CAPRELSA

vandetanib

PRODUCT INFORMATION

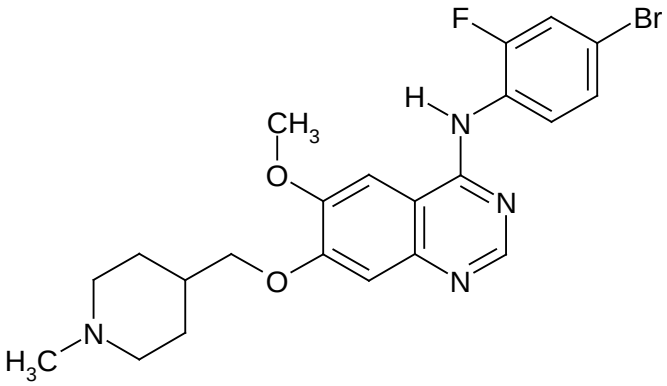
Vandetanib (CAPRELSA) may cause fatal or life-threatening ventricular arrhythmias (including torsades de pointes) or sudden death. These outcomes may be more likely in patients in whom vandetanib significantly prolongs the electrocardiogram QT interval.

- Do not use vandetanib in patients with congenital long QT syndrome
- Do not start vandetanib therapy if the corrected QT interval is >480 ms
- Do not start vandetanib therapy in patients with a history of torsades de pointes or other ventricular arrhythmias (unless risk factors contributing to these events have been corrected).
- Monitor for QT interval prolongation by periodic ECG measurements as recommended in the main product information text (see “PRECAUTIONS”). Follow the recommendations there about cessation of CAPRELSA if there is significant QT prolongation.
- Monitor for, and correct hypokalaemia, hypomagnesaemia and hypocalcaemia before starting therapy and periodically during therapy as recommended in “PRECAUTIONS”
- Do not use vandetanib concomitantly with any other drug known to prolong the QT interval unless there is no appropriate alternative therapy. If such use is necessary, more intensive ECG/electrolyte monitoring is indicated
- Vandetanib has a half-life of around 19 days. Risks of QT prolongation and arrhythmia remain for a period of weeks after cessation of therapy
- Vandetanib is metabolised by CYP3A4. Caution is required if concomitant CYP3A4 inhibitors are used, as the extent of increase in vandetanib exposure (and consequent risk of QT prolongation) is not well characterised.

NAME OF THE MEDICINE

Vandetanib

The chemical structure of vandetanib is:



Chemical name

N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine

Molecular formula

$C_{22}H_{24}BrFN_4O_2$

CAS number:

443913-73-3

DESCRIPTION

Vandetanib exhibits pH dependent aqueous solubility and is defined as having 'low solubility'. Vandetanib is not hygroscopic. The melting point of vandetanib is approximately 235°C. The molecule has 2 pKa values of 5.2 (for the aminoquinazolone moiety) and 9.4 (for the piperidine moiety).

Excipients

Calcium hydrogen phosphate, cellulose - microcrystalline, crospovidone, povidone, magnesium stearate, hypromellose, macrogol 300, titanium dioxide.

PHARMACOLOGY

Vandetanib is a tyrosine kinase inhibitor that inhibits vascular endothelial growth factor (VEGF)-stimulated VEGF receptor-2 tyrosine kinase. Vandetanib inhibits VEGF-stimulated endothelial cell migration, proliferation, survival and new blood vessel formation in *in vitro* models of angiogenesis. *In vivo* vandetanib

administration reduced tumour cell-induced angiogenesis, tumour vessel permeability and tumour microvessel density, and inhibited tumour growth and metastasis in human xenograft models of lung cancer in athymic mice.

In addition, vandetanib inhibits epidermal growth factor (EGF)-stimulated EGF receptor tyrosine kinase. Vandetanib inhibits EGFR-dependent cell proliferation and cell survival *in vitro*.

In vitro studies have shown that vandetanib also inhibits the activity of other tyrosine kinases, including rearranged during transfection (RET), breast tumour kinase (BRK) and VEGF receptor-3. Vandetanib is an antagonist of histamine receptors H_1 and H_2 and adrenergic receptor α_{2A}.

Pharmacokinetics

The pharmacokinetics of vandetanib at the 300 mg dose in MTC patients are characterised by a clearance of ~13.2 L/h, a volume of distribution of approximately 7450 L and plasma half-life of approximately 19 days.

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 ~8-fold on multiple dosing with steady state achieved from ~2 months.

Distribution

Vandetanib binds to human serum albumin and α1-acid-glycoprotein with in vitro protein binding being ~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 %).

Metabolism

Following oral dosing of 14C- vandetanib, unchanged vandetanib and metabolites vandetanib N-oxide and N desmethyl vandetanib were detected in plasma, urine and feces. 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 - desmethyl-vandetanib and vandetanib-N-oxide circulate at concentrations of ~11% and 1.4% of those of vandetanib.

Excretion

Within a 21 day collection period after a single dose of 14C-vandetanib, ~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.

Vandetanib was not a substrate of hOCT2 expressed in HEK293 cells. Vandetanib was an inhibitor of OCT2 inhibiting the uptake of the selective OCT2 marker substrate 14C-creatinine by HEKC-OCT2 cells, with a mean IC50 of approximately 2.1 µg/ml. This is higher than vandetanib plasma concentrations observed after multiple dosing at 300 mg (~0.81 µg/ml) and 100 mg (~0.32 µg/ml). Inhibition of renal excretion of creatinine by vandetanib offers an explanation for increases in plasma creatinine seen in human subjects receiving vandetanib.

CLINICAL TRIALS

A randomized, double-blind, placebo-controlled study (Study 58) was conducted to demonstrate safety and efficacy of CAPRELSA 300 mg versus placebo in 331 patients with unresectable locally advanced or metastatic medullary thyroid Cancer (MTC).

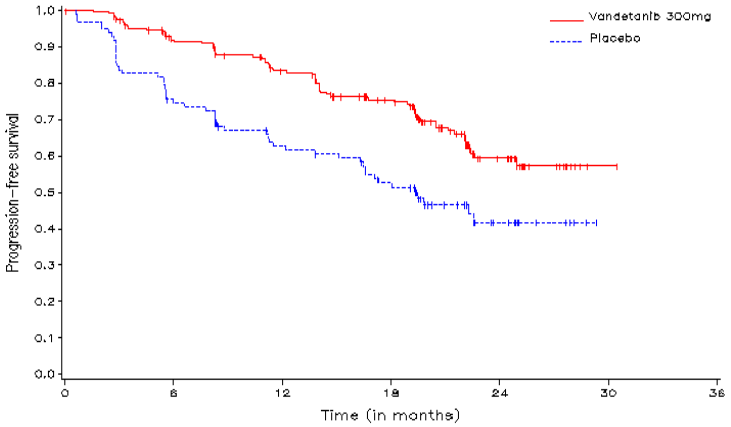
The primary objective of this study was to demonstrate an improvement in progression-free survival (PFS) with CAPRELSA compared to placebo. The secondary endpoints were evaluation of overall objective response rate (ORR), disease control rate (DCR) defined as stable disease (SD), partial response (PR) or complete response (CR) lasting 12 weeks, duration of response (DOR) and overall survival (OS). Biochemical response with CAPRELSA as compared to placebo as measured by calcitonin (CTN) and carcinoembryonic antigen (CEA) were also assessed as secondary endpoints.

Patients were treated with CAPRELSA 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 CAPRELSA.

The result of the primary analysis of PFS showed a statistically significant improvement in PFS for patients randomized 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 randomized to placebo was 19.3 months. The median PFS for patients randomized to CAPRELSA 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. At 12 months, the proportion of patients alive and progression-free was 63 (63%) for patients randomized to placebo and 192 (83%) for patients randomized to vandetanib. For vandetanib, a total of 73 (32%) of patients had progressed; 64 (28%) by RECIST progression and 9 (4%) by death in the absence of progression. The remaining 158 patients (68%) were censored in the analysis of PFS. For placebo, 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.

Fig 1. Kaplan Meier plot of Progression Free Survival



n at months	0	6	12	18	24	30	36
Vandetanib 300mg	231	198	171	141	42	1	0
Placebo	100	72	57	45	13	0	0

At the time of the primary analysis of PFS (data cut-off date 31 July 2009), 48 (15%) of the patients had died, and there was no significant difference in overall survival between treatment groups (Hazard ratio = 0.89; 99.98% CI = 0.28 – 2.85; p=0.712). At the time of this analysis, 32 patients (14%) on the vandetanib arm and 16 patients (16%) on the placebo arm had died.

There were 14 patients (5%) with unresectable locally advanced disease who were randomized to receive vandetanib, of whom 6 patients (42%) progressed and 3 (21%) patients had objective tumour responses. There were 3 patients with unresectable locally advanced disease who were randomized to placebo of whom there were no progression events and no responders.

Statistically significant advantages were also seen for vandetanib for the secondary endpoints of response rate, disease control rate, biochemical response, and time to worsening of pain, as shown in Table 1. The results for response rate and disease control rate are from the intention to- treat analysis, which includes patients who crossed-over from blinded treatment to open-label vandetanib before progression as assessed by the central read. Of the 13 patients who experienced a response following randomization to placebo, 12 patients experienced the response only after receiving open-label vandetanib. The data for calcitonin and CEA response, and for time to worsening of pain, are from the randomized phase of the study only.

Table 1: Summary of key efficacy findings in study 58

PROGRESSION-FREE SURVIVAL	N	Median PFS	HR[a]	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			
OBJECTIVE RESPONSE RATE[b]	**N**	**Response rate**	**OR[d]**	**95% CI**	**p-value**
Vandetanib 300 mg	104/231	45%	5.48	2.99, 10.79	<0.0001
Placebo	13/100	13%			
DISEASE CONTROL RATE[c]	**N**	**Response rate**	**OR[d]**	**95% CI**	**p-value**
Vandetanib 300 mg	200/231	87%	2.64	1.48, 4.69	0.001
Placebo	71/100	71%			
CTN (calcitonin) RESPONSE	**N**	**Response rate**	**OR[d]**	**95% CI**	**p-value**
Vandetanib 300 mg	160/231	69%	72.9	26.2, 303.2	<0.0001
Placebo	3/100	3%			
CEA (carcinoembryonic antigen) RESPONSE	**N**	**Response rate**	**OR[d]**	**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[a]**	**99.98% CI**	**p-value**
Vandetanib 300 mg	32/231 (14%)	Not reached	0.89	0.28, 2.85	0.712
Placebo	16/100 (16%)	Not reached			
TIME TO WORSENING OF PAIN[e]	**N**	**Median TWP**	**HR**	**97.5% CI**	**p-value**
Vandetanib 300 mg	114/231 (49%)	7.85 months	0.61	0.43, 0.87	0.006
Placebo	57/100 (57%)	3.25 months			

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

[b] Objective response rate is the proportion of patients with a best objective response of complete response (CR) or partial response (PR). Twelve of the thirteen patients randomized to placebo and having an objective response had the response while receiving vandetanib on the open label portion of the study.

[c] Disease Control Rate is the proportion of patients with a best objective response of complete response, partial response or Stable Disease at 24 weeks.

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

[e] TWP (Time to worsening of pain) was a composite endpoint, derived from opioid analgesic use and the worst pain item of the Brief Pain Index questionnaire (BPI).

N Number of events/number of randomized patients; OS, overall survival; PFS, progression-free survival; CI, confidence interval.

In Study 58, mutations in 6 exons were studied. However, RET mutation status was not able to be determined in 42% of the patients because many of the tumour samples were in poor condition. Mutation status was established for 155 patients, with 92% of these being the M918T mutation. Only 8 patients were confirmed to be RET mutation negative in all 6 exons studied. Of these 8 patients, 2 were randomized to the vandetanib arm and 6 to the placebo arm. Five of the 6 patients randomised to placebo received vandetanib in the open label phase following progression, and 2 of these patients had an objective response after receiving vandetanib on the open-label phase. Due to the small number of patients it is difficult to draw a firm conclusion on the benefits of vandetanib in patients with RET mutation negative tumours.

Supportive evidence for activity in RET mutation negative patients is provided by the data from 71 patients who were negative for the M918T mutation, but in whom some or all of the other mutation tests failed. Taken together with the 8 patients in whom all mutation tests were negative (a total of 79 patients, 46 randomised to vandetanib and 33 to placebo) the PFS hazard ratio was HR=0.57 (95% CI 0.29-1.13), in favour of vandetanib and the median PFS was 28 months for the vandetanib group and 18 months for the placebo group. The objective response rate in patients who received vandetanib was 34.8% (16/46). In addition, the responses in this subgroup of patients were durable as the median duration of response is estimated to be 18.4 months.

At various exposure durations, median haemoglobin levels in patients treated with vandetanib were increased by 0.5-1.5 g/dL compared to baseline. Animal data suggests this may be due to increased hepatic erythropoietin production in patients receiving vandetanib.

INDICATIONS

CAPRELSA is indicated for the treatment of patients with symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

CONTRAINDICATIONS

CAPRELSA must not be administered to patients with known hypersensitivity to the active substance, vandetanib, or to any of its excipients.

CAPRELSA must not be administered to patients with congenital long QT syndrome.

PRECAUTIONS

QTc Prolongation

Prolongation of the electrocardiogram QTc interval has been observed in patients receiving CAPRELSA (see ADVERSE EFFECTS). 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 QT prolongations occurred most often in the first 3 months of treatment, but continued to first occur after this time. In Study 58, at a dose of 300 mg per day, ECG QTcF prolongation to above 500 msec was observed in 7% patients in the CAPRELSA arm and 0 patients in the placebo arm. Electrocardiogram QTc prolongation appears to be dose-dependent and may be managed with appropriate monitoring, dose interruption and dose reduction as necessary.

Uncommonly torsade de pointes, ventricular tachycardia and sudden death have been reported in patients administered CAPRELSA 300 mg.

CAPRELSA treatment should not be started in patients whose corrected electrocardiogram QT interval is confirmed to be greater than 480 msec. CAPRELSA should not be given to patients who have a history of torsade de pointes or other ventricular arrhythmia unless all risk factors that contributed to torsade have been corrected. CAPRELSA has not been studied in patients with ventricular arrhythmias or recent myocardial infarction. Vandetanib has a long half life of 19 days (see PHARMACOKINETICS). This may result in slow resolution of QTc prolongation and present a risk of QTc prolongation after discontinuation of CAPRELSA.

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 levels should be maintained at 4 mmol/L or higher and 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.

CAPRELSA may be administered with drugs known to prolong the electrocardiogram QT interval if there is no appropriate alternative therapy. If such drugs are given to patients already receiving CAPRELSA, ECG monitoring of the QT interval as appropriate to the pharmacokinetics of the added drug should be performed.

Patients who develop a single value of corrected electrocardiogram QT interval of at least 500 msec should stop taking CAPRELSA. Dosing of CAPRELSA can be resumed at a reduced dose after return of the electrocardiogram QTc interval to baseline status has been confirmed.

Skin reactions

Severe skin reactions (including Stevens-Johnson syndrome), some leading to death, have been reported with CAPRELSA. Treatment of severe skin reactions has included systemic corticosteroids and permanent discontinuation of CAPRELSA. Mild to moderate skin reactions may manifest as rash, acne, dry skin, dermatitis, pruritis and other skin reactions (including photosensitivity reactions and palmer-plantar erythrodysesthesia syndrome). Mild to moderate skin reactions have been treated with topical and systemic corticosteroids, oral antihistamines and topical and systemic antibiotics. If CTCAE grade 3 or greater skin reactions occur, CAPRELSA treatment should be stopped until improved. Upon improvement, consideration should be given to continuing treatment at a reduced dose or permanent discontinuation of CAPRELSA.

Photosensitivity reactions are increased with CAPRELSA. Patients should be advised to wear sunscreen and protective clothing when exposed to the sun. Due to the long half life of CAPRELSA (19 days), protective clothing and sunscreen should continue for 4 months after discontinuation of treatment.

Ischemic Cerebrovascular Events

Ischemic cerebrovascular events have been observed with CAPRELSA and some cases have been fatal. In the randomized medullary thyroid cancer (MTC) study, ischemic cerebrovascular events were observed more frequently with CAPRELSA compared to placebo (1.3% compared to 0%) and no deaths were reported. The safety of resumption of CAPRELSA therapy after resolution of an ischemic cerebrovascular event has not been studied. Discontinue CAPRELSA in patients who experience a severe ischemic cerebrovascular event.

Haemorrhage

Serious haemorrhagic events, which in some cases were fatal, have been observed with CAPRELSA. There were no fatal bleeding events in the

randomized MTC study. Three patients died of fatal bleeding events while on CAPRELSA therapy in clinical studies. Do not administer CAPRELSA to patients with recent history of haemoptysis of ≥ 1/2 teaspoon of red blood. Discontinue CAPRELSA in patients with severe hemorrhage.

Hypothyroidism

In the randomized MTC study where 90% of the patients enrolled had prior thyroidectomy, increases in the dose of the thyroid replacement therapy were required in 49% of the patients randomized to CAPRELSA compared to 17% of the patients randomized to placebo. Thyroid-stimulating hormone (TSH) should be obtained at baseline, at 2 to 4 weeks and 8 to 12 weeks after starting treatment with CAPRELSA and every 3 months thereafter. If signs or symptoms of hypothyroidism occur, thyroid hormone levels should be examined and thyroid replacement therapy should be adjusted accordingly.

Diarrhoea

Diarrhoea is a known adverse effect of CAPRELSA and frequency of diarrhoea in the vandetanib arm of the pivotal MTC study was more than double that in the placebo arm (56% vs 25%). Routine anti-diarrhoeal agents are recommended for the treatment of diarrhoea. Serum electrolytes should be monitored as appropriate. If severe diarrhoea (CTCAE grade 3-4) develops, CAPRELSA should be stopped until diarrhoea improves. Upon improvement, treatment with CAPRELSA should be resumed at a reduced dose (see DOSAGE AND ADMINSTRATION and ADVERSE EFFECTS).

Hypertension

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

Heart failure

Heart failure has been observed in patients who received CAPRELSA. Temporary or permanent discontinuation of CAPRELSA may be necessary in patients with heart failure. It may not be reversible on stopping CAPRELSA. Some cases have been fatal. Patients with NYHA classification ≥2 heart failure were excluded from enrolment in the pivotal study of CAPRELSA in MTC.

Alanine aminotransferase elevations

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

Periodic monitoring of alanine aminotransferase is recommended in patients receiving CAPRELSA.

Interstitial lung disease

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

Reversible posterior leukoencephalopathy syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic oedema diagnosed by a MRI of the brain, has been observed infrequently in patients receiving CAPRELSA treatment in combination with chemotherapy or in paediatric patients with brain tumors receiving CAPRELSA as monotherapy. This syndrome should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function.

Pancreatitis

CAPRELSA may cause elevation in amylase and/or lipase. Pancreatitis has been reported. Discontinue CAPRELSA if pancreatitis occurs. Once pancreatitis has resolved, consider restarting CAPRELSA at a lower dose.

Effects on fertility

Vandetanib had no effect on fertility in male rats at up to 20mg/kg/day (similar to the clinical exposure based on AUC). In a female fertility study, there was a trend towards increased oestrus cycle irregularity at ≥10 mg/kg/day (~0.4 times the clinical exposue) and reduction in pregnancy incidence and increase in implantation loss at 25 mg /kg/day. In a repeat-dose toxicity study in rats, there was a decrease in the number of corpora lutea in the ovaries of rats given 75mg/kg/day (~2 times the clinical exposure) vandetanib for 1 month (no effect at 25mg/kg/day).

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.

Use in pregnancy – Category D

There are no adequate and well-controlled studies in pregnant women using CAPRELSA. Based on preclinical data, CAPRELSA may cause foetal harm when administered to a pregnant woman, as the risk that vandetanib is associated with

developmental abnormalities is predicted to be high. As expected from its pharmacological actions, vandetanib has shown significant effects on all stages of female reproduction in rats.

If CAPRELSA is used during pregnancy or if the patient becomes pregnant while receiving CAPRELSA, she should be apprised of the potential hazard to the foetus or potential risk for 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. Women of childbearing potential must use effective contraception during therapy and for at least four months following the last dose of CAPRELSA.

Vandetanib is embryotoxic and teratogenic in rat. Administration of vandetanib to pregnant rats during organogenesis between gestation day 6 and 15 increased the incidences of fetal heart vessel abnormalities at all doses tested (1-25 mg/kg/day), increased the incidences of pelvic cavitation of the kidneys and dilated ureter at 25 mg/kg/day, and delayed ossification of skull, vertebrae and sternum at ≥ 10 mg/kg/day. In a pre-/post-natal development study, pregnant rats dosed 25/mg/kg/day from gestation day 6 to 23 had total litter loss. The only maternal effect in the rat studies was decreased body weight gain at 25 mg/kg/day; there were no signs of maternal effects at lower dose. Exposures to vandetanib in pregnant rats were 0.03-1 times the clinical exposure based on AUC or C_{max}.

Use in lactation

There are no data on the use of CAPRELSA in breast feeding women. Breast feeding mothers are advised to discontinue nursing while receiving CAPRELSA therapy. Vandetanib was excreted into milk in rat and found in plasma of pups following dosing to lactating rats.

In rats dosed with 1 or 10 mg/kg/day vandetanib during gestation and lactation, decreased live litter size, reduced post-natal pup growth and delayed physical development were observed in all treated groups and delayed sexual maturation in females at 10 mg/kg/day. The maternal exposure to vandetanib during lactation was 0.08-0.8 times the clinical exposure based on AUC.

Paediatric use

CAPRELSA is not indicated for use in paediatric patients, as safety and efficacy of CAPRELSA in children have not been established.

Use in elderly

There is limited clinical data in patients aged over 75.

Genotoxicity

Vandetanib has shown no mutagenic or clastogenic potential in bacterial gene mutation assays, an *in vitro* chromosome aberration assay in human lymphocytes and a rat micronucleus assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with vandetanib.

Wound healing

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 CAPRELSA and subsequent elective surgery required to avoid the risks of impaired wound healing has not been determined. In the pivotal study of CAPRELSA in MTC, subjects were excluded from enrolment if they had had major surgery within 4 weeks of randomisation. In clinical studies of CAPRELSA, a small number of patients had surgery while receiving CAPRELSA and there were no reported wound healing complications.

Effects on ability to drive and use machines

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

INTERACTIONS WITH OTHER MEDICINES

Effect of vandetanib on other medicinal products

In vitro data suggest that vandetanib is a moderate CYP3A4 inducer. Therefore, since no clinical interaction studies have been performed, caution should be made when vandetanib is combined with CYP3A4 substrates, especially estroprogestatives, immunosuppressants like cyclosporin or tacrolimus, or antineoplastic agents like docetaxel and bortezomib.

Vandetanib is a weak inhibitor of the efflux pump P-glycoprotein (P-gp). The co-administration of vandetanib and medicinal products excreted by P-gp, such as dabigatran or digoxin may result in increased plasma concentrations of these medicinal products. Patients receiving dabigatran or digoxin and vandetanib may require increased clinical and biological surveillance and appropriate dose adjustments, if needed.

Vandetanib is an inhibitor of the organic cation transporter 2 (OCT2) transporter. Therefore, vandetanib may have the potential to decrease the elimination of medicinal products known to be excreted by OCT2 and increase a patient's exposure to these medicinal products. Metformin is a substrate of OCT2 and patients who are receiving vandetanib and metformin (or other substrate of OCT2) may require more careful monitoring, and possible dose adjustment of metformin.

Drugs that prolong the QT Interval

The administration of CAPRELSA with agents that may prolong the QT interval should be avoided (see PRECAUTIONS). Concomitant administration of CAPRELSA and ondansetron should be avoided, as this been shown to increase ondansetron exposure and result in an additive QTc prolonging effect.

Vitamin K antagonists

Due to increased thrombotic risk in patients with cancer the use of anticoagulant is frequent. In consideration of the high intra-individual variability of the response to anti-coagulation, 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.

Effect of other medicinal products on vandetanib

In a clinical study performed with healthy volunteers, the co-administration of vandetanib (a single dose of 300 mg) with itraconazole (repeated-doses of 200 mg, once daily), a potent CYP3A4 inhibitor, increases vandetanib plasma exposure about 9%. Since the itraconazole dose was under the minimal recommended dose to inhibit CYP3A4, (i.e 400 mg once day) caution should be made when itraconazole, and other potent CYP3A4 inhibitors (e.g. ketocoanzole, ritonavir and clarithromycin) are combined with vandetanib.

In a clinical study performed with healthy male subjects, the exposure to vandetanib was reduced by 40% when given together with the potent CYP3A4 inducer, rifampicin. Therefore, administration of vandetanib with rifampicin and other potent CYP3A4 inducers (e.g. carbamazepine, phenobarbital and St. John's Wort) should be avoided.

The effect of proton pump inhibitors on the gastrointestinal absorption of vandetanib has not been determined. Vandetanib demonstrates pH dependent solubility; therefore the co administration of vandetanib with proton pump inhibitors may reduce a patient's exposure to vandetanib. The concomitant use with these therapeutic classes is therefore not recommended.

Exposure to CAPRELSA is not affected by food.

ADVERSE EFFECTS

Overall Summary of Adverse Effects

Across all CAPRELSA (vandetanib) clinical studies, approximately 4000 patients have received CAPRELSA. This includes patients receiving CAPRELSA as monotherapy or in combination with chemotherapy, across a range of tumour types.

In the randomised, double blind, pivotal phase III clinical study (study 58) in unresectable locally advanced and metastatic medullary thyroid cancer patients, the safety analysis set included 330 patients (231 patients in the CAPRELSA arm and 99 patients in the placebo arm; 1 patient randomised to receive placebo did not receive treatment).

The most commonly reported (>20% incidence) adverse events (AEs) in the CAPRELSA arm of study 58 were diarrhoea, rash, nausea, hypertension, headache, fatigue, acne and decreased appetite. These events are consistent with the known safety profile of CAPRELSA and the mechanism of action of vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) inhibition.

The most commonly reported AEs that led to CAPRELSA dose reduction were diarrhoea, QTcF prolongation, and rash. Patients whose dose reduced from 300 mg to 200 mg or 100 mg remained on the lower dose for a median of 23 weeks or 29 weeks, respectively.

Adverse Events during Clinical Trials

The following adverse events have been identified in the pivotal clinical study (study 58) with patients receiving CAPRELSA monotherapy as treatment for unresectable locally advanced and metastatic medullary thyroid cancer (N=231).

Table 2 presents the adverse events reported at a very common (≥10%) frequency in either the vandetanib or placebo arm in study 58.

Table 2 Summary of patients who had at least 1 adverse event at a very common (≥10%) frequency in study 58 for medullary thyroid cancer

Preferred term (PT)	CAPRELSA 300 mg daily N=231[a] N (%)	Placebo N=99[a] N (%)
Gastrointestinal Disorders		
Diarrhoea	130 (56)	26 (26)
Nausea	77 (33)	16 (16)
Vomiting	34 (15)	7 (7)
Abdominal Pain	33 (14)	5 (5)
Dyspepsia	25 (11)	4 (4)

Preferred term (PT)	CAPRELSA 300 mg daily N=231[a] N (%)	Placebo N=99[a] N (%)
General disorders		
Fatigue	55 (24)	23 (23)
Asthenia	34 (15)	11 (11)
Investigations		
Electrocardiogram QT Prolonged	33 (14)	1(1)
Weight Decreased	24 (10)	9 (9)
Decreased Appetite	49 (21)	12 (12)
Hypocalcaemia	25 (11)	3 (3)
Psychiatric disorders		
Insomnia	30 (13)	10 (10)
Respiratory disorders		
Nasopharyngitis	26 (11)	9 (9)
Cough	25 (11)	10 (10)
Skin and Cutaneous Disorders		
Rash	104 (45)	11 (11)
Acne	46 (20)	5 (5)
Dry Skin	35 (15)	5 (5)
Dermatitis Acneiform	35 (15)	2 (2)
Pruritus	25 (11)	4 (4)
Photosensitivity Reaction	31 (13)	0
Nervous System Disorders		
Headache	59 (26)	9 (9)
Vascular disorders		
Hypertension	73 (32)	5 (5)

[a] Number (%) of patients with adverse events (AEs), by system organ class (SOC) then in decreasing order of frequency.

[b] Reported as an AE, not via confirmed electrocardiogram.

Only patients who took at least 1 dose of randomized treatment are included in this table. AEs that occurred while on CAPRELSA or in the 60-day follow-up period after the last dose of CAPRELSA are included.

Table 3 presents a summary of patients who experienced at least 1 serious adverse event with CAPRELSA during randomized treatment with a common (≥ 1% to <10%) or very common (≥10%) frequency in study 58.

Table 3 Summary of patients who experienced at least 1 serious adverse event with CAPRELSA during randomized treatment with a frequency of ≥1% in study 58

Preferred term (PT)	CAPRELSA 300 mg daily N=231[a] N (%)	Placebo N=99[a] N (%)
Infections and Infestations		
Pneumonia	5 (2.2)	0 (0.0)
Urinary Tract Infection	3 (1.3)	0 (0.0)
Gastrointestinal Disorders		
Diarrhoea	5 (2.2)	0 (0.0)
Abdominal Pain	3 (1.3)	0 (0.0)
Metabolism and Nutrition Disorders		
Decreased Appetite	4 (1.7)	0 (0.0)
Hypercalcaemia	3 (1.3)	0 (0.0)
Vascular Disorders		
Hypertensive Crisis	4 (1.7)	0 (0.0)
Hypertension	3 (1.3)	0 (0.0)
Psychiatric Disorders		
Depression	3 (1.3)	0 (0.0)

[a] Number (%) of patients with serious adverse events (SAEs), by system organ class (SOC) then in decreasing order of frequency.

Only patients who took at least 1 dose of randomized treatment are included in this table. SAEs that occurred while on CAPRELSA or in the 60-day follow-up period after the last dose of CAPRELSA are included.

Less Common Clinical Trial Serious Adverse Events (<1%)

The following serious adverse events were reported with CAPRELSA during randomized treatment with an uncommon (≥ 0.1% to <1%) frequency in study 58:

Cardiac Disorders: Arrhythmia (0.4%), atrial fibrillation (0.4%), bradycardia (0.4%), cardiac failure acute (0.4%), pericarditis (0.4%).

Eye Disorders: Glaucoma (0.4%), vision blurred (0.4%).

Gastrointestinal Disorders: Dysphagia (0.9%), vomiting (0.9%), gastrointestinal haemorrhage (0.4%), colitis (0.4%), gastritis (0.4%), ileus (0.4%), pancreatitis (0.4%), peritonitis (0.4%), pneumatosis intestinalis (0.4%), small intestinal perforation (0.4%).

General Disorders and Administration Site Conditions: Asthenia (0.4%), fatigue (0.4%), general physical health deterioration (0.4%), chest pain (0.4%), mucosal inflammation (0.4%).

Hepatobiliary Disorders: Cholecystitis (0.4%), cholelithiasis (0.4%).

Infections and Infestations: Bronchitis (0.9%), appendicitis (0.9%), diverticulitis (0.9%), sepsis (0.9%), abdominal wall abscess (0.4%), gastroenteritis bacterial (0.4%), gastroenteritis viral (0.4%), infected bites (0.4%), laryngitis (0.4%), pyelonephritis (0.4%), staphylococcal infection (0.4%), staphylococcal sepsis (0.4%), tracheitis (0.4%).

Injury, Poisoning and Procedural Complications: Joint injury (0.4%), stent occlusion (0.4%), venomous bite (0.4%).

Metabolism and Nutrition Disorders: Dehydration (0.9%), hypocalcaemia (0.9%), hypokalemia (0.9%), hypoglycaemia (0.4%), hyponatremia (0.4%), malnutrition (0.4%).

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps): Metastasis to bone (0.4%).

Nervous System Disorders: Loss of consciousness (0.9%), transient ischemic attack (0.9%), brain edema (0.4%), cerebral ischemia (0.4%), depressed level of consciousness (0.4%), peripheral sensorimotor neuropathy (0.4%).

Psychiatric Disorders: Bipolar disorder (0.4%).

Renal and Urinary Disorders: Nephrolithiasis (0.9%), anuria (0.4%), calculus ureteric (0.4%), renal colic (0.4%), renal failure (0.4%), tubulointerstitial nephritis (0.4%).

Respiratory, Thoracic and Mediastinal Disorders: Pneumonitis (0.9%), hemoptysis (0.4%), bronchospasm (0.4%), chylothorax (0.4%), dyspnea (0.4%), pneumonia aspiration (0.4%), respiratory arrest (0.4%), respiratory failure (0.4%).

Skin and Subcutaneous Tissue Disorders: Photosensitivity reaction (0.9%), pruritis (0.4%), rash (0.4%), skin ulcer (0.4%).

Vascular Disorders: Accelerated hypertension (0.4%), pelvic venous thrombosis (0.4%), vena cava thrombosis (0.4%).

Events such as torsade de pointes, Stevens-Johnson syndrome, erythema multiforme and reversible posterior leukoencephalopathy syndrome have been uncommon events in patients treated with vandetanib monotherapy.

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

Alopecia and nail disorders are also common (>5% occurrence) in patients treated with CAPRELSA.

Laboratory findings

Table 4 - Laboratory Abnormalities in Patients with MTC[2]

Laboratory Parameter	**CAPRELSA 300 mg N=231**		**Placebo N=99**	
Hematologic				
Protein in urine by dipstick (1+ or greater)	210 (90.9%)		28 (28.3%)	
Blood in urine by dipstick (1+ or greater)	79 (34.2%)		22 (22.2%)	
Increased haemoglobin (≥ 1.8g/dL)	28 (12%)		0 (0%)	
Chemistries				
Increased serum TSH	43 (18.6%)		1 (1%)	
Chemistries (graded)	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Increased creatinine[1]	38 (16%)	0	1 (1%)	0

1 The increases in serum creatinine were CTCAE grade 1-2, and may be related to inhibition of the human transport protein OCT2

2 Table 4 represents the incidence of laboratory findings in a randomized clinical trial in medullary thyroid cancer, not of reported adverse events.

Findings of increased serum lipase and increased serum amylase were observed in study 44, a randomised, double-blind, placebo controlled study and are presented in Table 5 below.

Table 5

Laboratory Parameter	**CAPRELSA 300 mg N=601 (amylase) N=588 (lipase)**		**Placebo N=297 for amylase N = 292 for lipase**	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3-4**
Increased serum amylase	143 (23.8%)	30 (5.0%)	46 (15.5%)	11 (3.7%)
Increased serum lipase	141 (24.0%)	24 (3.9%)	33 (11.3%)	9 (3.0%)

DOSAGE AND ADMINISTRATION

Treatment should be initiated and supervised by a physician experienced in treatment of cancers and in use of anticancer medicinal products.

Dosage in adults

CAPRELSA 300 mg oral tablets once daily. Dosing may also be by 3 x 100 mg tablets once daily.

CAPRELSA tablets may be taken with or without food.

CAPRELSA tablets may also be dispersed in half a glass (50 ml) of non-carbonated drinking water. No other liquids should be used. The tablet is dropped in water, without crushing, stirred until dispersed (approximately 10 minutes) and the resultant dispersion swallowed immediately. Any residues in the glass are mixed with half a glass of water and swallowed. The liquid can also be administered through nasogastric or gastrostomy tubes. Direct contact of crushed tablets with the skin or mucous membrane should be avoided. If such contact occurs, wash thoroughly. Avoid exposure to crushed tablets.

Duration

CAPRELSA may be administered until patients with medullary thyroid cancer are no longer benefiting from treatment.

Missing dose

If a patient misses a dose, they should take the next daily dose as prescribed.

Dose adjustments

In the event of CTCAE grade 3 or higher toxicity or prolongation of the electrocardiogram QT interval, dosing with vandetanib should be temporarily

stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1. 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.

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 unless all risk factors that contributed to Torsades have been corrected**.** 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 should be maintained at 4 mmol/L or higher and 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.

Special patient populations

Children or adolescents: CAPRELSA is not indicated for use in paediatric patients, as safety and efficacy of CAPRELSA in children have not been established.

Elderly (>65 years): No adjustment in starting dose is required for elderly patients. There is limited clinical data in patients aged over 75.

Renal Impairment: Patients with mild renal impairment have a safety profile similar to that of patients with normal renal function. Clinical data, together with pharmacokinetic data from volunteers suggests that no change in starting dose is required in patients with mild renal impairment. The starting dose should be reduced to 200 mg in patients with moderate (creatinine clearance ≥30 to <50 mL/min) renal impairment. A pharmacokinetic study suggests that in volunteers with severe renal impairment, exposure to vandetanib may be increased up to 2-fold. There is limited clinical experience in patients with severe renal impairment, so safety and efficacy have not been established and CAPRELSA is not recommended for use.

Hepatic impairment: A single dose pharmacokinetic study in volunteers indicated that hepatic impairment did not affect exposure to vandetanib. Pharmacokinetic data from volunteers suggests that no change in starting dose is required in patients with mild or moderate or severe hepatic impairment. There is limited data in patients with liver impairment (serum bilirubin greater than 1.5 times upper limit of normal). CAPRELSA is not indicated for use in patients with hepatic impairment, as safety and efficacy have not been established.

OVERDOSAGE

There is no specific treatment in the event of overdose with CAPRELSA 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 QT prolongation and torsade de pointes should be considered.

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 of CAPRELSA must be interrupted, and appropriate measures taken to assure that an adverse event has not occurred, ie, ECG within 24 hours to determine QTc prolongation.

Contact the Poisons Information Centre on 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

PVC/ PVDC blister sealed with aluminium foil containing 3 x 10 film-coated tablets.

100 mg tablet: White, round, bi-convex, film-coated tablet, intagliated with ‘Z100’ on one side and plain on the reverse side.

300 mg tablet: White, oval, bi-convex, film coated tablet, intagliated with ‘Z300’ on one side and plain on the reverse side.

Storage conditions

Store below 30°C.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4).

DATE OF FIRST INCLUSION IN THE ARTG

31st January 2013