placebo + TCS/ TCI**
Number of subjects randomised and dosed (Baseline PP NRS ≥ 4)	179	90
% of subjects with IGA 0 or 1 [a]	48.9*	34.4
% of subjects with EASI-75 [a]	53.4[§]	43.3
% of subjects with PP-NRS improvement ≥ 4 [a]	40.9[#]	17.8
% of subjects with PP NRS < 2 [a]	30.1[≠]	6.7
% of subjects with SD NRS improvement ≥ 4 [a]	31.8[∞]	20.0

[a] Subjects who received rescue treatment or with missing data were considered as non-responders
[≠]p-value < 0.0001, [#]p-value < 0.001, *p-value < 0.05, [∞]p-value = 0.0591, [§]p-value = 0.1824
Strata adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline

ARCADIA 1 and ARCADIA 2 – Adults and Adolescents – maintenance period, Week 16 to Week 48

The clinical response in nemolizumab responders (IGA 0/1 or EASI-75 at Week 16) was evaluated between Week 16 and Week 48 in ARCADIA 1 and ARCADIA 2 studies. For the maintenance treatment period, 507 nemolizumab responders were re-randomised to nemolizumab 30 mg Q4W, nemolizumab 30 mg Q8W or placebo Q4W (nemolizumab withdrawal) with concomitant TCS/TCI. The pooled efficacy results with descriptive analysis only for this period in the pivotal studies (ARCADIA 1 and ARCADIA 2) with nemolizumab at Week 48 are presented in Table 6.

Table 6 –Maintenance Period Pooled Efficacy Results for nemolizumab with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 at Week 48

	Nemolizumab + TCS/TCI Q4W N=169	**Nemolizumab + TCS/TCI Q8W N=169**	**Placebo + TCS/TCI Q4W (Nemolizumab withdrawal) N=169**
% of subjects with IGA 0 or 1[a]			
Week 16 (maintenance baseline)	84.0	84.0	77.5
Week 48	61.5	60.4	49.7
Strata-adjusted proportion difference (%)	11.8	10.7	
Strata-adjusted 95% CI	(1.3, 22.3)	(0.3, 21.0)	
% of subjects with EASI-75[a] (95% CI)			
Week 16 (maintenance/baseline)	96.4	96.4	92.9
Week 48	76.3	75.7	63.9
Strata-adjusted proportion difference (%)	12.4	11.8	
Strata-adjusted 95% CI	(2.7, 22.0)	(2.1, 21.5)	

[a] Subjects who received rescue treatment or with missing data were considered as non-responders

Clinical efficacy and safety in adults with prurigo nodularis

The efficacy and safety of nemolizumab as monotherapy was evaluated in two randomised, double-blind, placebo-controlled pivotal studies (OLYMPIA 1 and OLYMPIA 2) that enrolled a total of 560 subjects 18 years of age and older with moderate-to-severe prurigo nodularis. Disease severity was defined using an Investigator's Global Assessment (IGA) in the overall assessment of prurigo nodularis nodules on a severity scale of 0 to 4. Subjects enrolled in these two studies had an IGA score ≥ 3, severe pruritus as defined by a weekly average of the peak pruritus numeric rating scale (PP-NRS) score of ≥ 7 on a scale of 0 to 10, and greater than or equal to 20 nodular lesions. OLYMPIA 1 and OLYMPIA 2 assessed the effect of nemolizumab monotherapy on the signs and symptoms of prurigo nodularis, targeting improvement in skin lesions and pruritus over 16 weeks. OLYMPIA 1 had a 24-week treatment period and OLYMPIA 2 a 16-week treatment period.

In the nemolizumab treatment group, subjects weighing less than 90 kg received subcutaneous injections of nemolizumab 60 mg (2 injections of 30 mg) at Week 0, followed by 30 mg injections every 4 weeks, and subjects weighing 90 kg or more received subcutaneous injections of nemolizumab 60 mg (2 injections of 30 mg) at Week 0 and every 4 weeks.

Endpoints

Both OLYMPIA 1 and OLYMPIA 2 assessed the same two primary endpoints:

- Proportion of subjects with an improvement of ≥ 4 from baseline in Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16
- Proportion of subjects with an IGA success (defined as an IGA of 0 [Clear] or 1 [Almost Clear], and a ≥ 2-point improvement from baseline) at Week 16

Key secondary endpoints included PP NRS improvement ≥ 4 from baseline at Week 4, PP NRS < 2 at Week 4 and Week 16, Sleep Disturbance Numeric Rating Scale (SD NRS) improvement ≥ 4 from baseline at Week 4 and 16.

Baseline characteristics

In these studies, at baseline, 59.6% of subjects were female, 81.4% were white, the mean weight was 82.6 kg, the mean age was 55.2 years and 25.4% of subjects were older than 65 years of age. The baseline weekly average PP NRS score was a mean (SD) of 8.4 (0.9). Fifty-eight (58) % of subjects had a baseline IGA score of 3 (moderate PN) and 42% of subjects had a baseline IGA of 4 (severe PN).

Clinical response

Pivotal studies (OLYMPIA 1 and OLYMPIA 2) – Week 0 to Week 16

Results of the pivotal studies evaluating treatment of nemolizumab in OLYMPIA 1 and OLYMPIA 2 are presented in Table 7 and show significant improvement in nemolizumab treated subjects, compared to placebo for both primary endpoints (Figure 3 and Figure 4).

Table 7 - Efficacy Results for nemolizumab monotherapy (Q4W) in OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1		**OLYMPIA 2**	
	Nemolizumab	**Placebo**	**Nemolizumab**	**Placebo**
Number of subjects randomised	190	96	183	91
% of subjects with improvement of PP NRS ≥ 4 from baseline[a]				
Week 4	41.1*	6.3	41.0*	7.7
Week 16	58.4*	16.7	56.3*	20.9
% of subjects with IGA 0 or 1 at Week 16[a]	26.3[#]	7.3	37.7*	11
% of subjects with PP NRS < 2 [a]				
Week 4	21.6*	1.0	19.7*	2.2
Week 16	34.2*	4.2	35.0*	7.7
% of subjects with improvement of SD NRS ≥ 4 from baseline[a]				
Week 4	31.1*	5.2	37.2*	9.9
Week 16	50.0*	11.5	51.9*	20.9

[a] If a subject received any rescue therapy, composite variable strategy is applied, the underlying data at/after receipt of rescue therapy is set as worst possible value, and the response is derived from underlying data value. Subjects with missing results are considered as non-responders.
*p-value < 0.0001, [#]p-value = 0.0025 Strata adjusted using the randomised stratification variables (analysis centre and baseline body weight (< 90 kg, ≥ 90 kg)

Figure 3 – Proportion of Subjects with PP-NRS Improvement ≥ 4 from baseline to Week 16

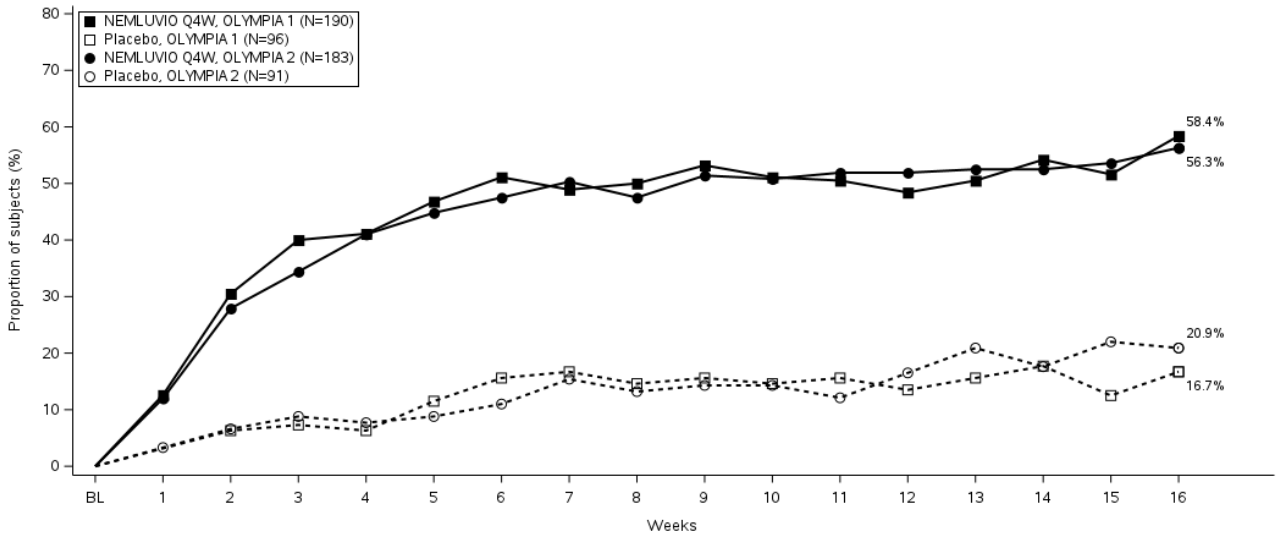
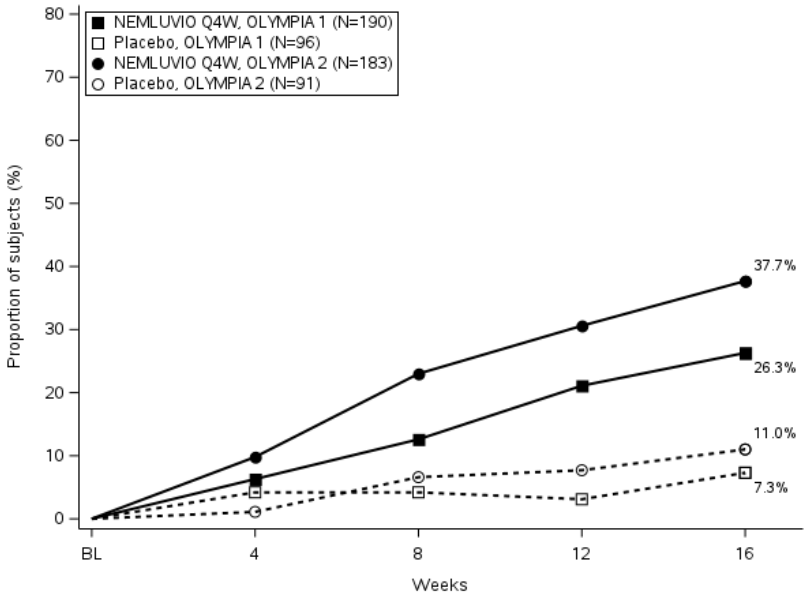


Figure 4 – Proportion of IGA responders from baseline to Week 16



5.2 Pharmacokinetic properties

Absorption

Following an initial subcutaneous dose of 60 mg in patients with AD or PN, the population PK estimated mean (SD) peak concentration (C_{max}) was 6.7 (2.20) µg/mL by approximately 6 days post dose.

Following multiple doses in subjects with atopic dermatitis, the population PK estimated mean (SD) steady-state trough concentrations of nemolizumab were 2.63 (1.27) µg/mL for 30 mg administered Q4W and 0.74 (0.44) µg/mL for 30 mg administered Q8W.

Following multiple doses in subjects with prurigo nodularis, the population PK estimated mean (SD) steady-state trough concentrations of nemolizumab 3.04 (1.23) µg/mL in patients with body weight < 90 kg for 30 mg administered Q4W; and 3.66 (1.63) µg/mL in patients with body weight ≥ 90 kg for 60 mg administered Q4W.

In both atopic dermatitis and prurigo nodularis population, steady state concentrations of nemolizumab were achieved by week 4 after a 60 mg loading dose and by week 12 without a loading dose.

A loading dose is proposed for subjects with PN with body weight < 90 kg. However, for subjects with body weight ≥ 90 kg no loading dose is proposed because the 60 mg dose was sufficient to achieve similar steady-state concentrations of nemolizumab as the 30 mg dose (with 60 mg loading dose) after the second dose (at Week 8).

Distribution

Based on a population PK analysis, the apparent volume of distribution (V/F) was 7.67 L.

Biotransformation

Specific metabolism studies were not conducted because nemolizumab is a protein. Nemolizumab is expected to be metabolised into small peptides by catabolic pathways.

Elimination

Nemolizumab is expected to be degraded in the same manner as endogenous IgG. In the population PK analysis, the terminal elimination half-life (SD) of nemolizumab was estimated to be 18.9 (4.96) days and apparent systemic clearance (Cl/F) was estimated to be 0.26 L/day.

Linearity/non-linearity

After a single dose, nemolizumab exhibited linear pharmacokinetics with exposures increasing in dose-proportional manner between 0.03 and 3 mg/kg.

After multiple doses, nemolizumab systemic exposure increased in an approximately dose-proportional manner across the SC dose range up to 30 mg. There was a slight decrease in bioavailability by 9% with the 60 mg SC dose.

Special populations

Gender, age and ethnicity
Gender, age (range 12 to 85 years for AD, and 18 to 84 years for PN), and ethnicity did not have a clinically relevant effect on the pharmacokinetics of nemolizumab.

Hepatic impairment
Nemolizumab, as a monoclonal antibody, is not expected to undergo significant hepatic elimination. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of nemolizumab. Mild to moderate hepatic impairment was not found to affect the PK of nemolizumab determined by population PK analysis. No data are available in patients with severe hepatic impairment.

Renal impairment
Nemolizumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of nemolizumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of nemolizumab. Very limited data are available in patients with severe renal impairment.

Body weight
Nemolizumab exposure was lower in subjects with higher body weight.

Atopic dermatitis
The difference in systemic exposure due to body weight had no clinically meaningful impact on efficacy. Dose adjustment based on body weight is not needed (see section 4.2).

Prurigo nodularis
The variability in systemic exposure due to body weight had a clinically meaningful impact on skin lesion efficacy as assessed by IGA response but not on pruritus improvement and does require dose adjustment in subjects with PN (see section 4.2).

Paediatric population

Atopic dermatitis
In the population PK analysis, no clinically relevant difference in the pharmacokinetics of nemolizumab was estimated in paediatric subjects 12-17 years of age compared to adults. Dose adjustment in this population is not recommended.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

The mutagenic potential of nemolizumab has not been evaluated; however monoclonal antibodies are not expected to alter DNA or chromosomes.

Carcinogenicity studies have not been conducted with nemolizumab. Evaluation of the available evidence related to IL-31 inhibition and animal toxicology data does not suggest carcinogenic potential.

No effects on fertility parameters were observed in sexually mature cynomolgous monkeys after a long-term subcutaneous treatment with nemolizumab. In the group of dams treated with 25 mg/kg of nemolizumab every two weeks from early organogenesis to delivery, a slight increase in the incidence of offspring death was observed during the early postnatal period. The dams exposures (AUC) were 43- or 34-fold higher than human exposure at maximum recommended human dose in AD or PN patients respectively. A relation of this finding to nemolizumab cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection

Sucrose
Trometamol
Trometamol hydrochloride (for pH-adjustment)
Arginine hydrochloride
Poloxamer 188

Solvent

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

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen

3 years

Once reconstitution steps are completed, Nemluvio must be used within 4 hours kept at room temperature (up to 25°C) or discarded.

If necessary, the carton containing the pre-filled pen can be removed from the refrigerator and kept at room temperature (up to 25°C) for a single period up to 90 days. The date of removal from the refrigerator shall be recorded in the space provided on the outer carton. Do not use Nemluvio if the expiry date has passed or if left out of the refrigerator for more than 90 days (whichever is earlier).

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

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

6.5 Nature and contents of container

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen

Single-use dual-chamber borosilicate glass type 1 cartridge in an auto-injector, with a stainless steel staked needle.

Pack size: 1 pre-filled pen, multipack containing 2 (2 packs of 1) pre-filled pens, multipack containing 3 (3 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for the administration of Nemluvio in a pre-filled pen are given at the end of the package leaflet.

Nemluvio must be removed from the refrigerator for 30-45 min before reconstitution.

Inspect Nemluvio visually prior to reconstitution. Do not use if powder is not white, or if liquid is cloudy, or particulate matter is visible. Prior to administration, check that the solution is clear and colourless to slightly yellow and does not contain particles.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Galderma International
La Defense 4, Tour Europlaza
20 Avenue Andre Prothin
92927 Paris La Defense Cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1901/001
EU/1/24/1901/002
EU/1/24/1901/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 february 2025

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/en.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) 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. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

Chugai Pharma Manufacturing Co. Ltd.
5-5-1 Ukima
Kita
115-0051 Tokyo
Japan

Name and address of the manufacturer(s) responsible for batch release

Q-Med AB
Seminariegatan 21
Uppsala Lan
752 28 Uppsala
Sweden

Nuvisan France S.A.R.L.
2400 Route Des Colles
06410 Biot
France

Galderma Laboratorium GmbH
Toulouser Allee 23a
40211 Duesseldorf
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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.

An updated RMP shall be submitted by {CHMP agreed deadline}.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen
nemolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 30 mg of nemolizumab per 0.49 ml dose after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: sucrose, trometamol, trometamol hydrochloride, arginine hydrochloride, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection



1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneouse use after reconstitution.
For single use only.

IMPORTANT: Read the package leaflet before use.
This pen requires specific steps before injection.

Press to open

To be printed on the carton inner partition:

IMPORTANT: Read the package leaflet before use.
This pen requires specific steps before injection.

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
After reconstitution, Nemluvio must be used within 4 hours or discarded.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original carton in order to protect from light.

Nemluvio can be stored at room temperature (up to 25°C) for a single period of up to 90 days.

Date removed from the refrigerator: __/__/__

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

Galderma International
La Defense 4, Tour Europlaza
20 Avenue Andre Prothin
92927 Paris La Defense Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1901/001 1 pre-filled pen

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nemluvio pen

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 OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen
nemolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

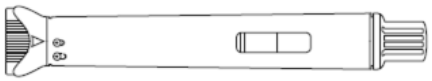
Each pre-filled pen contains 30 mg of nemolizumab per 0.49 ml dose after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: sucrose, trometamol, trometamol hydrochloride, arginine hydrochloride, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

 x 2

Multipack: 2 (2 packs of 1) pre-filled pens

 x 3

Multipack: 3 (3 packs of 1) pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneouse use after reconstitution.
For single use only.

IMPORTANT: Read the package leaflet before use.
This pen requires specific steps before injection.

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
After reconstitution, Nemluvio must be used within 4 hours or discarded.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original carton in order to protect from light.

Nemluvio can be stored at room temperature (up to 25°C) for a single period of up to 90 days.

Date removed from the refrigerator: __/__/__

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

Galderma International
La Defense 4, Tour Europlaza
20 Avenue Andre Prothin
92927 Paris La Defense Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1901/002	Multipack containing 2 (2 x 1) pre-filled pens
EU/1/24/1901/003	Multipack containing 3 (3 x 1) pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nemluvio pen

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

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen
nemolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 30 mg of nemolizumab per 0.49 ml dose after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: sucrose, trometamol, trometamol hydrochloride, arginine hydrochloride, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
1 pre-filled pen
Component of a multipack, can't be sold separately.



5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneouse use after reconstitution.
For single use only.

IMPORTANT: Read the package leaflet before use.
This pen requires specific steps before injection.

Press to open

To be printed on the carton inner partition:

IMPORTANT: Read the package leaflet before use.
This pen requires specific steps before injection.

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
After reconstitution, Nemluvio must be used within 4 hours or discarded.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original carton in order to protect from light.

Nemluvio can be stored at room temperature (up to 25°C) for a single period of up to 90 days.

Date removed from the refrigerator: __/__/__

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

Galderma International
La Defense 4, Tour Europlaza
20 Avenue Andre Prothin
92927 Paris La Defense Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1901/002	Multipack containing 2 (2 x 1) pre-filled pens
EU/1/24/1901/003	Multipack containing 3 (3 x 1) pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nemluvio pen

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

PEN LABEL

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

Nemluvio 30 mg
Powder and solvent for solution for injection
nemolizumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

Must be dissolved prior to use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen
nemolizumab

▼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.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Nemluvio is and what it is used for

Nemluvio contains the active substance nemolizumab, a monoclonal antibody (a specialised protein that recognises and attaches to a specific target).

Nemluvio is used in adults and adolescents 12 years of age and older to treat moderate-to-severe atopic dermatitis (also known as atopic eczema, when the skin is itchy, red and dry). It can be used when patients can be treated with systemic treatments (a medicine given by mouth or injection).

Nemluvio is also used in adults to treat moderate-to-severe prurigo nodularis (PN), also known as chronic nodular prurigo (CNPG), a long-term skin condition associated with a rash causing itchy bumps . It is used when patients can be treated with systemic treatments.

Nemolizumab, the active substance in Nemluvio, blocks the action of a protein called interleukin (IL)-31. IL-31 plays a major role in the skin inflammation and itching seen in people with atopic dermatitis and prurigo nodularis. By blocking IL-31, this medicine can reduce these symptoms .

2. What you need to know before you use Nemluvio

Do not use Nemluvio
- if you are allergic to nemolizumab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic, or you are not sure, ask your doctor, pharmacist or nurse for advice before using Nemluvio.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Nemluvio.

Traceability
It is important to keep a record of the batch number of your Nemluvio. Every time you get a new package of Nemluvio, note the date and the batch number (which is stated on the package after "Lot") and keep the information in a safe place.

Allergic reactions
Nemluvio can cause allergic (hypersensitivity) reactions, and these may be serious. Allergic reactions can occur shortly after you take this medicine, but may also happen later. You must look out for signs of these reactions while you are using Nemluvio. These may include:
- breathing problems
- swelling of the face, mouth, and tongue
- fainting, dizziness or feeling lightheaded due to low blood pressure
- hives
- itching
- skin rash

If you notice any signs of an allergic reaction, stop using Nemluvio and tell your doctor or seek medical help immediately.

Worsening asthma
If you have a severe respiratory condition like asthma, chronic obstructive pulmonary disease (COPD) or chronic bronchitis, tell your doctor before using Nemluvio. If your respiratory condition gets worse after you start Nemluvio treatment, tell your doctor immediately.

Vaccination
It is advised that you have completed the vaccinations plan recommended for you before you start taking Nemluvio. You should avoid vaccination with so-called live vaccines when using Nemluvio. Talk to your doctor regarding your current vaccinations plan.

Children and adolescents
- Do not give this medicine to children with atopic dermatitis below the age of 12 years and body weight below 30 kg; it has not been studied in this age group.
- Do not give this medicine to children and adolescents with prurigo nodularis below the age of 18 years; it has not been studied in this age group.

Other medicines and Nemluvio
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. Tell your doctor or pharmacist if you have recently had or are due to have a vaccination.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
The effects of this medicine in pregnant women are not known; therefore, it is preferable to avoid the use of Nemluvio during pregnancy unless your doctor advises you to use it.

Breast-feeding
It is not known whether Nemluvio passes into breast milk. Nemluvio may pass into breast milk in the first days after birth. You should therefore tell your doctor if you are breast-feeding or plan to breast-feed, so you and your doctor can decide if you can be given Nemluvio.

Driving and using machines
Nemluvio is unlikely to influence your ability to drive and use machines.

3. How to use Nemluvio

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
Treatment should be started and supervised by a doctor who has experience in the diagnosis and treatment of atopic dermatitis and prurigo nodularis.

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

Adults and adolescents patients with atopic dermatitis (12 years of age and older)
The recommended dose of Nemluvio is:
- A first dose of 60 mg (two 30 mg injections)
- Next doses of 30 mg every 4 weeks for 16 weeks

After 16 weeks of treatment, your doctor will check how well the medicine works for you. If your doctor decides that you will benefit from continued use of this medicine, you will continue on a 30 mg dose every 8 weeks.

Nemluvio can be used with or without eczema medicines used on the skin (topical).

Adults with prurigo nodularis (PN)
The recommended dose is based on body weight.

If you weigh less than 90 kg:
- A first dose of 60 mg (two 30 mg injections)
- Next doses of 30 mg every 4 weeks.

If you weigh 90 kg or more:
- A first dose of 60 mg (two 30 mg injections)
- Next doses of 60 mg (two 30 mg injections) every 4 weeks.

After 16 weeks of treatment, your doctor will check how well the medicine works for you, to decide if you will benefit from continued use of this medicine.

How to use Nemluvio
Carefully read the instructions for use before using Nemluvio. These are included at the end of this package leaflet. The instructions present step by step how you should use this medicine.

Nemluvio is given as an injection under your skin (subcutaneous injection) using the pre-filled pen. It should be injected into the front upper thigh or belly, avoiding a 5 cm area around the navel. If somebody else gives the injection, it can also be given into the upper arm.

You and your doctor or nurse will decide if you can inject this medicine yourself. Inject yourself only after you have been trained by your doctor or nurse. A caregiver may also give you your injection after proper training.

It is recommended that you change the injection site with each injection. Nemluvio should not be injected into skin that is tender, inflamed, swollen, sensitive or damaged, or skin that has bruises, scars or open wounds.

If you use more Nemluvio than you should
If you have used more Nemluvio than you should, or if you have taken the next dose too soon, talk to your doctor, pharmacist or nurse.

If you forget to use Nemluvio
Do not take a double dose to make up for a forgotten dose. If you forget to inject a dose of Nemluvio, take it as soon as possible, and then continue with your original schedule.

If you stop using Nemluvio
Do not stop using Nemluvio without speaking to your doctor first.

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

4. Possible side effects

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

Serious side effects

Common (may affect up to 1 in 10 people)
Nemluvio can cause allergic (hypersensitivity) reactions.
Stop using Nemluvio and tell a doctor or seek medical help immediately if you notice any signs of an allergic reaction. Signs may include:
- breathing problems
- swelling of the face, mouth, and tongue
- fainting, dizziness, feeling lightheaded due to low blood pressure
- hives
- itching
- skin rash

Other side effects

Common (may affect up to 1 in 10 people)
- Fungal skin infections such as ringworm of the body (body tinea) or athlete's foot (tinea pedis), fungal infection of the nail and jock itch
- Headache
- Worsening of asthma (in people with pre-existing asthma)
- Eczema
- Atopic dermatitis (itchy, red and dry skin in people prone to allergies)
- Discoid eczema (eczema nummular) (skin condition that causes itchy, dry, round or oval-shaped patches of inflammaed skin)
- Injection site reactions, including redness, itching, bruising, pain, irritation and swelling at the injection site

Uncommon (may affect up to 1 in 100 people)
- Increased number of white blood cells, which can be seen in blood test (eosinophilia)
- Blisters or fluid-filled spots on skin (signs of a skin condition called bullous pemphigoid)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Nemluvio

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

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

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

If necessary, Nemluvio may be kept at room temperature (up to 25°C) for a single period of up to 90 days. Write the date the pen was removed from the refrigerator in the space provided on the outer carton. Do not use Nemluvio if the expiry date has passed or 90 days after the date it was removed from the refrigerator (whichever is earlier).

Once the reconstitution steps are completed, Nemluvio must be used within 4 hours or discarded.

Do not use this medicine if you notice that the powder is not white.

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 Nemluvio contains
- The active substance is nemolizumab. Each single-use pre-filled pen contains 30 mg of nemolizumab.
- The other ingredients are:
  - *Powder:* sucrose, trometamol, trometamol hydrochloride (for pH-adjustment), arginine hydrochloride, poloxamer 188.
  - *Solvent:* water for injections.

What Nemluvio looks like and contents of the pack
Nemluvio powder and solvent for solution for injection in pre-filled pen consists of a single-use pre-filled pen enclosing a glass cartridge supplying a white powder and a clear, colourless liquid. The liquid is not visible from the inspection window before dissolving.

Nemluvio is available as 30 mg pre-filled pen in a pack containing 1 pre-filled pen or in multipacks comprising 2 or 3 cartons, each containing 1 pre-filled pen.

Not all pack sizes may be marketed.

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France

Manufacturers
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752 28 Uppsala
Sweden

Nuvisan France S.A.R.L.
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06410 Biot
France

Galderma Laboratorium GmbH
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40211 Duesseldorf
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

Other sources of information

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

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Instructions for use

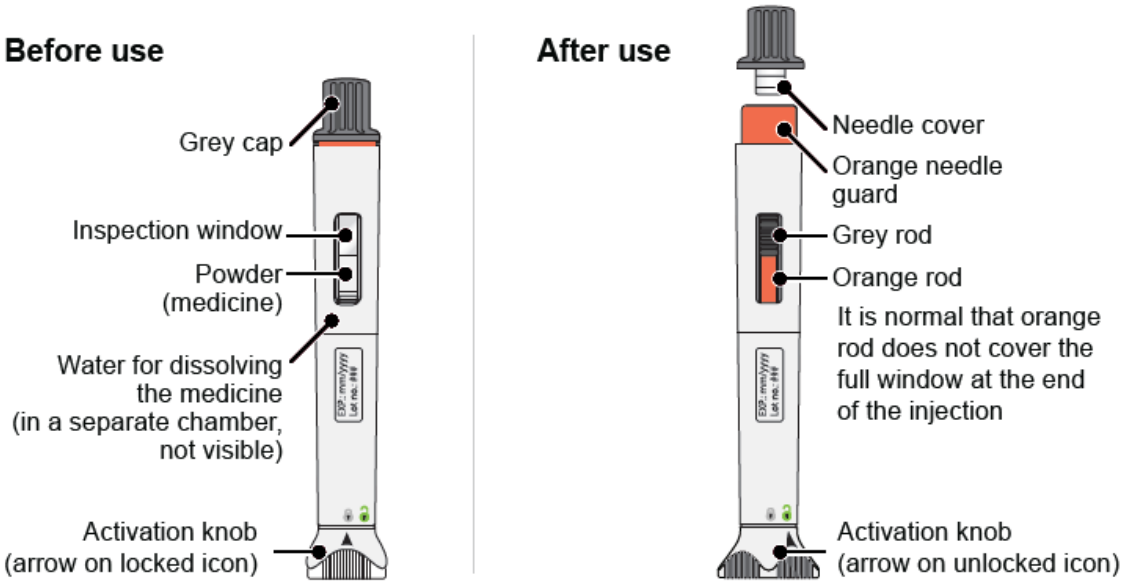
IMPORTANT: Read the package leaflet before use.
This pen requires specific steps before injection.

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen
(nemolizumab)

Do not inject yourself or someone else until you have been trained by a healthcare professional on how to inject Nemluvio.

Contact your healthcare professional if you have any questions.
Nemluvio is supplied as a single-use, pre-filled dual-chamber pen (called “Nemluvio pen” or “pen” in these instructions).
The pen contains two chambers, one with medicine (the powder) and one with water for dissolving the powder.
Before you can inject the medicine, you must mix the powder with the water, following the description below.

Device Overview
Nemluvio pre-filled dual-chamber pen



<u>Important Information</u>

What you need to know before use
- Read all the instructions carefully before using the Nemluvio pen.
- **Mark your calendar** ahead of time to remember when to take Nemluvio
- Follow all steps exactly as described. This makes sure that you get the correct dose of medicine.
- **Do not** use the Nemluvio pen if it has been dropped on a hard surface or is damaged, cracked or broken.

Storage Information
- **Keep the Nemluvio pen and all medicines out of the reach and sight of children.**
- Store the Nemluvio pen in the refrigerator between 2°C to 8°C.
- **Do not** freeze the Nemluvio pen.
- Store the Nemluvio pen in the original carton to protect it from light.

- The Nemluvio pen can be stored in the original package at room temperature up to 25°C for a single period of up to 90 days. If removed from the refrigerator, write down the date of removal on the carton, and use Nemluvio within 90 days.
- **Do not** use Nemluvio if the expiry date has passed or 90 days after the date it was removed from the refrigerator (whichever is earlier).
- Once the reconstitution steps are completed, Nemluvio must be used within 4 hours.

A. Preparing to inject Nemluvio

Step 1: Let Nemluvio reach room temperature

Injecting cold medicine might result in pain at the injection site. Take the Nemluvio carton out of the refrigerator and let it come to room temperature for 30 to 45 minutes before starting Step 2.

Do not:

- warm the pen with any heat source (such as microwave, direct sunlight). This might damage Nemluvio.
- directly expose the pen to liquids.

Note: In some cases, your doctor may prescribe two pens for use at the same time. If this applies to you, take out two pens and use one pen after the other.

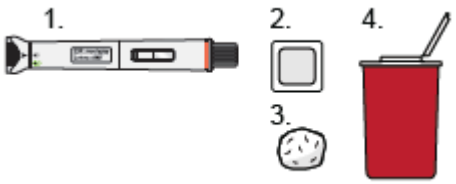
Step 2: Wash your hands with soap and dry your hands properly.

Step 3: Prepare the supplies

Remove the pen from the carton and place the following on a clean, flat and well-lit surface:

- Pen with medicine
- Alcohol wipes*
- Gauze pads or cotton balls*
- Sharps disposal container*

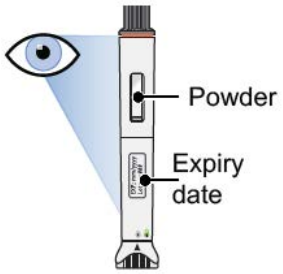
*Items not included in the carton.



Step 4: Check the Nemluvio pen to make sure:

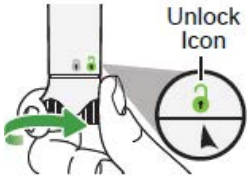
- The expiring date has **not** passed.
- The powder is white and **not** dissolved.
- The pen has **not** been dropped and is **not** damaged or cracked.

Do not use the pen unless all conditions above are met. If any condition is **not** met, throw away the pen and use a new one (see Step 13.5 "Throw away").



Step 5: Activate the Nemluvio pen

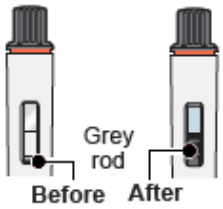
Hold the pen upright and turn activation knob to the right until it stops.
This starts the process of transferring water to the powder chamber.



Step 6: Wait until grey rod stops moving

Watch inspection window until grey rod has stopped moving.

Do not shake the pen before the grey rod has completely stopped to enable accurate dosing.



Step 7: Shake to dissolve the medicine

When the grey rod has completely stopped, shake the pen up and down for 30 seconds.



Step 8: Wait 5 minutes for bubbles to decrease

Wait for bubbles to decrease and the powder to dissolve completely. This will take about 5 minutes.



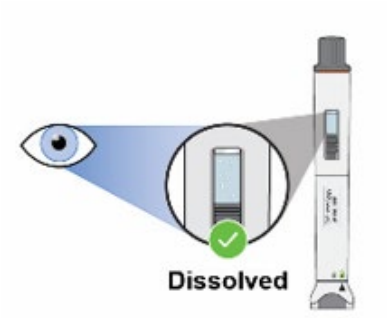
Note: If the medicine has not dissolved completely, shake again for 30 seconds and then wait 5 minutes.

Note: It is normal for a small foam layer or a few small air bubbles to remain in the dissolved medicine.

Step 9: Check the medicine in the inspection window

Check that the dissolved medicine:

- Is clear and colourless to slightly yellow,
- Does not contain particles.



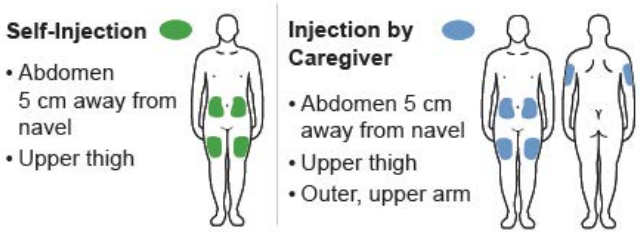
Do not use the pen if the dissolved medicine is cloudy or contains any particles.
Throw away the pen and use a new one (see Step 13.5 “Throw away”).

Note: After the medicine has dissolved, it must be used within 4 hours. During this time, it should be kept at room temperature (up to 25°C). If you have not used it within 4 hours, throw it away.

B. Injecting Nemluvio

Step 10: Select one injection site

You can self-inject in the abdomen or in the upper thigh.
A caregiver can also give the injection in the outer upper arm.



Where not to inject:

- Near your waistline or about 5 cm around the navel.
- Into tender, bruised, red skin, or areas with scars or stretch marks.
- Twice into the same site (for example, within 2.5 cm).

Step 11: Clean the injection site

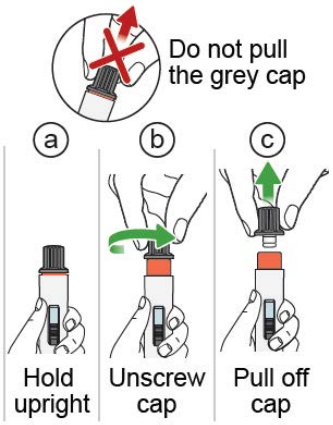


- Always use a new alcohol wipe to clean the injection site. This avoids contamination and infection.
- Let the skin **air dry**.

Do not:

- touch the injection site after cleaning.
- fan or blow air on the cleaned injection site.
- reuse the alcohol wipe.

Step 12: Twist the grey cap of to expose the needle guard



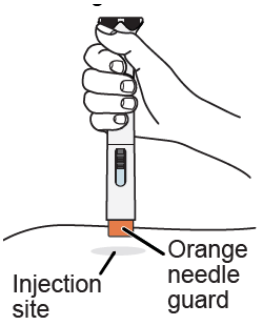
- **Hold** the pen **upright** to avoid leakage
- Unscrew the grey cap until the orange needle guard pops up.
- Gently pull the cap off the orange needle guard.
- After cap removal, please throw away the cap in a sharps disposal container (see Step 13.5 “Throw away”).

Do not:

- pull the grey cap when unscrewing to avoid damaging the device.
- touch the orange needle guard.

Note: If the cap cannot be removed, refer back to **Step 5** and make sure activation knob is turned completely to the right until it stops.

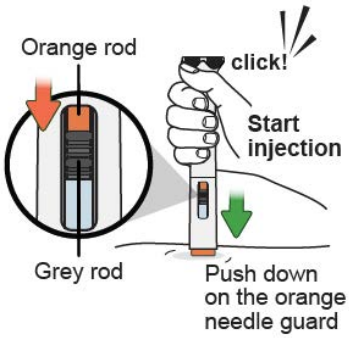
Step 13: Injection of the medicine

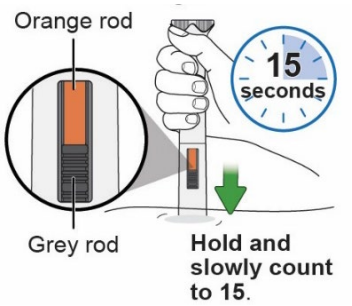


1. **Place the pen on the injection site vertically s**o that the orange needle guard is flat against the skin.

Note: Make sure you can easily see the inspection window during injection.

2. **Gently push the pen down until orange needle guard is completely pushed in**. The injection starts right away with a click. The orange rod and grey rod should be moving. **Keep pushing the pen down for 15 seconds.**





3. **Check inspection window** to make sure orange rod and grey rod have stopped. This means the injection has been completed.

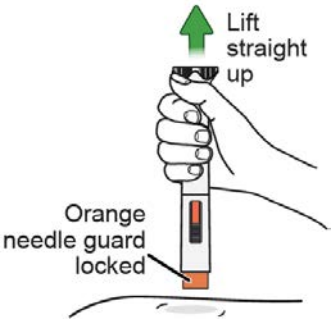
Do not lift pen until orange rod and grey rod have stopped moving.
If the orange rod is not visible please throw away the pen and use a new one (see Step 13.5 "Throw away").

Note: It is normal that the orange rod does not cover the whole inspection window at the end of injection.

4. **Lift the pen straight up** from your skin. The orange needle guard locks into place to cover the needle.

Note: If there is bleeding, press a cotton ball or gauze over the injection site.

Do not rub the injection site.



5. **Throw away** the used pen and the grey cap in a sharps disposal container right away after use. Avoid contact with the needle.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for nemolizumab, the scientific conclusions of PRAC are as follows:

In view of available data on Bullous Pemphigoid (BP) from the literature, spontaneous reports and clinical trial(s), including

- at least 12 possible cases of BP with close temporal relationship, confirmed BP diagnosis and recovery (with treatment) following withdrawal;
- and 2 probable literature cases with a close temporal relationship, confirmed BP diagnosis and recovery (with treatment) following withdrawal, without reoccurrence of BP after withdrawal, supportive anti-BP 180 data and excluding the influence of most confounding factors;
- although the potential mechanism of the AE remains to be elucidated;

the PRAC considers a causal relationship between nemolizumab and Bullous Pemphigoid is at least a reasonable possibility. The PRAC concluded that the product information of products containing nemolizumab should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for nemolizumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing nemolizumab is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.