ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Caprelsa 100 mg film-coated tablets
Caprelsa 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Caprelsa 100 mg tablets
Each film-coated tablet contains 100 mg of vandetanib.

Caprelsa 300 mg tablets
Each film-coated tablet contains 300 mg of vandetanib.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Caprelsa 100 mg tablets
The Caprelsa 100 mg tablet is a round, biconvex, white film-coated tablet with 'Z100' impressed on one side.

Caprelsa 300 mg tablets
The Caprelsa 300 mg tablet is an oval-shaped, biconvex, white film-coated tablet with 'Z300' impressed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Caprelsa is indicated for the treatment of aggressive and symptomatic Rearranged during Transfection (RET) mutant medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

Caprelsa is indicated in adults, children and adolescents aged 5 years and older.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in treatment of MTC and in the use of anticancer medicinal products and experienced in the assessment of electrocardiogram (ECG).

Rearranged during transfection (RET) status
Since the activity of Caprelsa, based on available data, is considered insufficient in patients with no identified RET mutation, the presence of a RET mutation should be determined by a validated test prior to initiation of treatment with Caprelsa. When establishing RET mutation status, tissue samples should be obtained if possible at the time of initiation of treatment rather than at the time of diagnosis.

Posology for MTC in adult patients
The recommended dose is 300 mg once a day, taken with or without food at about the same time each day.

If a dose is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.

Dose adjustments in adult patients with MTC
QTc interval should be carefully assessed prior to initiation of treatment. In the event of common terminology criteria for adverse events (CTCAE) grade 3 or higher toxicity or prolongation of the ECG QTc interval, dosing with vandetanib should be at least temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1 (see section 4.4). The 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets), and then to 100 mg if necessary. The patient must be monitored appropriately. Due to the 19-day half-life, adverse reactions including a prolonged QTc interval may not resolve quickly (see section 4.4).

Posology in paediatric patients with MTC
Dosing for paediatric patients should be on the basis of BSA in mg/m^2. Paediatric patients treated with Caprelsa and patients' caregivers must be given the dosing guide and be informed on the correct dose to be taken with the initial prescription and each subsequent dose adjustment. Recommended dosing regimens and dose modifications are presented in Table 1.

Table 1: Dosing nomogram for paediatric patients with MTC

BSA (m^2)	Start dose (mg)[a]	Dose increase (mg)[b] when tolerated well after 8 weeks at starting dose	Dose reduction (mg) [c]
0.7 - <0.9	100 every other day	100 daily	-
0.9 - <1.2	100 daily	7 day schedule: 100-200-100-200-100-200-100	100 every other day
1.2 - <1.6	7 day schedule: 100-200-100-200-100-200-100	200 daily	100 daily
≥ 1.6	200 daily	300 daily	7 day schedule: 100-200-100-200-100-200-100

[a] The starting dose is the dose at which treatment should be initiated
[b] Higher vandetanib doses than 150 mg/m2 have not been used in clinical studies in paediatric patients
[c] Patients with an adverse reaction requiring a dose reduction should stop taking vandetanib for at least a week. Dosing can be resumed at a reduced dose thereafter when fully recovered from adverse reactions

Dose adjustments in paediatric patients with MTC
- In the event of CTCAE grade 3 or higher toxicity or prolongation of the ECG QTc interval, dosing with vandetanib should be at least temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1.
- Patients who are on the starting dose ([a] in Table 1), should be recommenced at the reduced dose ([c] in Table 1).
- Patients who are on the increased dose ([b] in Table 1), should be recommenced at the starting dose ([a] in Table 1). If another event of common terminology criteria for adverse events (CTCAE) grade 3 or higher toxicity or prolongation of the ECG QTc interval occurs, dosing with Caprelsa should be at least temporarily stopped and resumed at a reduced dose ([c] in Table 1) when toxicity has resolved or improved to CTCAE grade 1.
- If a further event of CTCAE grade 3 or higher toxicity or prolongation of the ECG QTc interval occurs, dosing with vandetanib should be permanently stopped.

The patient must be monitored appropriately. Due to the 19-day half-life, adverse reactions including a prolonged QTc interval may not resolve quickly (see section 4.4).

Duration
Vandetanib may be administered until disease progression or until the benefits of treatment continuation do no longer outweigh its risk, thereby considering the severity of adverse events (see section 4.8) in relation to the degree of clinical stabilization of the tumour status.

Special patient populations
Paediatric population
Caprelsa should not be given to children below 5 years of age. The safety and efficacy of Caprelsa in children below 5 years of age have not been established. No data are available.
There is no experience in paediatric patients with hereditary MTC below 9 years of age (see section 5.1). Patients aged 5-18 years should be dosed according to the nomogram in Table 1. Vandetanib doses higher than 150 mg/m2 have not been used in clinical studies in paediatric patients.

Elderly
No adjustment in starting dose is required for elderly patients. There is limited clinical data with vandetanib in patients with MTC aged over 75.

Renal impairment in adult patients with MTC
A pharmacokinetic study in volunteers with mild, moderate and severe renal impairment shows that exposure to vandetanib after single dose is increased up to 1.5, 1.6 and 2-fold respectively in patients with mild, moderate (creatinine clearance ≥ 30 to < 50 ml/min) and severe (clearance below 30 ml/min) renal impairment at baseline (see section 5.2). Clinical data suggest that no change in starting dose is required in patients with mild renal impairment. There is limited data with 300 mg in patients with moderate renal impairment: the dose needed to be lowered to 200 mg in 5 out of 6 patients due to an adverse reaction of QT prolongation. The starting dose should be reduced to 200 mg in patients with moderate renal impairment; safety and efficacy have however not been established with 200 mg (see section 4.4). Vandetanib is not recommended for use in patients with severe renal impairment since there is limited data in patients with severe renal impairment, and safety and efficacy have not been established.

Renal impairment in paediatric patients with MTC
There is no experience with the use of vandetanib in paediatric patients with renal impairment. Considering the data available in adult patients with renal impairment:

- No change in starting dose is recommended in paediatric patients with mild renal impairment
- The reduced dose as specified in Table 1 should be used in paediatric patients with moderate renal impairment. Individual patient management will be required by the physician, especially in paediatric patients with low BSA.
- Vandetanib is not recommended in paediatric patients with severe renal impairment

Hepatic impairment
Vandetanib is not recommended for use in adult and paediatric patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of reference range (ULRR), this criterion does not apply to patients with Gilbert's Disease-and alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) greater than 2.5 times ULRR, or greater than 5.0 times ULRR if judged by the physician to be related to liver metastases), since there is limited data in patients with hepatic impairment, and safety and efficacy have not been established (see section 4.4).

Pharmacokinetic data from volunteers, suggests that no change in starting dose is required in patients with mild, moderate or severe hepatic impairment (see section 5.2).

Method of administration
Caprelsa is for oral use. For patients who have difficulty swallowing, vandetanib tablets may be dispersed in half a glass of non-carbonated drinking water. No other liquids should be used. The tablet is to be dropped in water, without crushing, stirred until dispersed (approximately 10 minutes) and the resultant dispersion swallowed immediately. Any residues in the glass are to be mixed with half a

glass of water and swallowed. The liquid can also be administered through nasogastric or gastrostomy tubes.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Congenital long QTc syndrome.
- Patients with a QTc interval over 480 msec.
- Concomitant use of vandetanib with the following medicinal products known to also prolong the QTc interval and/or induce Torsades de pointes: Arsenic, cisapride, erythromycin intravenous (IV), toremifene, mizolastine, moxifloxacin, Class IA and III antiarrhythmics (see section 4.5).
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

In view of the associated risks, it is important to limit treatment with vandetanib to patients who are in real need for treatment, i.e. with a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need of treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin (CTN) and/or carcinoembryonic antigen (CEA) as well as the rate of change of tumour volume during watchful waiting might help to identify not only patients in need for treatment but also the optimal moment to commence treatment with vandetanib.

QTc prolongation and Torsades de Pointes

Vandetanib at a dose of 300 mg is associated with a substantial and concentration dependent prolongation in QTc (mean 28 msec, median 35 msec). First QTc prolongations occurred most often in the first 3 months of treatment, but continued to first occur after this time. The half-life of vandetanib (19 days) renders this prolongation in QTc interval particularly problematic (see section 4.8). At a dose of 300 mg per day in MTC, ECG QTc prolongation to above 500 msec was observed in a phase III study in 11% of patients. ECG QTc prolongation appears to be dose-dependent. Torsades de pointes and ventricular tachycardia have been uncommonly reported in patients administered vandetanib 300 mg daily. The risk of Torsades may be increased in patients with electrolyte imbalance (see section 4.8).

Vandetanib treatment must not be started in patients whose ECG QTc interval is greater than 480 msec. Vandetanib should not be given to patients who have a history of Torsades de pointes**.** Vandetanib has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

An ECG, and levels of serum potassium, calcium and magnesium and thyroid stimulating hormone (TSH) should be obtained at baseline, at 1, 3, 6 and 12 weeks after starting treatment and every 3 months for at least a year thereafter. This schedule should apply to the period after dose reduction due to QTc prolongation and after dose interruption for more than two weeks. ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards. Frequent ECG monitoring of the QTc interval should be continued.

Serum potassium, serum magnesium and serum calcium should be kept within normal range to reduce the risk of ECG QTc prolongation. Additional monitoring of QTc, electrolytes and renal function are required especially in case of diarrhoea, increase in diarrhoea/dehydration, electrolyte imbalance and/or impaired renal function. If QTc increases markedly but stays below 500 msec, cardiologist advice should be sought.

The administration of vandetanib with substances known to prolong the ECG QTc interval is contraindicated or not recommended (see sections 4.3 and 4.5).

The concomitant use of vandetanib with ondansetron is not recommended (see section 4.5)

Patients who develop a single value of a QTc interval of ≥500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made.

Posterior reversible encephalopathy syndrome, PRES (Reversible posterior leukoencephalopathy syndrome-RPLS)
PRES is a syndrome of subcortical vasogenic oedema diagnosed by a MRI of the brain, has been observed infrequently with vandetanib treatment in combination with chemotherapy. PRES has also been observed in patients receiving vandetanib as monotherapy. This syndrome should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status.

Severe Cutaneous Adverse Reactions (SCARs) and other skin reactions
SCARs, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be life-threatening or fatal, have been reported in association with vandetanib treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. For suspected SJS or TEN, vandetanib should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, vandetanib should be permanently discontinued and an alternative treatment considered (as appropriate).

Photosensitivity reactions have been observed in patients who have received vandetanib. Care should be taken with sun exposure by wearing protective clothing and/or sunscreen due to the potential risk of phototoxicity reactions associated with vandetanib treatment.

Mild to moderate skin reactions can be managed by symptomatic treatment, or by dose reduction or interruption.

Diarrhoea
Diarrhoea is a disease related symptom as well as a known undesirable effect of vandetanib. Routine anti-diarrhoeal agents are recommended for the treatment of diarrhoea. QTc and serum electrolytes should be monitored more frequently. If severe diarrhoea (CTCAE grade 3-4) develops, vandetanib should be stopped until diarrhoea improves. Upon improvement, treatment should be resumed at a reduced dose (see sections 4.2 and 4.8).

Haemorrhage
Caution should be used when administering vandetanib to patients with brain metastases, as intracranial haemorrhage has been reported.

Heart failure
Heart failure has been observed in patients who received vandetanib. Temporary or permanent discontinuation of therapy may be necessary in patients with heart failure. It may not be reversible on stopping vandetanib. Some cases have been fatal.

Hypertension
Hypertension, including hypertensive crisis, has been observed in patients treated with vandetanib. Patients should be monitored for hypertension and controlled as appropriate. If high blood pressure cannot be controlled with medical management, vandetanib should not be restarted until the blood pressure is controlled medically. Reduction in dose may be necessary (see section 4.8).

Wound healing complications
No formal studies of the effect of vandetanib on wound healing have been conducted. Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF signalling pathway and has been reported in patients receiving vandetanib. Although evidence for an optimal duration of treatment interruption prior to scheduled surgery is very limited, temporary interruption of vandetanib should be

considered for at least 4 weeks prior to elective surgery based on individual benefit-risk. The decision to resume vandetanib following a major surgical procedure should be based on clinical judgment of adequate wound healing.

Osteonecrosis
Cases of osteonecrosis, including cases of osteonecrosis of the jaw, have been reported in patients treated with vandetanib. Some cases were reported in patients who had received prior or concomitant treatment with antiresorptive bone therapy. An oral examination should be performed prior to initiation of vandetanib and periodically during vandetanib therapy. Patients should be advised regarding oral hygiene practice. If possible, vandetanib treatment should be held at least 4 weeks prior to scheduled dental surgery or invasive dental procedures, especially in patients receiving agents associated with osteonecrosis, such as bisphosphonates. Vandetanib discontinuation should be considered in patients who experience osteonecrosis (see section 4.8).

Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating vandetanib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Renal failure
Renal failure has been reported in patients treated with vandetanib (see section 4.8). Dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Vandetanib exposure is increased in patients with impaired renal function. Vandetanib starting dose should be reduced to 200 mg in patients with moderate renal impairment (creatinine clearance ≥30 to <50 mL/min) and the QT interval should be closely monitored.

Vandetanib is not recommended for use in patients with severe renal impairment (clearance below 30 mL/min) (see sections 4.2, 5.1, and 5.2). There is no information available for patients with end-stage renal disease requiring dialysis.

Patients with hepatic impairment
Vandetanib is not recommended for use in patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of normal), since there is limited data in patients with hepatic impairment, and safety and efficacy have not been established. Pharmacokinetic data from volunteers, suggests that no change in starting dose is required in patients with mild, moderate or severe hepatic impairment (see sections 4.2 and 5.2).

Alanine aminotransferase elevations
Alanine aminotransferase elevations occur commonly in patients treated with vandetanib. The majority of elevations resolve while continuing treatment, others usually resolve after a 1-2 week interruption in therapy. Periodic monitoring of alanine aminotransferase is recommended.

Interstitial lung disease
Interstitial Lung Disease (ILD) has been observed in patients receiving vandetanib and some cases have been fatal. If a patient presents with respiratory symptoms such as dyspnoea, cough and fever, vandetanib treatment should be interrupted and prompt investigation initiated. If ILD is confirmed, vandetanib should be permanently discontinued and the patient treated appropriately.

CYP3A4 inducers
The concomitant use of vandetanib with strong CYP3A4 inducers (such as rifampicin, St John's Wort, carbamazepine, phenobarbital) should be avoided (see section 4.5).

CTN less than 500 pg/ml
The benefit of vandetanib in patients with CTN less than 500 pg/ml has not been determined, therefore use in patients with CTN < 500 pg/ml should be carefully considered because of the treatment related risks of vandetanib.

Paediatric population
Based on height measurements at all visits, all children and adolescents in a paediatric study demonstrated linear growth while receiving vandetanib. However, long term safety data in paediatric patients are not available.

Patient alert card
All prescribers of Caprelsa must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of Caprelsa therapy with the patient. The patient will be provided with the Patient Alert Card with each prescription.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Effect of vandetanib on other medicinal products
In healthy subjects, the exposure for midazolam (CYP3A4 substrate) was not affected when given together with a single dose of vandetanib at 800 mg.

Vandetanib is an inhibitor of the organic cation 2 (OCT2) transporter. In healthy subjects with wild type for OCT2, the $AUC_{(0-t)}$ and C_{max} for metformin (OCT2 substrate) were increased by 74% and 50%, respectively and CL_R of metformin was decreased by 52% when given together with vandetanib. Appropriate clinical and/or laboratory monitoring is recommended for patients receiving concomitant metformin and vandetanib, and such patients may require a lower dose of metformin.

In healthy subjects, the $AUC_{(0-t)}$ and C_{max} for digoxin (P-gp substrate) were increased by 23% and 29% respectively, when given together due to P-gp inhibition by vandetanib. Furthermore, the bradycardiac effect of digoxin may increase the risk of vandetanib QTc interval prolongation and Torsade de Pointes. Therefore, an appropriate clinical (e.g. ECG) and/or laboratory monitoring is recommended for patients receiving concomitant digoxin and vandetanib, and such patients may require a lower dose of digoxin. (For vandetanib monitoring, see sections 4.2 and section 4.4).

As regards other P-gp substrates such as dabigatran, a clinical monitoring is recommended in case of combination with vandetanib.

Effect of other medicinal products on vandetanib
In healthy subjects, no clinically significant interaction was shown between vandetanib (a single dose of 300mg) and the potent CYP3A4 inhibitor, itraconazole (repeated doses of 200mg once daily). In healthy male subjects, the exposure to vandetanib was reduced by 40% when given together with the potent CYP3A4 inducer, rifampicin. Administration of vandetanib with potent CYP3A4 inducers should be avoided.

In healthy subjects, the C_{max} for vandetanib was decreased by 15% while the $AUC_{(0-t)}$ for vandetanib was not affected when given together with omeprazole. Neither the C_{max} nor the $AUC_{(0-t)}$ for vandetanib was affected when given together with ranitidine. Therefore, no change in dose of vandetanib is required when vandetanib is given with either omeprazole or ranitidine.

Pharmacodynamic interactions
Biliary excretion of unchanged vandetanib is one of the excretion pathways for vandetanib. Vandetanib is not a substrate of multidrug resistance protein 2 (MRP2), p-glycoprotein (P-gp) or breast cancer resistance protein (BCRP).

Medicinal products known to prolong QTc interval
Vandetanib has been shown to prolong the ECG QTc interval; Torsades de pointes have been uncommonly reported. Therefore, the concomitant use of vandetanib with medicinal products known to also prolong the QTc interval and/or induce Torsades de pointes is either contraindicated or not recommended depending on existing alternative therapies.

- Combinations contraindicated (see section 4.3): Cisapride, erythromycin intravenous (IV), toremifene, mizolastine, moxifloxacin, arsenic, Class IA and III antiarrhythmics
- Combinations not recommended: Methadone, haloperidol, amisulpride, chlorpromazine, sulpiride, zuclopenthixol, halofantrine, pentamidine and lumefantrine.

If there is no appropriate alternative therapy, not recommended combinations with vandetanib may be made with additional ECG monitoring of the QTc interval, evaluation of electrolytes and further control at onset or worsening of diarrhoea.

Results of a pharmacodynamic and pharmacokinetic interaction study indicated that co-administration with ondansetron in healthy patients appeared to have little effect on the pharmacokinetics of vandetanib, but had a small additive effect on the prolongation of the QTc interval of approximately 10 ms. Therefore, the concomitant use of ondansetron with vandetanib is not recommended. If ondansetron is administered with vandetanib, closer monitoring of serum electrolytes and ECGs and aggressive management of any abnormalities is required.

Vitamin K antagonists
Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation is frequent. In consideration of the high intra-individual variability of the response to anticoagulation, and the possibility of interaction between vitamin K antagonists and chemotherapy, an increased frequency of the INR (International Normalised Ratio) monitoring is recommended, if it is decided to treat the patient with vitamin K antagonists.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males & females
Women of childbearing potential and fertile men must use effective contraception during therapy and for at least four months following the last dose.

Pregnancy
There is a limited amount of data on the use of vandetanib during pregnancy. As expected from its pharmacological actions, vandetanib has shown significant effects on all stages of female reproduction in rats (see section 5.3).

If vandetanib is used during pregnancy or if the patient becomes pregnant while receiving vandetanib, she should be apprised of the potential for foetal abnormalities or loss of the pregnancy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the foetus.

Breast-feeding
There are no data on the use of vandetanib in breast-feeding women. Vandetanib and/or its metabolites is excreted into milk in rats and found in plasma of pups following dosing to lactating rats (see section 5.3).

Breast-feeding is contraindicated while receiving vandetanib therapy.

Fertility
There are no data on the effect of vandetanib on human fertility. Results from animal studies indicate that vandetanib can impair male and female fertility (see section 5.3).

Effects on reproduction in paediatric patients treated with vandetanib are not known.

4.7 Effects on ability to drive and use machines

No studies to establish the effects of vandetanib on ability to drive and use machines have been conducted. However, fatigue and blurred vision have been reported and those patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions have been diarrhoea, rash, nausea, hypertension, and headache.

Tabulated list of adverse reactions

The following adverse reactions have been identified in clinical studies with patients receiving vandetanib as treatment for MTC and in post-marketing setting. Their frequency is presented in Table 2, adverse reactions using Council for International Organizations of Medical Sciences (CIOMS III), listed by MedDRA System Organ Class (SOC) and at the preferred term level and then by frequency classification. Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 2: Adverse reactions and system organ class				
System Organ Class	**Very common**	**Common**	**Uncommon**	**Not known**
Infection and infestation disorders	Nasopharyngitis bronchitis, upper respiratory tract infections, urinary tract infections	Pneumonia, sepsis, influenza, cystitis, sinusitis, laryngitis, folliculitis, furuncle, fungal infection, pyelonephritis	Appendicitis, staphylococcal infection, diverticulitis, cellulitis, abdominal wall abscess	
Endocrine disorders		Hypothyroidism		
Metabolism and nutrition disorders	Appetite decreased, Hypocalcaemia	Hypokalaemia, hypercalcaemia, hyperglycaemia, dehydration, hyponatremia	Malnutrition	
Psychiatric disorders	Insomnia, Depression	Anxiety		
Nervous system disorders	Headache, paraesthesia, dysaesthesia, dizziness	Tremor, lethargy, loss of consciousness, balance disorders, dysgeusia	Convulsion, clonus, brain oedema	
Eye disorders	Vision blurred, corneal structural change (including corneal deposits and corneal opacity)	Visual impairment, halo vision, photopsia, glaucoma, conjunctivitis, dry eye, keratopathy	Cataract, accommodation disorders	
Cardiac disorders	Prolongation of ECG QTc interval(*) (**)		Heart failure, acute heart failure, rate and rhythm disorders, cardiac conduction	

			disorders, ventricular arrhythmia and cardiac arrest	
Vascular disorders	Hypertension	Hypertensive crisis, ischaemic cerebrovascular conditions		Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders		Epistaxis, haemoptysis, pneumonitis	Respiratory failure, pneumonia aspiration	
Gastrointestinal disorders	Abdominal pain, diarrhoea, nausea, vomiting, dyspepsia	Colitis, dry mouth, stomatitis, dysphagia, constipation, gastritis, gastrointestinal haemorrhage	Pancreatitis, peritonitis, ileus, intestinal perforation, faecal incontinence	
Hepatobiliary disorders		Cholelithiasis		
Skin and subcutaneous tissue disorders	Photosensitivity reaction, rash and other skin reactions (including acne, dry skin, dermatitis, pruritus), nail disorders	Palmar-plantar erythrodysesthesia syndrome, alopecia	Bullous dermatitis	Stevens-Johnson syndrome/Toxic epidermal necrolysis (***), erythema multiforme
Musculoskeletal and connective tissue disorders				Osteonecrosis, osteonecrosis of the jaw
Renal and urinary disorders	Proteinuria, nephrolithiasis	Dysuria, haematuria, renal failure, pollakiuria, micturition urgency	Chromaturia, anuria	
General disorders and administration site conditions	Asthenia, fatigue, pain, oedema	Pyrexia	Impaired healing	
Investigations	ECG QTc interval prolonged	Increase of serum ALT and AST, weight decreased blood creatinine increased	Increased haemoglobin, serum amylase increased	

* 13.4% vandetanib patients had QTc (Bazett's) ≥ 500 ms compared with 1.0% placebo patients. QTcF prolongation was > 20 ms in over 91% of patients, > 60 ms in 35%, > 100 ms in 1.7%. Eight percent of patients had a dose reduction due to QTc prolongation.
** including two deaths in patients with QTc > 550 ms (one due to sepsis and one due to heart failure)
*** See section 4.4

Description of selected adverse reactions
Events such as Torsades de pointes, interstitial lung disease (sometimes fatal) and PRES (RPLS) have occurred in patients treated with vandetanib monotherapy. It is expected that these would be uncommon adverse reactions in patients receiving vandetanib for MTC.

Ocular events such as blurred vision are common in patients who received vandetanib for MTC. Scheduled slit lamp examinations have revealed corneal opacities (vortex keratopathies) in treated patients; however, routine slit lamp examinations are not required for patients receiving vandetanib.

At various exposure durations, median haemoglobin levels in patients treated with vandetanib were increased by 0.5-1.5 g/dl compared to baseline.

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.

Paediatric population
Paediatric clinical trial data with vandetanib in MTC (see section 5.1) obtained during drug development is limited to 16 patients aged 9 years to 17 years with hereditary medullary thyroid carcinoma (Study IRUSZACT0098). Whilst the study size is small owing to the rarity of MTC in children, it is considered representative of the target population. The safety findings in this study are consistent with the safety profile of vandetanib in adult patients with MTC. Long term safety data in paediatric patients are not available.

4.9 Overdose

There is no specific treatment in the event of overdose with vandetanib and possible symptoms of overdose have not been established. An increase in the frequency and severity of some adverse reactions, like rash, diarrhoea and hypertension was observed at multiple doses at and above 300 mg in healthy volunteer studies and in patients. In addition, the possibility of QTc prolongation and Torsades de pointes should be considered. Vandetanib doses higher than 150 mg/m2 have not been used in clinical studies in paediatric patients.

Adverse reactions associated with overdose are to be treated symptomatically; in particular, severe diarrhoea must be managed appropriately. In the event of an overdose, further doses must be interrupted, and appropriate measures taken to assure that an adverse event has not occurred, i.e. ECG within 24 hours to determine QTc prolongation. Adverse reactions associated with overdose may be prolonged due to the long half-life of vandetanib (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: antineoplastic agent, protein kinase inhibitor, ATC Code: L01EX04

Mechanism of action and pharmacodynamic effects
Vandetanib is a potent inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2 also known as kinase insert domain containing receptor [KDR]), epidermal growth factor receptor (EGFR) and RET tyrosine kinases. Vandetanib is also a sub-micromolar inhibitor of vascular endothelial receptor-3 tyrosine kinase.

Vandetanib inhibits VEGF-stimulated endothelial cell migration, proliferation, survival and new blood vessel formation in *in vitro* models of angiogenesis. In addition, vandetanib inhibits epidermal growth factor (EGF)-stimulated EGF receptor tyrosine kinase in tumour cells and endothelial cells. Vandetanib inhibits EGFR-dependent cell proliferation and cell survival *in vitro*. Vandetanib also inhibits both wild type and the majority of mutated, activated forms of RET, and significantly inhibits the proliferation of MTC cell lines *in vitro*.

In vivo vandetanib administration reduced tumour cell-induced angiogenesis, tumour vessel permeability, tumour microvessel density, and inhibited tumour growth of a range of human xenograft tumour models in athymic mice. Vandetanib also inhibited the growth of MTC xenograft tumours *in vivo*.

The precise mechanism of action of vandetanib in locally advanced or metastatic MTC is unknown.

Clinical efficacy in adults

Clinical data from MTC
A randomised, double-blind, placebo-controlled study (Study 58) was conducted to demonstrate safety and efficacy of vandetanib 300 mg versus placebo. This study included 331 patients with unresectable locally advanced or metastatic MTC. Only patients with CTN ≥ 500 pg/mL (conventional units) or ≥ 146.3 pmol/L (international standard units) were enrolled. Of the patients enrolled in the study 10 patients on vandetanib and 4 on placebo (4% of all patients) had a World Health Organization performance status (WHO PS) score of ≥ 2 and 28 (12.1%) patients on vandetanib and 10 (10.1%) on placebo had cardiac impairment. Cardiac impairment was defined as patients with previous cardiovascular abnormality.

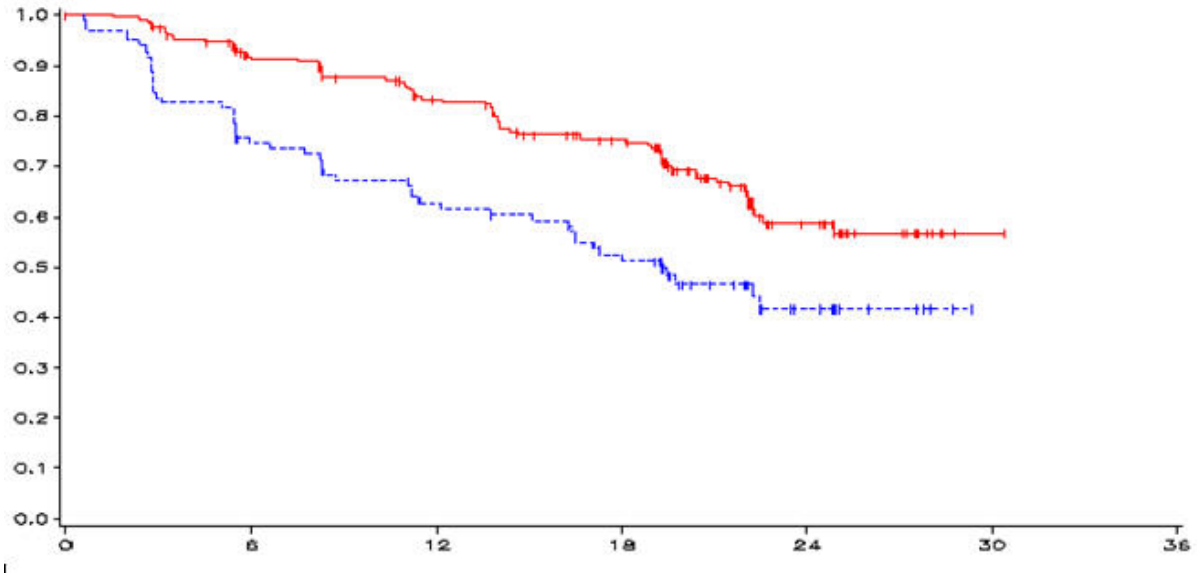
The primary objective of this study was to demonstrate an improvement in progression-free survival (PFS) with vandetanib compared to placebo. The secondary endpoints were evaluation of overall objective response rate (ORR), disease control rate (DCR) defined as, partial response (PR) or complete response (CR) or stable disease (SD) lasting at least 24 weeks, duration of response (DOR), time to worsening of pain based on Brief Pain Inventory (BPI) worst pain scale, and overall survival (OS). The PFS primary endpoint, ORR and DCR were based on centralized, independent blinded review of the imaging data. Biochemical response with vandetanib as compared to placebo as measured by CTN and CEA was also assessed as secondary endpoints.

Patients were treated with vandetanib or placebo until they reached objective disease progression. Upon objective disease progression based on the investigator's assessment, patients were discontinued from blinded study treatment and given the option to receive open-label vandetanib. Twenty-eight of the 231 patients (12.1%) on vandetanib and 3 of the 99 (3.0%) on placebo discontinued treatment because of an adverse event. Fourteen of the 28 patients (50%) who stopped vandetanib for an adverse event discontinued without a dose reduction. Five out of 6 patients (83%) with moderate renal failure who were treated with vandetanib had a dose reduction to 200 mg for adverse reaction; 1 patient required a further reduction to 100 mg.

The result of the primary analysis of PFS showed a statistically significant improvement in PFS for patients randomised to vandetanib compared to placebo (Hazard Ratio (HR) = 0.46; 95% Confidence Interval (CI) = 0.31-0.69; p=0.0001).

The median PFS for patients randomised to vandetanib has not been reached; however, based on statistical modelling of data observed up to the 43rd percentile, the median PFS is predicted to be 30.5 months with 95% confidence interval 25.5 to 36.5 months. The median PFS for patients randomised to placebo was 19.3 months. At 12 months, the proportion of patients alive and progression-free was 192 (83%) for patients randomised to vandetanib and 63 (63%) for patients randomised to placebo. In the vandetanib arm, a total of 73 (32%) patients progressed: 64 (28%) by response evaluation criteria in solid tumours (RECIST) progression and 9 (4%) by death in the absence of progression. The remaining 158 patients (68%) were censored in the analysis of PFS. In the placebo arm, a total of 51 (51%) of patients had progressed: 46 (46%) by RECIST progression and 5 (5%) by death in the absence of progression. The remaining 49 patients (49%) were censored in the analysis of PFS.

Figure 1: Kaplan Meier plot of PFS



months	0	6	12	18	24	30	36
n-vandetanib	231	196	169	140	40	1	0
n-placebo	100	71	57	45	13	0	0

____ vandetanib 300 mg, ------ placebo, y-axis=PFS, x-axis=time in months, n-vandetanib=number of patients at risk-vandetanib, n-placebo=number of patients at risk-placebo

HR = 0.46, 95%CI (0.31-0.69), p = 0.0001

PFS	N	Median PFS	HR	95% CI	p-value
Vandetanib 300 mg	73/231 (32%)	Not reached (predicted 30.5 months)	0.46	0.31, 0.69	0.0001
Placebo	51/100 (51%)	19.3 months			

Survival status and the median final overall survival (81.6 months in the vandetanib arm and 80.4 months in the placebo arm) were similar across both treatment arms. There was no statistically significant difference in final OS (HR 0.99, 95.002% CI 0.72, 1.38, p=0.9750). Results should be interpreted with caution due to the high percentage of patients in the placebo arm switching to open-label vandetanib (79.0% [79/100] of patients).

Most (95% of the patients) had metastatic disease. Fourteen patients treated with vandetanib, and 3 with placebo had unresectable locally advanced disease only. There is limited clinical experience with vandetanib in patients with unresectable locally advanced disease and without metastasis.

Statistically significant advantages were seen for vandetanib for the secondary endpoints of response rate, disease control rate, and biochemical response.

Table 3: Summary of other efficacy findings in study 58

ORR[a]	N	Response rate	OR[b]	95% CI	p-value
Vandetanib 300 mg	104/231	45%	5.48	2.99, 10.79	< 0.0001
Placebo	13/100	13%			
DCR[a]	**N**	**Response rate**	**OR[b]**	**95% CI**	**p-value**
Vandetanib 300 mg	200/231	87%	2.64	1.48, 4.69	0.001
Placebo	71/100	71%			
CTN Response	**N**	**Response rate**	**OR[b]**	**95% CI**	**p-value**
Vandetanib 300 mg	160/231	69%	72.9	26.2, 303.2	< 0.0001
Placebo	3/100	3%			
CEA Response	**N**	**Response rate**	**OR[b]**	**95% CI**	**p-value**
Vandetanib 300 mg	119/231	52%	52.0	16.0, 320.3	< 0.0001
Placebo	2/100	2%			
OVERALL SURVIVAL	**N**	**Median OS**	**HR[c]**	**95% CI**	**p-value**
Vandetanib 300 mg	116/231	81.6 months	0.99	0.72, 1.38	0.9750
Placebo	52/100	80.4 months			

[a] Overall response rate = complete + partial responses. Disease control rate = response rate + stable disease at 24 weeks. Intent-to-treat (ITT) analysis includes patients who received open-label vandetanib before progression according to the central read.

[b] OR=Odds Ratio. A value > 1 favours vandetanib. The analysis was performed using a logistic regression model with treatment as the only factor.

[c] HR= Hazard Ratio. A value <1 favours vandetanib. The analysis was performed using a log rank test with treatment as the only factor.

N=Number of events/number of randomised patients

A statistically significant advantage was seen for vandetanib for the secondary endpoint of time to worsening of pain (derived as a composite endpoint using the worst pain score from BPI and patient reported opioid analgesic use) (vandetanib 49%, placebo 57%, HR 0.61, 97.5%CI 0.43-0.87, p< 0.006: 8 vs. 3 months). There were no statistically significant differences observed for the exploratory endpoint of diarrhoea (reported as stool frequency).

RET mutation status

RET mutation status reanalysis in Study 58

In Study 58, RET mutation testing was initially performed by using the polymerase chain reaction (PCR) based Amplification Refractory Mutation System (ARMS) assay for the M918T mutation, and direct sequencing of DNA for mutations in exons 10, 11, 13, 14, 15 and 16 (site of M918T mutation) on all sporadic patients where DNA was available (297/298). For reanalysis of samples lacking M918T mutation, the RET sequences were enriched using a custom Agilent SureSelect reagent and sequenced on an Illumina sequencer. Data processing and automated calling of RET variants were carried out using the Broad Genome Analysis ToolKit (GATK) pipeline with manual curation of any difficult cases using Broad Integrative Genomics Viewer (IGV).

Initially, 79 patients had no M918T mutation identified. Of these 79 patients, 69 had enough tissue sample to allow a post-hoc reanalysis of RET mutation status based on new available assays. Most patients were reclassified as RET mutant (52/69) and 17/69 patients had no RET mutation (M918T or other) detected (11 with vandetanib and 6 with a placebo). Patients reclassified as RET mutant (N =

52) were pooled with those 187 patients initially identified as RET mutant, leading to a total number of 239 RET mutant patients (172 treated with vandetanib and 67 treated with a placebo). Results were based on a blinded central review of imaging.

Table 4: Efficacy end-points in RET mutant patients

Efficacy end-point (Vandetanib vs placebo)	**Patients with RET mutation (n=239)**
Objective response rate	51.7% vs 14.9%
Efficacy endpoint PFS HR (95% confidence interval)	0.46 (0.29, 0.74)
2-year PFS rate	55.7% vs 40.1%

Clinical efficacy in paediatric patients:
A Phase I/II single-center open-label, single-arm study (Study IRUSZACT0098) assessed the activity of vandetanib in 16 patients with unresectable locally advanced or metastatic hereditary MTC. Characteristics of the patients at study entry were the following: mean age 14.2 years (range 9-17 years), 50% female, 50% male, 93.8% White, 26.7% Hispanic and 6.3% were Black. Most patients (81.3%) had undergone partial or total thyroidectomy prior to study entry. Starting vandetanib dose was 100mg/m^2/day for all patients except for one who started at 150mg/m^2/day. After having well tolerated the first 1 or 2 cycles of therapy (1 cycle = 28 days), the remaining patients continued on 100 mg/m^2 of treatment. The primary efficacy outcome was ORR according to RECIST v 1.0. The objective response rate observed was 43.8%, all of which were partial responses. 31.3% of patients had stable disease for at least 8 weeks. Disease Control Rate including best response or Stable Disease $\geq$ 24 weeks was 75.0%. There is no experience with Caprelsa in patients 5-8 years of age in this study.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of vandetanib absorption is slow with peak plasma concentrations typically achieved at a median of 6 hours, range 4-10 hours, after dosing. Vandetanib accumulates approximately 8-fold on multiple dosing with steady state achieved from approximately 2 months.

Distribution
Vandetanib binds to human serum albumin and alpha-1-acid-glycoprotein with *in vitro* protein binding being approximately 90%. In *ex vivo* plasma samples from colorectal cancer patients at steady state exposure after 300 mg once daily, the mean percentage protein binding was 93.7% (range 92.2 to 95.7%). The pharmacokinetics of vandetanib at the 300 mg dose in MTC patients are characterised by a volume of distribution of approximately 7450 l.

Biotransformation
Following oral dosing of ^{14}C- vandetanib, unchanged vandetanib and metabolites vandetanib N-oxide and N-desmethyl vandetanib were detected in plasma, urine and faeces. A glucuronide conjugate was seen as a minor metabolite in excreta only. N-desmethyl-vandetanib is primarily produced by CYP3A4, and vandetanib-N-oxide by flavin-containing monooxygenase enzymes (FM01 and FMO3). N-desmethyl-vandetanib and vandetanib-N-oxide circulate at concentrations of approximately 11% and 1.4% of those of vandetanib.

Elimination
The pharmacokinetics of vandetanib at the 300 mg dose in MTC patients are characterised by a clearance of approximately 13.2 l/h. and plasma half-life of approximately 19 days. Within a 21 day collection period after a single dose of ^{14}C-vandetanib, approximately 69% was recovered with 44% in

faeces and 25% in urine. Excretion of the dose was slow and further excretion beyond 21 days would be expected based on the plasma half-life.

Special populations
Renal impairment
A single dose pharmacokinetic study in volunteers indicated that exposure to vandetanib is enhanced (up to 1.5, 1.6 and 2-fold) in mild, moderate and severe renal impaired subjects respectively compared to subjects with normal renal function (see sections 4.2, 4.4 and 4.5).

Hepatic impairment
A single dose pharmacokinetic study in volunteers indicated that hepatic impairment did not affect exposure to vandetanib. There is limited data in patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of normal (see sections 4.2 and 4.4).

Food effect
Exposure to vandetanib is not affected by food.

Pharmacokinetics in paediatric population
The pharmacokinetic parameters of vandetanib in paediatrics MTC patients aged 9-17 years were similar to those in adults. Vandetanib exposure in children between 5-8 years old with glioma-related indications was comparable to MTC patients aged 9-18 years. Dosing at 100mg/m^2/day of the indicated posology (function of BSA) in paediatrics delivers similar exposure to that achieved in adults at 300 mg daily.

5.3 Preclinical safety data

Vandetanib has shown no mutagenic or clastogenic potential.

In repeat-dose toxicity studies of up to 9 months duration, effects included emesis, body weight loss and diarrhoea in dogs and physeal dysplasia in young dogs and rats with open growth plates. In rats, effects on teeth, kidney and skin were noted. These findings occurred at clinically-relevant plasma concentrations, were largely reversible within 4 weeks of cessation of dosing and were attributable to inhibition of vascular endothelial growth factor receptor (VEGFR) or EGFR.

Effects noted in other studies included inhibition of human ether-à-go-go related gene (hERG) current and prolongation of QTc interval in dogs. Elevation of systolic and diastolic blood pressure was observed in rats and dogs. In mice, vandetanib was shown to delay but not prevent wound healing. Vandetanib also showed evidence of phototoxic potential in an *in vitro* cytotoxicity assay. In an animal model of wound-healing, mice dosed with vandetanib had reduced skin-breaking strength compared with controls. This suggests that vandetanib slows but does not prevent wound healing. The appropriate interval between discontinuation of vandetanib and subsequent elective surgery required to avoid the risks of impaired wound healing has not been determined. In clinical studies, a small number of patients had surgery while receiving vandetanib and there were no reported wound healing complications.

Reproductive toxicology
In a fertility study of male rats, no effect on copulation or fertility rate were observed when untreated females were mated with males treated with vandetanib; however, in the same study there was a slight decrease in the number of live embryos and an increase in preimplantation loss. In a female fertility study, there was a trend towards increased oestrus cycle irregularity, a slight reduction in pregnancy incidence and increase in implantation loss. In a repeat-dose toxicity study in rats, there was a decrease in the number of *corpora lutea* in the ovaries of rats given vandetanib for 1 month.

In rats, embryofoetal toxicity was evident as foetal loss, delayed foetal development, heart vessel abnormalities and precocious ossification of some skull bones. In a rat pre- and post-natal development study, at doses producing maternal toxicity during gestation and/or lactation, vandetanib

increased pre-birth loss and reduced post-natal pup growth. Vandetanib was excreted into milk in rat and found in plasma of pups following dosing to lactating rats.

Carcinogenicity
Vandetanib has shown no carcinogenic potential effect in a 6 month carcinogenicity study in rasH2 transgenic mice. A 2-year carcinogenicity study in rats was impaired by low survival in the high dose female group and limited exposure of the animals to vandetanib; however, no carcinogenic effects were observed in the remaining animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Crospovidone (type A)
Povidone (K 29-32)
Magnesium stearate

Film-coating
Hypromellose
Macrogol (300)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/ PVDC/Alu blisters, sealed with aluminium foil, each containing 30 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Esteve Pharmaceuticals S.A., Passeig de la Zona Franca 109, Planta 4, 08038 Barcelona, Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/749/001
EU/1/11/749/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 February 2012

Date of latest renewal: 15 November 2022

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. 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. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Genzyme Ireland Ltd.
IDA Industrial Park,
Old Kilmeaden Road,
Waterford
Ireland

Sanofi Winthrop Industrie
30-36 avenue Gustave Eiffel,
37100 Tours,
France

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**

The requirements for submission of periodic safety update reports 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 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.

- **Additional risk minimisation measures**

Prior to launch of CAPRELSA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where CAPRELSA is marketed, all healthcare professionals (HCPs) and patients / caregivers who are expected to prescribe, dispense and use CAPRELSA have access to/are provided with an **educational package** containing:

HCPs

- The summary of Product Characteristics (SmPC);
- The educational material, including:
  - Information about the risks associated with CAPRELSA:
    - QTc prolongation and Torsades de pointes
    - Posterior reversible encephalopathy syndrome (PRES);
    - Teeth and bone development abnormalities in pediatric patients
    - Medication errors in the pediatric population
  - The Physicians' dosing and monitoring guide for paediatric patients;
- The dosing and monitoring guide for paediatric patients and patient's caregivers;
- The Patient Leaflet;
- The Patient Alert Card.

Patients / caregivers

- The dosing and monitoring guide for paediatric patients and patient's caregivers;
- The Patient Leaflet;
- The Patient Alert Card.

The **HCPs educational materials** should include the following key elements:

<u>QTc prolongation and Torsades de pointes</u>

- CAPRELSA prolongs the QTc interval and can cause Torsades de pointes and sudden death
- CAPRELSA treatment must not be started in patients:
  - Whose ECG QTc interval is greater than 480 msec;
  - Who have congenital long QTc syndrome;
  - Who have a history of Torsades de pointes unless all risk factors that contributed to Torsades de pointes have been corrected;
- The need for an ECG, and serum levels of potassium, calcium and magnesium and thyroid stimulating hormone (TSH) and the times and situations when it should be performed;
- Patients who develop a single value of corrected ECG QTc interval of at least 500 msec should stop taking CAPRELSA. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pre-treatment status has been confirmed and correction of possible electrolyte imbalance has been made;
- If QTc increases markedly but stays below 500 msec, the advice of a cardiologist should be sought;
- Details of medicinal products where the co-administration of CAPRELSA is either contraindicated or not recommended;
- The role and use of the Patient Alert Card.

<u>Posterior reversible encephalopathy syndrome (PRES) also known as reversible posterior leukoencephalopathy syndrome (RPLS)</u>

- PRES should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. A brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status;
- The need to counsel patients about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and the actions to take;
- The role and use of the Patient Alert Card.

<u>Teeth and bone development abnormalities in pediatric patients</u>

- Vandetanib was found not to impair linear growth in clinical trials conducted in children and adolescents;

- Vandetanib has demonstrated adverse effect on growing tissue that relies on vascularization such as teeth and growth plates in non-clinical studies;
- The need to closely monitor teeth and bone abnormalities in the paediatric population;

Medication errors in the paediatric population

The **Physicians' dosing and monitoring guide for paediatric patients** should contain the following key elements:

- How CAPRELSA dose for infants and adolescents is calculated;
- The posology regimens according to patient's body surface area (BSA), including a visual representation of the two-week posology regimen per BSA;
- How CAPRELSA is used / administered;
- Instructions on how to use the dosing and monitoring guide and the daily tracker for paediatric patients and caregivers.

The **dosing and monitoring guide for patients and patient's caregivers** should contain the following key elements:

- What CAPRELSA is, what it treats, how it is administered;
- How CAPRELSA dose is calculated;
- What are the side effects associated with CAPRELSA and which monitoring is requested;
- How to use the daily tracker table (including examples of a completed daily tracker);
- The general daily tracker for 14 days and blank copies of the daily tracker.

The **Patient Alert Card** should include the following key elements:

- Information about the risks of QTc prolongation and Torsades de pointes, and Posterior reversible encephalopathy syndrome (PRES);
- Signs or symptoms of the safety concerns and when to seek attention from a HCP;
- Not to stop taking CAPRELSA, or change the dose, without consulting the prescriber;
- Contact details of the CAPRELSA prescriber.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Caprelsa 100 mg film-coated tablets
vandetanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg vandetanib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

Esteve Pharmaceuticals S.A.
Passeig de la Zona Franca 109 Planta 4
08038 Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/749/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Caprelsa 100 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 BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Caprelsa 100 mg tablets
vandetanib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Esteve Pharmaceuticals S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Caprelsa 300 mg film-coated tablets
vandetanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg vandetanib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

Esteve Pharmaceuticals S.A.
Passeig de la Zona Franca 109 Planta 4
08038 Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/749/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Caprelsa 300 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 BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Caprelsa 300 mg tablets
vandetanib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Esteve Pharmaceuticals S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient
Caprelsa 100 mg film-coated tablets
Caprelsa 300 mg film-coated tablets
vandetanib

In addition to this leaflet you will be given the Patient Alert Card, which contains important safety information that you need to know before you are given Caprelsa and during treatment with Caprelsa.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet and the patient alert card. You may need to read it again.
- It is important that you keep the Alert Card with you during treatment.
- 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 Caprelsa is and what it is used for
2. What you need to know before you take Caprelsa
3. How to take Caprelsa
4. Possible side effects
5. How to store Caprelsa
6. Contents of the pack and other information

1. What Caprelsa is and what it is used for

Caprelsa is a treatment for adults and children aged 5 years and above with:

Type of medullary thyroid cancer that is called Rearranged during Transfection (RET) mutant and which cannot be removed by surgery or has spread to other parts of the body.

Caprelsa works by slowing down the growth of new blood vessels in tumours (cancers). This cuts off the supply of food and oxygen to the tumour. Caprelsa may also act directly on cancer cells to kill them or slow down their growth.

2. What you need to know before you take Caprelsa

Do not take Caprelsa:
- if you are allergic to vandetanib or any of the other ingredients of this medicine (listed in Section 6).
- if you have a heart problem that you were born with called ‘congenital long QTc syndrome’. This is seen on an electrocardiogram (ECG).
- if you are breast-feeding.
- if you are taking any of the following medicines: arsenic, cisapride (used to treat heartburn), erythromycin intravenous and moxifloxacin (used to treat infection), toremifene (used to treat breast cancer), mizolastine (used to treat allergies), Class IA and III antiarrhythmics (used to control heart rhythm).

Do not take Caprelsa if any of the above applies to you. If you are not sure, talk to your doctor.

Warnings and precautions
Talk to your doctor or pharmacist before taking Caprelsa:
- If you are sensitive to the sun. Some people who are taking Caprelsa become more sensitive to the sun. This can cause sunburn. While you are taking Caprelsa, protect yourself when you go outside by always using sunscreen and wearing clothes to avoid exposure to the sun.
- If you have high blood pressure.
- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- If you need to have a surgical procedure. Your doctor may consider stopping Caprelsa if you will be undergoing a major surgical procedure as Caprelsa may affect wound healing. Caprelsa may be restarted once adequate wound healing is established.
- If you are taking medicines to prevent bone complications of your thyroid cancer or for osteoporosis.
- If you have any kidney problems.

Severe Cutaneous Adverse Reactions (SCARs), including Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN), have been reported in association with vandetanib treatment. Stop using Caprelsa and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Determination of RET status of your cancer will be needed, before initiating Caprelsa treatment.

Monitoring of your blood and your heart:
Your doctor or nurse should perform tests to check the levels of your blood potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH) as well as the electrical activity of your heart with a test called an electrocardiogram (ECG). You should have these tests:
- Before starting Caprelsa
- Regularly during Caprelsa treatment
- 1, 3 and 6 weeks after starting Caprelsa
- 12 weeks after starting Caprelsa
- Every 3 months thereafter
- If your doctor or pharmacist changes your dose of Caprelsa
- If you start taking medicines that affect your heart
- As instructed by your doctor or pharmacist

Children
Caprelsa should not be given to children below 5 years of age.

Other medicines and Caprelsa
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines that you buy without a prescription and herbal medicines. This is because Caprelsa can affect the way some medicines work and some medicines can have an effect on Caprelsa.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- itraconazole, ketoconazole, ritonavir, clarithromycin, rifampicin and moxifloxacin (medicines used to treat infections)
- carbamazepine and phenobarbital (used to control seizures)
- ondansetron (used to treat nausea and vomiting)
- cisapride (used to treat heart burn), pimozide (used to treat uncontrolled repeated movements of the body and verbal outbursts) and halofantrine and lumefantrine (used to treat malaria)
- methadone (used to treat addiction), haloperidol, chlorpromazine, sulpiride, amisulpride, and zuclopenthixol, (used to treat mental illness)
- pentamidine (used to treat infection)
- vitamin K antagonists and dabigatran often referred to as ‘blood thinners’

- cyclosporine and tacrolimus (used to treat transplant rejection), digoxin (used to treat irregular heart rate), and metformin (used to control your blood sugar)
- proton pump inhibitors (used to treat heartburn)

You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregivers.

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 for advice before taking this medicine. This is because Caprelsa may harm an unborn child. Your doctor will discuss with you the benefits and risks of taking Caprelsa during this time.
- If you may become pregnant you must use effective contraception when you are taking Caprelsa and for at least four months after the last dose of Caprelsa. If you are a fertile man, you must use effective contraception during treatment with Caprelsa and for at least four months after your last dose of Caprelsa.

You must not breast-feed during treatment with Caprelsa for the safety of your baby.

Driving and using machines
Use caution before driving or using machines. Keep in mind Caprelsa may make you feel tired, weak, or cause blurred vision.

3. How to take Caprelsa

Use in adults
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- The recommended dose is 300 mg each day.
- Take Caprelsa about the same time each day.
- Caprelsa may be taken with or without food.

Use in children and adolescents
The doctor will tell you how many tablets of Caprelsa to give to your child. The amount of Caprelsa given will depend on your child's body weight and height. The total daily dose in children must not exceed 300 mg. The treatment may either be given to your child as a once-daily dose, an every other day dosing or a repeating 7-day schedule as indicated in the dosing guide that has been given to you by your doctor. It is important that you keep this dosing guide and show it to your caregiver.

If you have trouble swallowing the tablet
If you have trouble swallowing the tablet, you can mix it with water as follows:
- Take half a glass of still (non-carbonated) water. Only use water, do not use any other liquids.
- Put the tablet into the water.
- Stir the tablet until it has dispersed into the water. This may take about 10 minutes.
- Then drink it straight away.

To make sure there is no medicine left, refill the glass halfway with water and drink it.

If you get side effects
If you get side effects always tell your doctor. Your doctor may tell you to take Caprelsa at a lower or increased dose (such as two 100 mg tablets or one 100 mg tablet). Your doctor may also prescribe other medicines to help control your side effects. The side effects of Caprelsa are listed in Section 4.

If you take more Caprelsa than you should
If you take more Caprelsa than you have been prescribed, talk to a doctor or go to a hospital straight away.

If you forget to take Caprelsa

What to do if you forget to take a tablet depends on how long it is until your next dose.
- **If it is 12 hours or more until your next dose**: Take the missed tablet as soon as you remember. Then take the next dose at the normal time.
- **If it is less than 12 hours until your next dose**: Skip the missed dose. Then take the next dose at the normal time.

Do not take a double dose (two doses at the same time) to make up for a forgotten tablet.

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. If you get side effects, your doctor may tell you to take Caprelsa at a lower dose. Your doctor may also prescribe other medicines to help control your side effects.

Tell your doctor straight away if you notice any of the following side effects – you may need urgent medical treatment:
- Fainting, dizziness or heart rhythm changes. These may be signs of a change in the electrical activity of your heart. They are seen in 8% of people taking Caprelsa for medullary thyroid cancer. Your doctor may recommend you take Caprelsa at a lower dose or stop taking Caprelsa. Caprelsa has uncommonly been associated with life-threatening changes in heart rhythm.
- Stop using Caprelsa and seek medical attention immediately if you notice any of the following symptoms: reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson-syndrome, toxic epidermal necrolysis).
- Severe diarrhoea.
- Serious breathlessness, or sudden worsening breathlessness, possibly with a cough or a high temperature (fever). This may mean that you have an inflammation of the lungs called 'interstitial lung disease'. This is uncommon (affects less than 1 in 100 people) but can be life-threatening.
- Seizures, headache, confusion or finding it difficult to concentrate. These may be signs of a condition called RPLS (Reversible Posterior Leukoencephalopathy Syndrome). These usually go away when Caprelsa is stopped. RPLS is uncommon (affects less than 1 in 100 people).

Tell your doctor straight away if you notice any of the side effects above.

Other side effects include:
Very common (affects more than 1 in 10 people):
- Diarrhoea. Your doctor may prescribe a medicine to treat this. If it gets severe, tell your doctor straight away.
- Abdominal pain.
- Skin rash or acne.
- Depression.
- Tiredness.
- Feeling sick (nausea).
- Upset stomach (dyspepsia).
- Nail disorders.
- Being sick (vomiting).
- Loss of appetite (anorexia).
- Weakness (asthenia).
- High blood pressure. Your doctor may prescribe a medicine to treat this.
- Headache.
- Fatigue.
- Trouble sleeping (insomnia).
- Inflammation of the nasal passages.

- Inflammation of the main air passages to the lungs.
- Upper respiratory tract infections.
- Urinary tract infections.
- Numbness or tingling of the skin.
- Abnormal sensation of the skin.
- Dizziness.
- Pain.
- Swelling caused by excess fluid (oedema).
- Stones or calcium deposits in the urinary tract (nephrolithiasis).
- Blurred vision, including mild changes in the eye which can lead to blurred vision (corneal opacity).
- Sensitivity of the skin to sunlight. While you are taking Caprelsa, protect yourself when you go outside by always using sun cream and wearing clothes to avoid exposure to the sun.

Common (affects less than 1 in 10 people)
- Dehydration.
- Severe high blood pressure.
- Weight loss.
- Stroke or other conditions where the brain may not get enough blood.
- A type of rash that affects the hands and feet (hand foot syndrome).
- Sore mouth (stomatitis).
- Dry mouth.
- Pneumonia.
- Toxins in the blood as a complication of infection.
- Flu.
- Inflammation of the urinary bladder.
- Inflammation of the sinuses.
- Inflammation of the voice box (larynx).
- Inflammation of a follicle, especially a hair follicle.
- Boil.
- Fungal infection.
- Kidney infection.
- Loss of body fluid (dehydration).
- Anxiety.
- Tremor.
- Drowsiness.
- Fainting.
- Feeling unsteady.
- Increased pressure in the eye (glaucoma).
- Coughing up of blood.
- Inflammation of the lung tissue.
- Difficulty swallowing.
- Constipation.
- Inflammation of the lining of the stomach (gastritis).
- Gastrointestinal bleeding.
- Gallstones (cholelithiasis).
- Painful urination.
- Kidney failure.
- Frequent urination.
- Urgent desire to urinate.
- Fever.
- Nose bleed (epistaxis).
- Dry eye.
- An irritation of the eyes (conjunctivitis).

- Visual impairment.
- Halo vision.
- Seeing flashes of light (photopsia).
- Disorder of the cornea of the eye (keratopathy).
- A type of diarrhoea (colitis).
- Loss of hair from the head or body (alopecia).
- Changes in taste of foods (dysgeusia).

Uncommon (affects less than 1 in 100 people)
- Heart failure.
- Inflammation of the appendix (appendicitis).
- Bacterial infection.
- Inflammation of the diverticula (small bulging pouches that can form in your digestive system).
- Bacterial skin infection.
- Abdominal wall abscess.
- Malnutrition.
- Involuntary muscle contraction (convulsions).
- Rapidly alternating muscular contraction and relaxation (clonus).
- Swelling of the brain.
- Clouding of the lens of the eye.
- Heart rate and rhythm disorders.
- Loss of heart function.
- Failure of the lungs to function properly.
- Pneumonia that happens when you breathe in foreign matter into your lungs.
- Bowel obstruction.
- Hole in your bowel.
- Inability to control your bowel movements.
- Abnormal colour of urine.
- Lack of urine.
- Inability to heal properly.
- Inflammation of the pancreas (pancreatitis).
- Blistering of skin (bullous dermatitis).

Not known (frequency cannot be estimated from the available data)
- An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).
- Death of bone tissue due to low blood flow (Osteonecrosis, osteonecrosis of the jaw).
- Reddish non-elevated, target like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes, which can be preceded by fever and flu like symptoms. These serious skin rashes can be potentially life threatening (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- A skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme).

The following side effects may be shown in tests that may be carried out by your doctor:
- Protein or blood in your urine (shown in a urine test).
- Heart rhythm changes (shown in an ECG). Your doctor may tell you to stop taking Caprelsa or take Caprelsa at a lower dose.
- Abnormalities in your liver or pancreas (shown in blood tests). These do not usually cause symptoms but your doctor may want to monitor them.
- Decreased levels of calcium in your blood. Your doctor may need to prescribe or change your thyroid hormone treatment.
- Decreased levels of potassium in your blood.
- Increased levels of calcium in your blood.
- Increased levels of glucose in your blood.

- Decreased levels of sodium in your blood.
- Decrease in thyroid function.
- Increased levels of red cells in your blood.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist **straight away**.

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 Caprelsa

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 blister and the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away 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 Caprelsa contains
- The active substance is vandetanib. Each tablet contains 100 or 300 mg of vandetanib.
- The other ingredients are calcium hydrogen phosphate dihydrate, microcrystalline cellulose, crospovidone (type A), povidone (K29-32), magnesium stearate, hypromellose, macrogol and titanium dioxide (E171).

What Caprelsa looks like and contents of the pack
Caprelsa 100 mg is a white round film-coated tablet with “Z100” imprinted on one side.
Caprelsa 300 mg is a white oval-shaped film-coated tablet with “Z300” imprinted on one side.

Caprelsa comes in blister packs of 30 tablets.

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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