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.

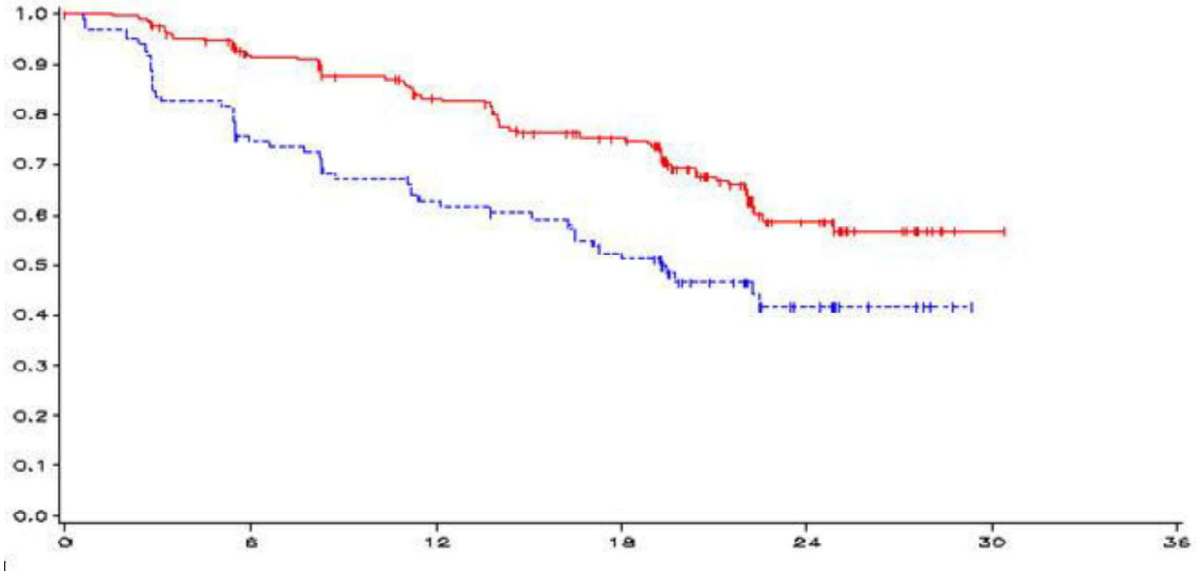
The primary objective of this study was to demonstrate an improvement in progression-free survival (PFS) with vandetanib compared to placebo. The secondary endpoints were evaluation of overall objective response rate (ORR), disease control rate (DCR) defined as, partial response (PR) or complete response (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