Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for vandetanib

Proprietary Product Name: Caprelsa

Sponsor: AstraZeneca Pty Ltd

August 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission:	New Chemical Entity
Decision:	Approved
Date of Decision:	15 January 2013
Active ingredient:	Vandetanib
Product Name:	Caprelsa
Sponsor's Name and Address:	AstraZeneca Pty Ltd Alma Road North Ryde NSW 2113
Dose forms:	Film-coated tablet/dispersible tablet
Strengths:	100 mg and 300 mg
Pack size:	30 tablet blister
Approved Therapeutic use:	For the treatment of patients with symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.
Route of administration:	Oral
Dosage:	300 mg once daily
ARTG Numbers:	384355 (100 mg tablet blister pack) 384354 (300 mg tablet blister pack)

Product background

This AusPAR describes an application by the sponsor, AstraZeneca Pty Ltd, to register a new chemical entity, vandetanib (Caprelsa), for the following indication:

> *Treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC).*

The proposed dose is 300 mg (1 x 300 mg or 3 x 100 mg tablets) once daily, until there is no longer benefit from treatment.

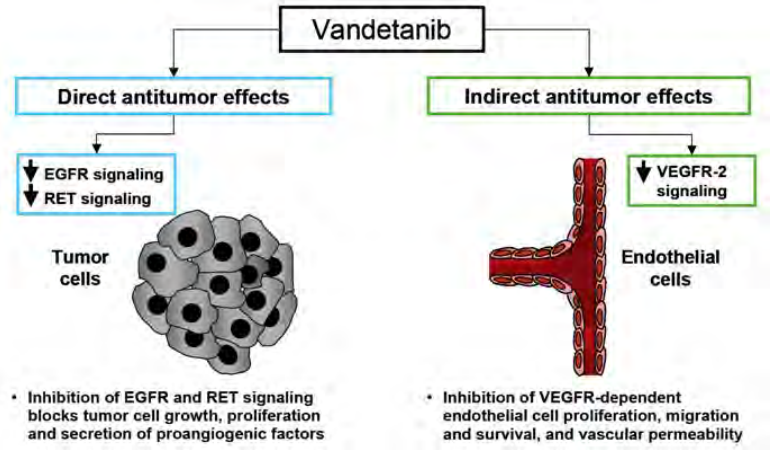
MTCs are rare neuroendocrine neoplasms derived from parafollicular cells of the thyroid, accounting for approximately 5% of thyroid neoplasms. MTC is hereditary in 20-30% (as part of multiple endocrine neoplasia syndromes 2A or 2B or familial MTC) but mostly is

sporadic.[1] Germline activating mutations in the proto oncogene Rearranged During Transfection (RET) are present in almost all hereditary MTCs. RET mutations are found in >50% of sporadic MTCs.

Vandetanib is an inhibitor of the tyrosine kinase which forms the catalytic domain of the Vascular Endothelial Growth Factor (VEGF) receptor. VEGF facilitates tumour progression by stimulating angiogenesis and increasing vascular permeability. Therefore, it is expected that vandetanib will inhibit angiogenesis in solid tumours and hence reduce growth. Vandetanib also has additional activity against Epidermal Growth Factor Receptor (EGFR) and RET receptor dependent tumour growth. The pathways of cancer that are targeted by vandetanib are (Figure 1):

- Indirect inhibition of tumour growth through anti angiogenic effects on endothelial cell proliferation, migration and survival;
- Direct inhibition of EGFR and/or RET dependent tumour growth.

Figure 1: Three key signalling pathways targeted by vandetanib in cancer.



Regulatory status

Vandetanib was designated as an orphan drug for the treatment of patients with unresectable locally advanced or metastatic MTC on 15 September 2010. Table 1 provides a list of major countries in which a similar application has been submitted and/or approved and the status of these applications at the time of the current submission.

[1] Solomon B, Rischin D. (2012) Progress in molecular targeted therapy for thyroid cancer: vandetanib in medullary thyroid cancer. *J Clin Oncol.* 30: 119-21.

Table 1: Submission and approval status of Caprelsa in other countries.

Country	Submission date	Approval date	Comment
Canada	26 January 2011	12 January 2012	
European Union*	3 September 2010	17 February 2012	Conditional marketing authorisation, dependent on the completion of an open label trial comparing RET negative and RET positive patients with sporadic medullary thyroid cancer.
New Zealand	N/A	N/A	
Switzerland	16 September 2011	1 May 2012	
United States	7 July 2010	6 April 2011	Post marketing commitments were imposed (conduct of carcinogenicity studies in 2 animal species and conduct of a randomised clinical study comparing 150mg and 300mg doses of vandetanib).

*Centralised procedure. Rapporteur was AFSSAPS in France and co-rapporteur was MEB Netherlands.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Vandetanib ('ZD6474', $C_{22}H_{24}BrFN_4O_2$, molecular weight = 475.4 g/mol) (Figure 2) is a substituted quinazoline; it is synthetic. It is achiral. Structurally, vandetanib is quite closely related to erlotinib and, particularly, gefitinib (Figure 3).

Figure 2: Structure of vandetanib.

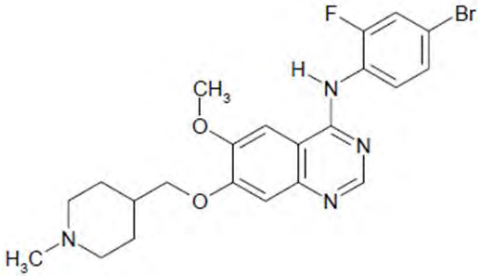
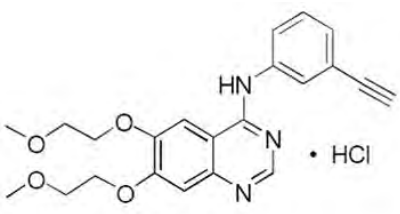
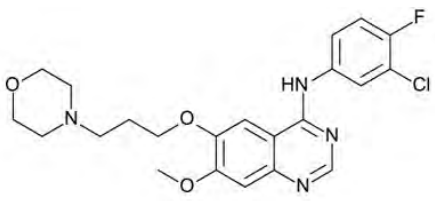


Figure 3: Structure of erlotinib and gefitinib.



erlotinib
Tarceva 25, 100 + 150 mg tablets
EGFR inhibitor



gefitinib
Iressa 250mg tablet
EGFR inhibitor

Vandetanib is a crystalline solid (melting point 235°C). Two pKa values are reported: 5.2 for the aminoquinazoline and 9.4 for the piperidine; it is basic. The reported partition coefficient (Log P) is 4.7 at pH 11.

Solubility is strongly pH dependent: 0.1 M HCl 41 mg/mL; pH 3 buffer 6.4 mg/mL; pH 7 buffer 0.3 mg/mL; water 0.008 mg/mL. Solubility thus might be an issue for achlorhydric patients. Vandetanib is described as a Biopharmaceutics Classification System (BCS) Class II molecule (high permeability, low solubility). The drug substance is milled and particle size is controlled. Polymorphic forms have been investigated and solvates and hydrates exist.

Drug product

The sponsor seeks to register Caprelsa 100 mg and 300 mg vandetanib film coated tablets. (The tablets are also referred to by another tradename, Zactima, within the submission.)

The tablets are manufactured from a common granulate so that the tablet cores are directly scaled. Both tablets are white, but they are distinguished by shape, size and markings. The tablets are not scored.

The recommended dose is 300 mg once daily (as 1 x 300 mg or 3 x 100 mg tablets) taken with or without food. The PI also states that Caprelsa tablets may be dispersed in 50 mL of non water over 10 minutes, allowing administration of an oral liquid directly or via a nasogastric or gastrostomy tube. Given Study 30 comparing tablets and an oral solution, bioavailability of the dispersion should be the same as the tablets.

Tablets are made by wet granulation using conventional excipients. The proposed finished product specifications do not include routine testing of tablet batches for dissolution, uniformity of content, nor degradation products. The evaluator does not think that there is sufficient data to accept this approach. Tablet dissolution, when tested, uses a paddle apparatus at 100 rpm with 1000 mL of aqueous 0.5% w/v sodium lauryl sulfate (SLS). The limit needs tightening.

The chemistry aspects of the application are acceptable with conditions of registration relating to batch testing.

Clinical trial formulations

A number of different formulations have been used during clinical development.

Phase I tablet formulations

The first vandetanib tablets used were size matched 1, 5 and 25 mg tablets. The higher strength tablets had slow disintegration times. To allow use of higher doses, 25, 100 and 200 mg tablets were developed.

Vandetanib Phase IIa tablet formulations

Another set of size matched 100, 300 and 400 mg tablets were developed. The tablets (19 mm x 10 mm elliptical) were considered undesirably large for marketing.

Vandetanib Phase IIb, Phase III and commercial vandetanib tablet formulations

Only 100 and 300 mg tablets were used in Phase III clinical studies. The shape of the 300 mg strength was changed to differentiate it from the Phase IIb tablet. The Phase III clinical tablet presentations are equivalent to the proposed commercial vandetanib Tablet presentations.

The clinical evaluation identifies one pivotal efficacy study (Study 58): this used tablets with the same formulation as proposed for registration (also used in Phase III Studies 32,

36 and 57). Given this, the lack of formal bioequivalence comparisons with earlier formulations is considered reasonable.

Biopharmaceutics

Vandetanib is relatively slowly absorbed (median Tmax [time to reach maximum plasma concentration following drug administration] 6 h, range 4-24 h). It binds to human serum albumin and α1-acid-glycoprotein. It is metabolised to desmethyl vandetanib (which is active) and vandetanib N-oxide, and slowly eliminated (t½ [elimination half life] ~19 days).

No absolute bioavailability study has been undertaken, even though it is very likely that an intravenous (IV) formulation could be formulated. Nevertheless, the sponsor argued that an IV formulation would have tolerability problems (inflammation at the infusion site and QT prolongation concerns).

Given the very close similarity of the 100 mg and 300 mg tablet formulations, bioequivalence of the strengths is accepted based on *in vitro* data.

Two bioavailability studies were considered by the Pharmaceutical Chemistry Section.

- Study D4200C00030 was a comparison of single 300 mg doses given as four tablet formulations and an oral solution in healthy subjects (23 enrolled, 12 completed). The study used an incomplete crossover design with long intervals between doses (6 or 5 weeks, which did not give complete washout). The study compared four deliberately made tablet formulation variants (not earlier clinical trial formulations). The variant tablets had slower dissolution *in vitro*, including the proposed tablet formulation. Unusually, observed mean bioavailability (maximum plasma drug concentration [Cmax] and the area under the plasma concentration-time curve [AUC]) was somewhat higher with the proposed tablet than the oral solution (just outside standard bioequivalence limits). This indicates that the tablets are 'optimally formulated'. Tablet manufacturing variations slightly reduced bioavailability (~10%).
- Study D4200C00024 was a study of the effect of food. It was a randomised three way crossover study in 16 healthy volunteers with a 6 week washout, comparing single 300 mg doses taken fasted (fasting also 2 h after dosing) or 30 minutes after starting a standard high fat breakfast, with replication of one of these doses. Food slightly reduces Cmax, but within standard bioequivalence limits. The PI thus recommends dosing with or without food.

The Pharmaceutical Subcommittee (PSC) notes (below) that, given low solubility in neutral solution, vandetanib bioavailability might be lower in achlorhydric patients.

Advisory committee considerations

The application was considered at the 145th (2012/3) meeting of the PSC, which recommended:

1. The PSC endorsed all the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic aspects of the application by the sponsor to register Caprelsa film coated tablets containing 100 mg and 300 mg of vandetanib. In particular, the PSC supported the concerns raised by the evaluator in relation to the proposal not to routinely test tablet dissolution, uniformity of content and degradation products and the questions relating to Study D4200C00030.
2. The PSC advised that all outstanding issues should be addressed to the satisfaction of the TGA.

3. The PSC noted the sponsor's justification for not providing an absolute bioavailability study. The PSC considered that an absolute bioavailability study could have been undertaken with a micro IV dose.
4. The PSC noted that the pharmacometric analyses provided had not been formally reviewed. This is particularly concerning as the data were used to:
   - Determine the likely impact of dose regimen on QTc.
   - Underpin a claim of "equivalence" of the different formulations used throughout the development of the products.
   - Provide evidence of lack of impact of various patient specific demographic variable of pharmacokinetics.
   - Provide evidence that there were no important pharmacokinetic differences between healthy subjects and patients.
   - Examine the impact of the proposed dosing regimen on response to therapy.
5. The PSC noted the following apparent issues with the modelling:
   - The model building process in some of the pharmacometric analyses was not very clear, and possibly poor. These analyses were not formally reviewed by the TGA, and require formal evaluation.
   - Model control streams and data were only provided in printable form which would prevent any evaluation or testing of the model by a reviewer.
   - While it appeared in one report that "oriental" patients respond to any vandetanib exposure to a far greater extent than other races, very little detail of the model (including its development and evaluation) that was used to predict this was provided. However, a later report contradicted this result. This is potentially a very important finding and warrants formal evaluation.
   - The cumulative exposure for the typical patient was not shown and so it was difficult to determine where the proposed 300 mg/day dose regimen sits on the relationship. Furthermore, the expected range of values for cumulative exposure over time in the population was not shown. As a result there is not real support/justification that the dose regimen proposed is "optimal".
6. The attention of the clinical Delegate and the Advisory Committee on Prescription Medicines (ACPM) should be drawn to the possible reduced bioavailability of vandetanib from these products in achlorhydric patients.
7. In the PI:
   - The "Description" section should be amended to include the pKa, solubility and partition coefficient as functions of pH.
   - The reference to 2 fluid ounces in the "Dosage and Administration" section should be changed to common Australian units (that is, 60 mL).
8. There is no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the ACPM.

Population pharmacokinetic studies are not reviewed by the Pharmaceutical Chemistry Section. The PI will be reviewed following ACPM consideration.

Quality summary and conclusions

Registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects with conditions of registration relating to batch testing.

III. Nonclinical findings

Introduction

Vandetanib (Caprelsa) is a new chemical entity. The sponsor has applied to register 100 and 300 mg tablets for the treatment of patients with unresectable locally advanced or metastatic MTC.

The sponsor submitted nonclinical data consisting of studies on primary, secondary and safety pharmacology, pharmacokinetics, single and repeat dose toxicity, genotoxicity, reproductive and developmental toxicity and phototoxicity. The *in vitro* and *in vivo* studies were satisfactorily designed, with the pivotal safety related studies Good Laboratory Practice (GLP) compliant. One deficiency of the nonclinical data was the lack of toxicokinetic data for the active metabolite, N-desmethyl vandtanib, in toxicity studies.

Pharmacology

Primary pharmacology

Vandetanib has been identified as a multiple kinase inhibitor, inhibiting VEGF dependent angiogenesis and EGFR and RET receptor dependent tumour growth. *In vitro* and *in vivo* pharmacology studies have been performed utilising *in vitro* recombinant enzyme assays to evaluate the potency and selectivity of vandetanib, *in vitro* cellular assays and *in vivo* assays of tumour growth. The *in vitro* studies showed that vandetanib inhibits multiple tyrosine kinases with the greatest activity against EGFR, RET and VEGFR-2 (IC50 [concentration at which 50% of the activity is inhibited] ranging from 0.020-0.50 μM depending on the assay methodology). Vandetanib also has potent activity against BRK (IC50 0.036-0.11 μM) and inhibits VEGFR-3 (IC50 0.1-0.3 μM), with less activity against VEGFR-1 (IC50 0.3-1.6 μM). Most kinase inhibition studies showed 5-7 fold selectivity for VEGFR-2 versus VEGFR-1. Higher concentrations of vandetanib inhibited the activity of other tyrosine kinases, including certain ephrin receptors (EphA1 and EphB2), and SRC related kinases (YES, LCK, LYN, SRC). Overall, vandetanib *in vitro* demonstrated selectivity for VEGFR-2, EGFR, RET and BRK over members of other families of protein kinases (AGC, CAMK, CMGC, STE and others), with potent activity against some receptors including H1, H2 and adrenergic α2A.

In comparison with other tyrosine kinase inhibitors, which are in late stage clinical development or have been approved for the treatment of cancer, vandetanib has comparable activity with gefitinib against EGFR, with sunitinib and cediranib against RET, and with sorafenib, motesanib and sunitinib against VEGFR-2 (Table 2). Kinase inhibition assays have showed that some RET mutations (for example, RET V804L and V804M) were resistant to vandetanib while other mutations (for example, L858R) are activating mutations, conferring greater sensitivity to vandetanib.

Table 2: Activities (IC50 in μM) of vandetanib and other tyrosine kinase inhibitors in kinase inhibition assays.

Kinase	Vandetanib	Sunitinib	Sorafenib	Gefitinib	Cediranib	Valatinib	Motesanib
VEGFR-2 (KDR)	0.038-0.053	0.143	0.027	11	-	-	0.027
EGFR	0.024-0.5	-	27.23	0.013	-	-	8.84
RET	0.02-0.52	0.053, 0.184	0.153	>1, 18	0.056	>1	0.724
VEGRF-3 (Flt-4)	0.11-0.26	-	-	22	-	-	-
VEGFR-1 (Flt-1)	0.29-1.6	-	-	>100	-	-	-
BRK	0.036-0.11	>100	-	1.6	-	-	-

Vandetanib was shown to be active against the proliferation of some cancer cell lines, but other cell lines of the same cancer were resistant to vandetanib. Studies suggested that inhibition of EGFR signalling is a significant determinant of the activity of vandetanib against cancer cells. There have been no data to date investigating activity of vandetanib against MTC cells *in vitro*, although vandatanib was shown to inhibit papillary thyroid carcinoma (PTC) cell lines carrying the RET/PYC3 and RET/PTC1 rearrangement.

In an *in vitro* study utilising an angiogenesis assay with HUVEC (human umbilical vein endothelial cell), vandetanib (10-500 nM) was found to reduced vascular tubule growth (total area of tubule growth; total tubule length; total number of branch points). The inhibitory effect of vandetanib on tubule growth (IC50 0.03-0.09 μM) was comparable to the IC50 generated against KDR-RTK (VEGFR-2) activity and VEGF stimulated proliferation in HUVEC. Vandetanib has also been shown to inhibit endothelial cell proliferation, survival, migration and invasion *in vitro*, inhibit blood vessel formation in mice with xenografts of human colon cancer (HT29) cells, and reduce angiogenesis and VEGF induced vascular permeability in the murine model of human lung cancer (NCI-H441) at PO (per os; oral administration) doses of 25-50 mg/kg/day.[2] In a matrigel model of angiogenesis in mice, vandetanib at PO doses of 12.5-50 mg/kg/day significantly, dose dependently inhibited VEGF dependent new blood vessel development. Vandetanib at 50 and 100 mg/kg/day also inhibited tumour cell induced new blood vessel formation in nude mice intradermally implanted with human non small cell lung carcinoma (NSCLC) (A549) cells.[3]

In a range of *in vivo* test systems, vandetanib was found to be active against a range of cancers (for example, human lung, prostate cancers) with once daily PO dosing (50-100 mg/kg/day) in nude mice and in the K-ras-dependent murine model of lung cancer. Vandeatnib treatment was shown to suppress tumour growth and metastasis in a murine othotopic human lung cancer (H441) model and prolonged survival.[4] Oral treatment of these mice with vandetanib at 50 mg/kg/day resulted in plasma Cmax of 2058 ng/mL, which was 2.5 fold higher than the expected human Cmax of 857 ng/mL at the proposed clinical dose of 300 mg/day. The activity of vandetanib against MTC was not investigated in nonclinical animal models.

In mice implanted subcutaneously with human breast cancer xenografts, the combination of vandetanib and docetaxel produced greater antitumour activity compared with either

[2] Wu W, *et al.* (2007) Targeted therapy of orthotopic human lung cancer by combined vascular endothelial growth factor and epidermal growth factor receptor signalling blockade. *Mol Cancer Ther.* 6: 471-483.
[3] Wedge SR, *et al.* (2002) ZD6474 inhibits vascular endothelial growth factor signalling, angiogenesis and tumour growth following oral administration. *Cancer Research* 62: 4645-4655.
[4] Wu W, *et al.* (2007) Targeted therapy of orthotopic human lung cancer by combined vascular endothelial growth factor and epidermal growth factor receptor signalling blockade. *Mol Cancer Ther.* 6: 471-483.

drug alone but the combination was also associated with greater toxicity (body weight loss).

Secondary pharmacodynamics and safety pharmacology

The secondary pharmacodynamics data consisted of two *in vitro* studies and one published *in vivo* article. The *in vitro* studies tested vandetanib in a panel of 334 radio ligand binding and enzyme assays covering a diverse range of enzymes, receptors, ion channels and transporters with significant activity, defined as > 50% inhibition, detected in 59 of the 334 targets investigated. Low Ki (inhibition constant) values (< 1 μM or 475 ng/mL) were obtained for histamine H1 (0.068 μM) and H2 (0.599 μM), adrenergic α2A (0.090 μM), adrenergic α2B (0.100 μM), adrenergic α2C (0.607 μM), imidazoline I2 (0.565 μM), dopamine D1 (0.753 μM) and D5 (0.948 μM), serotonin transporter (0.803 μM), 5-HT2A (0.813 μM) and 5-HT2B (1.19 μM). Functional assays with three receptors showed that vandetanib was an antagonist of H1, H2 and adrenergic α2C, with IC50 values of 9, 13 and 33 μM, respectively. While the Ki values were similar to the free fraction of the clinical steady state plasma Cmax (~85.7 ng/mL or 0.18 μM), the IC50 observed in the functional assays were > 50 fold higher than the free fraction of human Cmax.

The *in vivo* mouse study investigated cutaneous wound healing by giving PO daily doses of 50 and 100 mg/kg vandetanib or vehicle. Results from the study showed that mice treated with vandetanib had significantly lower wound breaking strength associated with a reduction in fibrosis and epithelial proliferation at both 7 and 28 days post wounding, suggesting that vandetanib, in a clinical setting, could slow wound healing in patients.

Safety pharmacology studies were performed to examine the potential effects of vandetanib on cardiovascular, renal, respiratory, central, peripheral and autonomic nervous systems, as well as the gastrointestinal (GI) tract. The studies found that vandetanib had no effect on a range of behaviours in mice over a period of 1 h following a PO dose of 50 mg/kg. The only finding was a small increase in rectal temperature (+1.4°C after 1 h). However, values were within the normal range and the small increase was relative to a slightly lower mean pre dose value (34.6°C, compared with 35.1°C in the control group). A Functional Observational Battery (FOB) test in rats showed that there was a decrease in open field activities (time to exit centre circle at all doses [40, 200 and 1000 mg/kg/day PO] and number of line crossings and supported rears at 200 and 1000 mg/kg) and a decrease in landing foot splay at 1000 mg/kg. However, the decrease in time to exit centre circle showed no dose relationship, and the low dose (40 mg/kg) could be considered as the No Observed Effect Level (NOEL). The study found that the central nervous system (CNS) effects were associated with decreased body weight gain at 200 and 1000 mg/kg, as well as piloerection at 1000 mg/kg. The FOB findings could be a reflection of general toxicity of the drug, but high brain distribution of the drug observed in rats suggest that the FOB observations were possibly direct effects on the CNS. Based on the pharmacokinetic data in tumour bearing mice, plasma Cmax at the PO dose of 50 mg/kg was ~2.5 times the human Cmax at the clinical dose of 300 mg. Based on plasma concentrations (at 4 h post dose) measured in the respiratory study in rats (Study 20060012PCR), the plasma Cmax (709 ng/mL) at 40 mg/kg in rats was similar to the expected clinical value (857 ng/mL). The Cmax (1663 and 2494 ng/mL, respectively) at 200 and 1000 mg/kg were 2 and 3 times, respectively, the Cmax in patients.

Clinically relevant and important findings in the cardiovascular studies were:

1. Inhibition of potassium channel in the human ether-a-go-go gene (hERG) assay by vandetanib (IC50 0.4 μM) and the N-desmethyl and N-oxide metabolites (respective IC50 1.3 and 4.0 μM);
2. Increased APD in canine Purkinje fibres *in vitro*;
3. Prolongation of QTc intervals in dogs by IV administration; and

4. Increased blood pressure in rats and dogs.

Studies found that vandetanib caused a concentration dependent increase in APD70 and APD90, with statistically significant increases at >1 μM. Overall, the effect was found to be greater at low frequency stimulation and low potassium conditions, indicating that at low heart rates the effect may be increased.

Studies using rat models found that PO administration of vandetanib (12.5 or 50 mg/kg) resulted in increased systolic and diastolic blood pressures, which were further increased after repeated dosing of 12.5 mg/kg/day for 7 days. In dogs, a single PO dose of vandetanib at 5, 15 or 40 mg/kg did not alter blood pressure or electrocardiogram (ECG) except for a decrease in heart rate at 40 mg/kg (by ~20 mmHg or 20%). Heart rates were also decreased in dogs after IV infusion compared to vehicle control values at plasma concentrations of 1.36 μM with no further increases at high concentrations, although the difference between vehicle and treated groups was not statistically significant. In the same IV study, QTc interval was increased at plasma vandetanib concentrations of >1.36 μM (compared with a clinical Cmax 1.8 μM) and blood pressures increased at the highest dose with a plasma concentration of 3.16 μM. Vandetanib also caused a dose dependent increase in T wave amplitude and polarity. Based on the plasma concentrations in the pharmacokinetic studies, the plasma Cmax of vandetanib in rats at 12.5 mg/kg PO and in dogs at 40 mg/kg PO were below the expected clinical Cmax. Very low exposures were achieved in the repeat dose toxicity studies in dogs, in which no consistent effects on BP or QTc were observed. The nonclinical study findings suggest that vandetanib may cause prolongation of QT intervals and increases in blood pressure in patients at the proposed clinical daily dose of 300 mg.

The potential effects on the cardiovascular function of vandetanib with the anti emetic drug, ondansetron, which is known to carry a QT interval prolongation risk, were studied in the hERG channel assay and in dogs. Treatment of mammalian cells expressing hERG with both vandetanib and ondansetron (each at concentrations around their respective IC50) resulted in approximately 70% inhibition of the potassium channel, indicating an additive effect. However, in dogs vandetanib administered by the IV route did not enhance ondansetron induced QTc interval prolongation at the plasma vandetanib concentration of 1886 ng/mL (~2 times the expected clinical Cmax), suggesting the lack of additive activities on QTc interval.

No significant effects on the respiratory function were observed in rats at oral doses up to 200 mg/kg. At a higher dose of 1000 mg/kg, there was an increase in peak inspiratory flow associated with a decrease in inspiration time. Overall, the results indicate that vandetanib is not expected to cause significant effects on the respiratory function in patients. Vandetanib also caused a dose dependent inhibition of gastric emptying and intestinal transit at 40-1000 mg/kg, suggesting potential effects on GI tract motility in patients.

No diuretic activity was seen in rats after a PO dose of 50 mg/kg vandetanib. Increases in urinary protein and decreases in urinary potassium and chloride were observed in the 6-24 h urine collection, but not in the 0-6 h collection. Similar findings (increased protein, as well as decreased potassium and sodium) were observed in the repeat dose toxicity studies in rats, but not in dogs. The results suggest that, in a clinical setting, vandetanib may cause increased urinary excretion of protein and decreased potassium, sodium and chloride excretion in patients.

Pharmacokinetics

Absorption, distribution, metabolism and excretion were studied in rats and dogs, with metabolism and excretion studied in mice models for nonclinical pharmacology and toxicology. Tissue distribution was investigated in albino and pigmented rats, as well as

tumour xenografts in mice. Human enzymes responsible for the metabolism of vandetanib and the potential for vandetanib to inhibit and induce CYP450 enzymes were investigated in vitro, with vandetanib also assessed as a possible substrate/inhibitor of specific transporter proteins.

Vandetanib was highly permeable in the *in vitro* Caco-2 cell assay. Absorption was high in animal species with bioavailabilities of ~90% in rats and ~56% in dogs. Absorption was relatively slow with Tmax typically 3-5 h. Plasma clearance was ~15 ml/min/kg in rats (~20% of liver blood flow) and ~35 ml/min/kg in dogs (slightly greater than liver blood flow). Although clearance was relatively high, the elimination was slow because of the high volume of distribution (~27 L/kg in rats, 44 L/kg in dogs). Fast clearance (13.2 L/h = 220 mL/min) and large volume of distribution (~7450 L or 106 L/kg at a body weight of 70 kg) were also reported in humans. The half life of vandetanib was ~30 h in rats and ~20 h in dogs, which were markedly shorter than the half life in humans (~19 days or 456 h). The high volume of distribution was consistent with extensive tissue distribution observed in rats and also in mice. Tissue concentrations of drug related materials were higher than in blood, and there was evidence of penetration into the brain and binding to melanin. Distribution into blood cells was evident in all species, with blood/plasma ratio for all drug related materials being ~1.5 in rats, ~1.8 in dogs, and ~1 in humans. Binding to plasma protein was high (mouse 90%, rat 83%, dog 86%, rabbit 88%, human 90%), and albumin was the main protein responsible for plasma protein binding (76% for human plasma albumin).

In repeat dose toxicology studies in rats and dogs, increasing exposures were achieved with increasing dose levels. At the oral dose of 5 mg/kg/day, there was evidence of accumulation in rats and minimal accumulation in dogs. Exposures (based on AUC and Cmax) achieved in the pivotal toxicity studies were consistently below the exposure in patients at the daily dose of 300 mg except that the exposure in the one month rat study at 25 and 75 mg/kg/day was comparable with and ~2 fold higher than the clinical exposure, respectively (Table 3).

Table 3: Relative exposure to vandetanib in toxicity studies by oral administration.

Species	Study (Dosing duration)	Dose (mg/kg/day)	Sampling time	$AUC_{0-24\,h}$ (ng·h/mL)	C_{max} (ng/mL)	ER_{AUC}[c]	ER_{Cmax}[c]
Rat	TAR2937 (1 month)	5	1 day[a]	1555	97	0.08	0.1
		25	28 days	22585	1213	1.1	1.4
		75	23 days	34448	1853	1.7	2.2
	TPR2939 (6 months)	1	26 weeks	799	39.6	0.04	0.05
		5	26 weeks	4257	225	0.2	0.3
		20/10	26 weeks	8114	427	0.4	0.5
Dog	TAD1041 (14 days)	5	14 days	1265	83	0.06	0.1
		25	14 days	4240	332	0.2	0.4
		40	14 days	5782	353	0.3	0.4
	TAD1042 (1 month)	5	29 days	678	54	0.03	0.06
		15	29 days	2380	156	0.12	0.18
		40	29 days	ND	ND	–	–
	TPD1043 (9 months)	1	9 months	218	12	0.01	0.01
		5	9 months	1035	61	0.05	0.07
		20/15	9 months	2273	160	0.11	0.19
Pregnant rat	TTR/2938 (GD 6 -15)	1	9 days[d]	-	21.5	-	0.03
		10	9 days	-	347	-	0.4
		25	9 days	-	867	-	1.0
Lactating rat	AA/29682 (GD 6 or 16 – PND 8)	1	24 days[e]	1240	72.8	0.06	0.08
		10	24 days	13785	719	0.7	0.8
		10	14 days	11503	649	0.6	0.8
Human	CER[b]	300 mg	Steady state	19829	857	–	–

[a] no data after repeated dosing; [b] Steady state AUC_{0-24} and C_{max} values from the Clinical Evaluation Report; ER, animal/human exposure ratio based on AUC or C_{max}; c, animal/human exposure ratio based on AUC or C_{max}; d, after the last dose on GD 15; e, on PND 7; ND, no data; GD, gestation day; PND, post-natal day.

Metabolic profiles of vandetanib were qualitatively similar in animal species and humans. Two major metabolites, N-desmethyl and N-oxide vandetanib, were produced in the animal species (rat and dog) used in toxicity studies and humans, although there were quantitative differences between species. *In vitro* assays using human liver microsomes showed that the formation of N-desmethyl vandetanib was predominantly mediated by CYP3A4 and vandetanib-N-oxide by FMO1 and FMO3. The animal species used for the safety assessment of vandetanib are considered appropriate. Vandetanib and metabolites are excreted mainly in rat and dog faeces. Studies in rats showed high biliary excretion and evidence of conversion of the N-oxide metabolite to the parent compound in the intestinal tract. Similarly, a high percentage of dose is excreted in faeces of humans, although the proportion excreted in human urine (~25% of dose, ~69% total dose recovery) was higher than in animal species (rat: ~6-15% of dose, ~85% total dose recovery; dog: ~7% of dose, ~66% total dose recovery). N-desmethyl vandetanib displayed similar activity to vandetanib in kinase inhibition assays and cellular function assays (EGF, VEGF or bFGF stimulated HUVEC proliferation). The N-oxide metabolite was ~50 fold less active in HUVEC proliferation assays and had similar or lower activities in kinase inhibitory assays compared to the parent compound (Table 4).

Table 4: Comparative pharmacological activity (mean IC50 in μM) of vandetanib and major metabolites.

	Tyrosine kinase activity				HUVEC proliferation		
	KDR (VEGFR-2)	Flt-1 (VEGRF-1)	EGFR	FGFR1	VEGF-stimulated	EGF-stimulated	bFGF-stimulated
Vandetanib	0.04	1.60	0.50	3.60	0.06	0.17	0.80
N-desmethyl-vandetanib	0.07	0.90	0.17	6.20	0.02	0.12	0.95
N-oxide-vandetanib	0.20	1.92	0.46	10.20	3.10	8.80	> 10

Exposures to metabolites N-desmethyl and N-oxide vandetanib were determined in rats and dogs in single dose pharmacokinetic studies. The single dose studies showed that exposures (based on plasma AUC) to N-desmethyl vandetanib and vandetanib-N-oxide were ~1.5% and ~3% of vandetanib AUC, respectively, of the exposure to vandetanib in rats, and ~50% and ~25% in dogs, compared to 7-10% and 1.4-1.8% in healthy human volunteers after a single oral dose (see: clinical evaluation report). Assessment of these metabolites in NSCLC cancer patients after repeated dosing showed accumulation of 3.5-fold for N-desmethyl vandetanib and 1.9-fold for N-oxide vandetanib after 24 weeks of administration. Plasma concentrations of the metabolites were not measured in animal species following repeated dosing and this omission is considered a deficiency of the nonclinical data. Based on the exposures to these metabolites after a single PO dose, the exposure of rats to the most active metabolite, N-desmethyl vandetanib relative to the parent drug in the toxicity studies were lower compared to that of humans. However, the relative exposure of dogs to this metabolite was higher compared that observed in humans. Nonetheless, exposures of both animal species to vandetanib alone or the parent and the N-desmethyl metabolite were below the expected human exposure at the clinical dose of 300 mg/day (Table 5).

Table 5: Comparative exposures to vandetanib and N-desmethyl vandetanib (major active human metabolite) in toxicity studies by oral administration.

Species	Study (Dosing duration)	Dose (mg/kg/day)	Sampling time	AUC_{0-24h} (ng·h/mL)			ER[c]	
				Vandetanib	N-desmethyl vandetanib[a]	Total[b]	Vandetanib	Total[b]
Rat	TAR2937 (1 month PO)	5	1 day[a]	1555	23.3	1578	0.08	0.07
		25	28 days	22585	339	22924	1.1	1.1
		75	23 days	34448	517	34965	1.7	1.6
	TPR2939 (6 months PO)	1	26 weeks	799	12.0	811	0.04	0.04
		5	26 weeks	4257	63.9	4321	0.2	0.2
		20/10	26 weeks	8114	122	8236	0.4	0.4
Dog	TAD1041 (14 days PO)	5	14 days	1265	633	1898	0.06	0.09
		25	14 days	4240	2120	6360	0.2	0.3
		40	14 days	5782	2891	8673	0.3	0.4
	TAD1042 (1 month PO)	5	29 days	678	339	1017	0.03	0.05
		15	29 days	2380	1190	3570	0.12	0.16
		40	29 days	ND	ND	-	–	-
	TPD1043 (9 months PO)	1	9 months	218	109	327	0.01	0.01
		5	9 months	1035	518	1553	0.05	0.07
		20/15	9 months	2273	1137	3410	0.11	0.16
Pregnant rat	TTR/2938 (GD 6 -15)	1	9 days[d]	21.5[f]	0.32[f]	21.8[f]	0.03[f]	0.02[f]
		10	9 days	347[f]	5.2[f]	352[f]	0.4[f]	0.4[f]
		25	9 days	867[f]	13[f]	880[f]	1.0[f]	0.9[f]
Lactating rat	AA/29682 (GD 6 or 16 – PND 8)	1	24 days[e]	1240	18.6	1259	0.08	0.06
		10	24 days	13785	207	13992	0.8	0.6
		10	14 days	11503	173	11676	0.8	0.5
Human	CER[b]	300 mg	Steady state	19829	1983	21812	–	-

[a] Based on the N-desmethyl vandetanib AUC of 1.5% (rat), 50% (dog) and 10% (human) of the parent drug AUC in single dose pharmacokinetic studies; [b] Vandetanib and the N-desmethyl metabolite; [c] Animal/human exposure ratio based on AUC; [d] After the last dose on GD 15; [e] On PND 7; [f] C_{max} or ER based on C_{max}; GD, gestation day; PND, post-natal day.

Vandetanib and its metabolites were highly excreted into milk of rats and found in plasma of pups following dosing of lactating rats post partum, indicating drug exposure of pups. The major component in milk was vandetanib, with trace amounts of the N-desmethyl and N-oxide metabolites.

Pharmacokinetic drug interactions

Since vandetanib is mainly cleared by metabolism by CYP3A4 to form N-desmethyl vandetanib and by FMO1 and FMO3 to form vandetanib N-oxide, the clearance of vandetanib may be affected by CYP3A4, FMO1 or FMO3 inhibitors or inducers. However, since the N-desmethyl vandetanib, the most predominant metabolite in humans, has similar pharmacological activities to the parent drug, as shown in kinase and cell proliferation assays *in vitro*, CYP3A4 inhibitors or inducers may not significantly alter the efficacy of the drug if the clearance of the N-desmethyl metabolite is similar to the parent drug. Furthermore, *in vitro* studies with human liver microsomes with selective CYP450 substrates showed weak inhibition of CYP2D6, with IC50 and Ki values 25 and 13 µg/mL respectively, compared to the clinical Cmax of 0.857 µg/mL. Neither vandetanib nor the N-desmethyl metabolite displayed time dependent inhibition of CYP450 enzymes. Therefore, from these *in vitro* results vandetanib is not expected to result in significant inhibition of the metabolism of other drugs cleared by CYP450.

In the 1 month repeat dose toxicity study in rats, where CYP450 was measured at the end of the study, no dose dependent or biologically significant induction of CYP450 was observed. An *in vitro* study with human hepatocytes showed induction of CYP1A2, 2C9 and

3A4 activities at 0.24-0.95 μg/mL. The maximum induction compared to the vehicle control was 3 fold for CYP1A2, 2.3 fold for CYP2C9, and 17 fold for CYP3A4, which were 28%, 38% and 33% of the respective positive control (β-naphthoflavone for CYP1A2 and rifampicin for CYP2C9 and 3A4). The in vitro study findings suggest that repeated dosing in patients may induce CYP1A2, 2C9 and 3A4.

The Caco-2 cell assay showed similar permeability at both directions, suggesting that vandetanib is not a substrate of P-gp. In addition, an *in vitro* assay with MDCKII cells expressing MDR1 (P-gp), BCRP or MRP1 indicated that vandetanib was not a substrate of these transporters. Vandetanib displayed weak inhibition of MDR1 (IC50 8.7 μg/mL) and BCRP (IC50 11.9 μg/mL). The lack of significant inhibition of MDR1 and BCRP is consistent with the observation in tissue distribution studies in mice and rats showing relatively high levels of vandetanib and/or its metabolites in brain, that is, lack of or weak efflux pumping by the P-pg and BCRP transporters at the blood brain barrier.

Assessment of the effect of vandetanib on OCT2 in HEK cells expressing OCT2 indicated that vandetanib is an inhibitor of OCT2 (IC50 ~2.1 μg/mL compared with clinical Cmax 0.857 μg/mL), suggesting vandetanib may inhibit excretion of OCT2 substrates (for example, metformin, pindolol, creatinine). Effects on other transporters were not studied.

Toxicology

Vandetanib was tested for its potential to cause systemic toxicity following PO and IV administration in mice and by PO administration in rats in single dose studies. Repeat dose studies included IV dosing for up to 2 weeks in rats and dogs and PO administration for up to 6 months in rats and 9 months in dogs.

Acute toxicity

The single dose studies were well summarised in the nonclinical overview. A single PO dose of vandetanib at 2000 mg/kg to mice was not tolerated and 1000 mg/kg dose resulted in the death of 1 out of 10 mice. Clinical signs included hunched posture, trembling/shaking, cold, decreased breathing rate, subdued behaviour and piloerection. The single IV study in mice dosed with 50 mg/kg of vandetanib resulted in 1 of 10 mice dying immediately after administration. The remaining animals were observed for 14 days and clinical signs included irregular breathing, subdued behaviour, hunched posture and eyes partially closed. However, the mice recovered from the observed clinical signs within 90 min post dose. No salient histopathological findings were observed in either study.

In rats, 2 females dosed with 2000 mg/kg PO died approximately 5 h after dosing and the remaining animals (male and female) were killed on Day 4. Observed clinical signs for all surviving female rats on Day 1 included piloerection, hunched posture, and distended abdomen. Male rats exhibited no signs of toxicity on Days 1 and 2. Subsequent observations included thin appearance, loss of skin tone, tip toe gait, hollowed and distended abdomen, eyes partly closed, hunched posture, subdued behaviour, piloerection, urine staining and deposits on the nose, resulting in their termination on Day 4. The histopathological findings included hepatocyte vacuolation, fat deposition and necrosis in the liver, ulceration in the stomach, mucosal single cell necrosis and erosion in the duodenum, and macrophage vacuolation in the spleen. The study found no atypical observations or histopathological findings at 1000 mg/kg.

Repeat dose toxicity

Repeat dose toxicity studies in rats and dogs identified a range of target organs including gastrointestinal tracts, skeletal system, skin, kidneys and liver, and phospholipidosis in multiple organs. Ovaries were also affected (see discussion below under 'Reproductive

toxicity'). Most changes were probably attributable to the VEGFR or EGFR inhibitory activity of vandetanib, and have been reported for other VEGF and/or EGF kinase inhibitors. The doses were limited by toxicity. The high dose in the 6 month study in rats and 9 month study in dogs had to be reduced in both test species due to mortalities in rats or GI toxicity in dogs, and dosing of the high dose groups of the 1 month rat study and the 1 month dog study was stopped on Days 25 and 15, respectively, before the completion of the scheduled 30 day dosing duration. The studies in both dog and rat showed evidence of recovery by the end of the withdrawal period. Exposures in the repeat dose toxicity studies were generally below those achieved in clinical studies at 300 mg/day.

GI effects were the dose limiting toxicities in the dog studies by PO administration. The GI effects, which were reversible, were manifested as loose/abnormal faeces and emesis, associated with reduced food consumption and body weight gain. There were no associated histopathological GI changes in the 1 or 9 month studies, although mild focal mucosal atrophy and crypt epithelial hyperplasia of the colon were observed in the shorter term 2 week dog study at higher doses (40 mg/kg/day), and ulceration of the stomach and single cell necrosis and erosion of the duodenal mucosa in rats receiving a single PO lethal dose of 2000 mg/kg. No obvious GI tract disturbances were seen in repeat dose studies in rats, apart from reduced food consumption and body weight gain, which could be related to effects on other organ systems. The NOEL for GI tract effects in the 9 month dog study was 1 mg/kg/day (ER 0.01).

Effects on bone were observed in both species. Daily PO dosing of vandetanib for 1 month resulted in a dose related, reversible dysplasia of the epiphyseal growth plates of long bones in rats at 25 or 75 mg/kg/day and in dogs at 40 mg/kg/day. Epithyseal growth plate hypertrophy was reported in a 14-day study in rats at PO doses of 50 or 100 mg/kg/day.[5] Dysplasia of incisor teeth was present in high dose (75 mg/kg/day) rats in the one month study after a one month recovery period and in high dose decedents in the 6 month rat study at 20/10 mg/kg/day. Abnormal teeth growth was also seen in a fertility study in rats at 25 mg/kg/day. Teeth abnormalities were not reported in the dog studies.

Renal papillary necrosis was observed in rats dosed PO at 25 and 75 mg/kg/day for 1 month and was still present at the end of the 1 month recovery period. This finding was not seen in the 6 month rat study or in any dog study. In the 6 month rat study, the incidence or severity of cortical epithelial brown pigmentation and cortical tubular basophilia were increased at 20/10 mg/kg/day. Mild to moderate cortical tubular vacuolation was observed in dogs dosed with 9.5 or 19 mg/kg/day IV for 10 days but was not observed up to 16 mg/kg/day IV for 14 days or by PO administration. Increased urinary excretion of protein and decreased excretion of electrolytes (potassium, sodium and chloride) were observed in a safety pharmacology study in rats at 50 mg/kg and the 1 month repeat dose toxicity study in rats at 25 and 75 mg/kg/day, but not in dogs. However, plasma levels of electrolytes were unaffected by treatment. Lower total plasma protein and albumin were detected in dogs at high doses (40 mg/kg/day for 1 month and 20/15 mg/kg/day for 9 months) and in rats at high IV doses (25 mg/kg/day for 10 days). However, the decreases in the total plasma protein and albumin were probably related to GIT disturbances and/or hepatic toxicity, rather than altered renal function.

Histopathological and/or ultrastructural changes consistent with the induction of phospholipidosis were present in all repeat dose rat studies and in dogs dosed with vandetanib by IV injection. Histological appearances of phospholipidosis were foamy macrophages in lungs, spleen and lymph nodes, and sometimes in other organs (liver, kidneys, trachea), and under electronic microscope they appeared as myelinic whorls. This

[5] Wedge SR, *et al.* (2002) ZD6474 inhibits vascular endothelial growth factor signalling, angiogenesis and tumour growth following oral administration. *Cancer Research* 62: 4645-4655.

is a common finding for cationic amphiphilic drugs,[6] which have been approved for a wide range of clinical indications, including other tyrosine kinase inhibitors (for example, gefitinib and crizotinib) for the treatment of cancer.

Skin lesions (scaly tail, muzzle epidermal microabscesses, folliculitis) were observed in rats following repeated dosing at 75 mg/kg/day for 1 month and > 5 mg/kg/day for 6 months.

A single PO dose at 2000 mg/kg in rats resulted in hepatocyte vacuolation, fat deposition and necrosis. Increased plasma transaminases (alanine transaminase [ALT], aspartate transaminase [AST]), suggesting hepatic toxicity, were seen in rats by IV or PO dosing, with histological evidence of hepatic effects only in the 2 week IV study at 17.5 mg/kg/day (mild hepatocyte necrosis) and the 1 month study at 75 mg/kg/day (hepatocyte vacuolation). Increases in plasma alkaline phosphatase (ALP), AST, ALP and glutamate dehydrogenase (GLDH) were also observed in some dogs in the 9 month PO study, but the changes were not dose-related. The increased ALP, AST, ALP and GLDH in plasma may be partly attributable to damage of other tissues, such as the GI tract and bone.

Small, dose related haematological changes (increased red blood cells, hematocrit, haemoglobin, white blood cells, and platelets) were seen in rat studies by both the PO and IV routes, and the changes generally showed reversal after cessation of dosing.

Genotoxicity

Three *in vitro* studies showed no mutagenic potential in bacterial mutation assays and no evidence of clastogenic activity in the *in vitro* cytogenetics assay in human lymphocytes *in vitro* or a micronucleus test in rats.

Carcinogenicity

An assessment of carcinogenicity potential had not been conducted by the sponsor. The proposed indication is for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer. Published guidelines[7] indicate thatcarcinogenicity studies are not warranted to support marketing of anticancer drugs to treat patients with advanced cancer.

Reproductive toxicity

The reproductive toxicity of vandetanib was investigated in a series of studies to assess embryofoetal toxicity, male and female fertility as well as pre and post natal development. Vandetanib significantly affected all stages of female reproduction in rats with a decrease in the number of corpora lutea observed in the ovaries of rats dosed at 75 mg/kg/day (ER ~2 based on AUC) in the 1 month toxicology study; the NOEL for this effect was 25 mg/kg/day (ER ~1). In a female fertility study with dosing starting 2 weeks prior to mating, there was a trend towards increased oestrus cycle irregularity in animals dosed at 10 or 25 mg/kg/day (not at 1 mg/kg/day; ER ~0.2 at 1 mg/kg/day and ~0.4 at 10 mg/kg/day) and decreased fertility index at 25 mg/kg/day. The high dose was also associated with abnormal teeth growth.

[6] Mesens, N *et al.* (2012) Phospholipidosis in rats treated with amiodarone: Serum biochemistry and whole genome micro-array analysis supporting the lipid traffic jam hypothesis and the subsequent rise of the biomarker BMP. *Toxicologic Pathology* 40: 491-503.
[7] European Medicines Agency, "ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals Step 5 (EMA/CHMP/ICH/646107/2008)", May 2010, Web, accessed 12 July 2013 <www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500043471.pdf>.

An increase in early intra uterine deaths, resulting in a reduced number of live embryos, was observed at 25 mg/kg/day. Following a 4 week withdrawal period before mating, no effects on oestrus cycles, fertility, pre or post implantation losses, or on the number of live embryos were evident.

Male reproductive performance was assessed by pairing male rats from the 6 month repeat dose toxicity study during week 9 of dosing with undosed females. This study found that administration of vandetanib of up to 20 mg/kg/day (ER ~1) did not affect male reproductive performance.

In a preliminary embryofoetal development study, pregnant rats PO dosed with 20 mg/kg/day vandetanib between either gestation Days 1-7 or Days 7-16 demonstrated an increase in post implantation loss at 20 mg/kg/day. A main embryofoetal developmental toxicity study in rats dosed with 1, 10 and 25 mg/kg/day during organogenesis (gestation days [GD] 6 to 15) showed increased embryofoetal loss at 25 mg/kg/day (ER ~1), decreased foetal and placental weights at ≥ 10 mg/kg/day, delayed ossification of skull, vertebrae and sternum and precocious ossification of skull bones at ≥ 10 mg/kg/day (ER ~0.4), and heart vessel abnormalities at all doses. There were also increased incidences of increased pelvic cavitation of the kidneys and dilated ureter at the high dose. When dosed with 25 mg/kg/day vandetanib from GD 6 to 23 (expected parturition), rats had total litter death/resorption. The only maternal effect was decreased body weight gain at 25 mg/kg/day; there were no signs of maternal effects at lower doses. The embryofoetal effects were probably related to the pharmacological actions of vandetanib. Placental transfer of vandetanib was not studied, but the embryofoetal findings suggest vandetanib and/or its metabolites cross the placental barrier. In summary, vandetanib is embryotoxic and teratogenic in rats, suggesting that vandetanib is a pregnancy category D drug, consistent with other tyrosine kinase inhibitors.

A rat pre and post natal development study using doses of 1 and 10 mg/kg/day from GD 6 or 10 mg/kg/day (ER ~0.7 in lactating rats) from GD 16 until weaning showed slight maternal toxicity during gestation and/or lactation, characterised by reduced maternal weight gain and food consumption. Live litter size was decreased at all doses, and increased stillbirths were observed at 10 mg/kg/day. Reduced post natal pup growth and delayed development (pinna unfolding, incisor eruption, eye opening) occurred in all treated groups and delayed sexual maturation (vaginal opening) in females at 10 mg/kg/day from GD6. There were no effects on behavioural tests, mating performance, fertility and gestation of the F1 generation. Vandetanib and traces of its active metabolites were excreted in rat milk, with a milk/plasma ratio of ~6 (based on AUC) for drug related materials. Vandetanib was also detected in pup plasma, confirming milk excretion of vandetanib.

Comments on the safety specification of the risk management plan

Nonclinical safety concerns that have not been adequately addressed by clinical data or are currently of unknown significance to human usage in the Nonclinical Safety Specification of the Risk Management Plan (RMP) are generally consistent with those of the nonclinical evaluator. However, effects on pup development from in utero and/or milk, which are unlikely to have been addressed by clinical data, should be included. Specifically, reduced post natal pup growth, delayed physical and sexual development were observed in rats dosed with vandetanib during late gestation and lactation.

The following nonclinical findings of safety concerns are addressable by clinical data. Whether they have been addressed by clinical data requires evaluation by the RMP evaluator.

- Potassium channel inhibition in hERG assays, action potential duration (APD) prolongation in canine Purkinje fibres, QTc interval prolongation in dogs by IV administration (but not PO dosing);
- Increased blood pressure in rats and dogs;
- GI tract toxicity: dose limiting toxicity in dogs (loose/abnormal faeces, emesis, mild focal mucosal atrophy and crypt epithelial hyperplasia of the colon), also seen in rats at very high doses (ulceration of the stomach and single cell necrosis and erosion of the duodenal mucosa);
- Skin lesions (scaly tail, muzzle epidermal microabscesses, folliculitis) in rats: common findings for EGFR inhibitors;
- Renal toxicity (renal papillary necrosis, cortical epithelial brown pigmentation and cortical tubular basophilia; plasma urea and creatinine unaffected), and increased urinary excretion of protein and decreased electrolytes (K, Na, Cl) in rats; and
- Phospholipidosis in multiple organs - a common finding for cationic amphiphilic drugs, which have been approved for a wide range of clinical indications, including other tyrosine kinase inhibitors for the treatment of cancer.

Nonclinical summary and conclusions

Summary

- The sponsor has submitted an application to register a new chemical entity, vandetanib (Caprelsa), for the treatment of patients with unresectable locally advanced or metastatic MTC.
- Nonclinical studies provided adequate information to support the application, were satisfactorily designed with a majority of the studies administering vandetanib via PO and pivotal studies were GLP compliant. One deficiency was the lack of toxicokinetic data for the active metabolites in the toxicity studies in both animal species (rat and dog). Based on the exposures to the active metabolites after a single PO dose, exposures of both animal species to vandetanib alone or the parent and the N-desmethyl metabolite were below the expected human exposure at the clinical dose of 300 mg/day.
- Extensive *in vitro* and *in vivo* pharmacology studies have been performed. The studies *in vitro* screening across protein kinase families demonstrated that vandetanib inhibits tyrosine kinases (with greatest activity against EGFR, VEGFR-2, RET and BRK), and angiogenesis. It inhibited wild type RET protein and RET proteins harbouring activating mutations found in some MTC and papillary thyroid carcinoma (PTC), and was less effective at inhibiting RET protein with V804M/L gatekeeper mutations.
- *In vivo* studies found vandetanib to be active against a range of cancers (for example, human lung, prostate cancers) with one daily PO dosing in nude mice and in the K-ras-dependent murine model of lung cancer. Vandetanib treatment was shown to suppress tumour growth and metastasis in a murine othoropic human lung cancer model and prolonged survival. However, the activity of vandetanib against MTC was not investigated in nonclinical animal models.
- *In vitro* secondary pharmacology studies tested vandetanib in a panel of 334 radio ligand binding and enzyme assays covering a diverse range of enzymes, receptors, ion channels and transporters. Vandetanib was found to significantly bind to 59 out of 334 receptors or enzyme targets, particularly histamine receptors H1 and H2, and adrenergic receptors α2A , α2B and α2C.

- A mouse study investigating cutaneous wound healing showed that vandetanib treatment was associated with delayed wound healing and reduced skin breaking strength and fibrosis, suggesting that vandetanib may slow wound healing in humans.
- Core battery, follow up and supplemental safety pharmacology studies showed that vandetanib:
  - Inhibited the potassium channel in the hERG assay, increased APD in canine Purkinje fibres *in vitro*, and prolonged QTc intervals in dogs by IV administration (but not by PO administration), suggesting it may cause prolongation of QT intervals and increase in blood pressure in patients; additive hERG inhibition was observed for vandetanib and ondansetron;
  - Increased systolic and diastolic blood pressures in rats;
  - Inhibited gastric emptying and intestinal transit in rats suggesting potential effects on GI motility in human patients;
  - Increased urinary protein and decreased urinary potassium, sodium and chloride in rats (but not in dogs), suggesting that vandetanib may cause increased urinary excretion of protein and decreased potassium, sodium and chloride excretion in patients.
- Pharmacokinetics was determined in rats and dogs by PO and IV administration. Studies showed that vandetanib was well absorbed in rat and dog with a high volume of distribution. Metabolism was limited in mouse, rat and dog with the unchanged drug being the major component in mouse, rat and dog plasma and excreta. The major human metabolites, N-desmethyl and N-oxide vancetanib, were also formed in the animal species. The N-desmethyl metabolite showed similar pharmacological activities to vandetanib. The formation of the N-desmethyl vandetanib was mediated by CYP3A4, and N-oxide metabolite by FMO1 and FMO3.
- Vandetanib and the major metabolites displayed no time-dependent inhibition of CYP450 enzymes. No enzyme induction was observed in rats, but an in vitro study with human hepatocytes showed induction of CYP1A2, 2C9 and 3A4 activities, suggesting potential for induction of these enzymes in patients. Vandetanib is not a substrate or inhibitor of P-gp, but it is an inhibitor of OCT2 (IC50 ~2.1 μg/mL compared with a clinical Cmax 0.857 μg/mL), suggesting vandetanib may inhibit excretion of OCT2 substrates (for example, metformin, pindolol, creatinine).
- Vandetanib was excreted in the milk of rats and detected in the blood for suckling rat pups following dosing to the dams.
- Single dose oral studies were conducted in mice and rats by both PO and IV administration. Overall, the studies showed that a dose of 2000 mg/kg vandetanib was not tolerated and no atypical observations or histopathological findings were found in animals dosed with 1000 mg/kg vandetanib.
- Repeat dose toxicity studies were conducted in rats and dogs. The doses were limited by toxicity, and exposures based on AUC and Cmax were generally below the clinical exposure at 300 mg/day. The following effects were observed:
  - Skin lesions in rats and dogs;
  - Hepatobiliary toxicity in rats, and increases in plasma ALT, AST and GLDH activities;
  - GI effects, emesis and body weight loss in dogs and at very high doses in the single dose study in rats;
  - Renal papillary necrosis in rats;

  - Phospholipidosis primarily in lungs, lymph nodes and spleen in rats (PO and IV) and dogs (IV dosing only).

- Vandetanib showed no mutagenic potential in bacterial mutation assays, and no evidence of clastogenic activity in an *in vitro* cytogenetics assay or *in vivo* micronucleus test.
- No carcinogenicity studies were conducted, which is acceptable for the treatment or patient with advanced cancer.
- Vandetanib significantly affected all stages of female reproduction in rats. Reproductive toxicity studies found that vandetanib:
  - Decreased the number of corpora lutea;
  - Increased oestrus cycle irregularity;
  - Increased (dose related) early intra uterine deaths, and post implantation loss;
  - Reduced foetal weight and delayed ossification;
  - Increased heart vessel, kidney and ureter abnormalities and precocious ossification of some skull bones;
  - Delayed post natal development;
  - No effect on male reproductive performance at up to 20 mg/kg/day.
- Vandetanib possesses phototoxic potential based upon the results of an in vitro phototoxicity assay.

Conclusions and recommendation

- *In vitro* primary pharmacology studies demonstrate that vandetanib acts as an inhibitor of both VEGFR-2 and EGFR signalling and that it inhibits angiogenesis. *In vivo*, vandetanib demonstrated anti tumour activity in tumour models consistent with inhibition of VEGFR-2 dependent angiogenesis. Vandetanib was active against a range of cancers (for example, human lung, prostate cancers) with one daily PO dosing in nude mice and in the K-ras dependent murine model of lung cancer. However, the activity of vandetanib against thyroid cancer was not investigated in nonclinical animal models or with MTC cells *in vitro*.
- Safety pharmacology findings suggest that vandetanib might cause QT interval prolongation and induce hypertension in patients. It could also inhibit GI tract motility, disturb urinary protein and electrolytes (potassium, sodium and chloride) excretion, and inhibit excretion of the transporter, OCT2 substrates (for example, metformin, pindolol, creatinine). Vandetanib has high affinity to histamine receptors H1 and H2, and adrenergic receptors α2A , α2B and α2C, and may affect physiological functions through these receptors.
- Vandetanib was well absorbed in the toxicology species (rat and dog) with increasing exposures achieved with increasing doses. However, exposures to vandetanib and its active metabolites achieved in toxicity studies were generally below the clinical exposure due to dose limiting toxicity.
- Toxicity findings were consistent with the pharmacological action (that is, inhibition of VEGFR and EGFR). Target organs were bone (and teeth), GI tract, liver, kidneys and phospholipidosis, which were also observed for other tyrosine kinase inhibitors.
- There was no evidence of genotoxicity.

- Vandetanib affected all stages of female reproduction in rats and was found to be teratogenic in rats. Consistent with other tyrosine kinase inhibitors, the pregnancy category D is considered appropriate.
- The pharmacological mechanisms of action support oncology indications. Nonclinical studies showed a wide range of target organs at exposures below the clinical exposure. The proposed clinical use is approvable only if the safety concerns identified in the nonclinical studies (see above) have been adequately addressed by clinical data.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The submission contained the following clinical information:

- 15 clinical pharmacology studies, including 13 that provided pharmacokinetic data and 2 that provided pharmacodynamic data.
- 7 population pharmacokinetic analyses.
- 1 pivotal Phase III efficacy/safety study in patients with MTC.
- 2 Phase II efficacy/safety studies in patients with MTC.
- 15 other Phase II/III efficacy/safety studies in patients with cancers other than MTC.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included pharmacokinetic data from 13 clinical pharmacology studies (8 studies in volunteers; 5 studies in patients with malignant disease), and 7 population pharmacokinetic studies in patients with malignant disease.

Evaluator's overall conclusions on pharmacokinetics

Data on the pharmacokinetics of vandetanib are derived primarily from studies in healthy volunteers, and the population pharmacokinetic analysis in patients with MTC from the pivotal Phase III study (Study 58). However, the pharmacokinetics of vandetanib have not been completely characterised and the deficiencies in the submitted data are summarised below:

- There was no absolute bioavailability study. However, the sponsor satisfactorily justified the absence of an absolute bioavailability study on the basis that an IV infusion solution of vandetanib has the potential to cause local tissue damage at the site of the infusion.
- The submission included a mass balance study in healthy volunteers. However, recovered radioactivity was incomplete due to the long plasma half life of vandetanib and the low radiolabelled dose administered. Consequently, it was not possible to quantify the metabolite profiles in plasma or excreta samples or to quantify the relative contributions of specific clearance pathways to the overall elimination of vandetanib.

- *In vitro* data indicate that vandetanib can induce CYP1A2, CYP2C9, and CYP3A4 enzymes (Study KMX067), but there were no formal pharmacokinetic interaction studies between vandetanib and substrates of these CYPs.
- The solubility of vandetanib is pH dependent with solubility being greater in acidic solutions. However, there no pharmacokinetic interaction studies between vandetanib and drugs which can increase intragastric pH (that is, antacids, PPIs, H2-antagonists). Co administration of drugs which can increase intragastric pH and vandetanib have the potential to decrease the solubility and, consequently, the absorption of vandetanib.

The key features of the pharmacokinetics of vandetanib from the submitted data are summarised below:

- Vandetanib pharmacokinetics were reasonably described by a two compartment model with first order absorption and first order distribution and elimination (population pharmacokinetic analysis, Study 58).
- Key estimated mean (standard deviation) steady state parameters derived from the population pharmacokinetic analysis (Study 58) in all patients (n=230) with MTC dosed to Day 56 with vandetanib up to 300 mg daily including dose reductions were: accumulation ratio 7.70 (3.31); Cmax 4 h post dose 810 (293)ng/mL; clearance 13.84 (4.05) L/h; trough concentration 754 (276)ng/mL; half life 18.95 (11.33) days; and exposure 18782 (6842) ng.h/mL.
- The commercial vandetanib 300 mg tablet was bioequivalent to a vandetanib solution following single oral doses. Post hoc analysis showed that the gmean Cmax and $AUC_{0\text{-inf}}$ values for the tablet were 4% and 10% higher, respectively, relative to the solution, with the 90% Confidence Intervals (CIs) for the relevant ratios being completely enclosed within the standard bioequivalent limits of 0.8 to 1.25.
- Absorption following oral administration of a single 300 mg dose of the commercial tablet formulation was 8 hours (range: 6 to 18 h) (Study 30). In the population pharmacokinetic analysis of pooled data from 4 studies in patients with cancer (01, 02, 03, 04) and 5 clinical pharmacology studies in healthy volunteers (12, 15, 21, 24, 30), no differences were identified between patients and volunteers for the predicted Cmax, the estimated Tmax, the relative percentage of drug absorbed over time or the apparent clearance. In this population pharmacokinetic analysis most subjects reached 100% of the drug absorbed by 6 to 9 h after administration. Steady state exposure was reached after 1 to 2 months of dosing for most patients.
- There were no formal dose proportionality studies. Comparisons of Cmax and AUC values suggested approximate dose proportionality across the single dose range 300 mg to 1200 mg in healthy volunteers (Study 12), and between single dose 100 mg and 300 mg in patients with malignant tumours (01, 04, 43). The pharmacokinetics of vandetanib were linear across the dose range 300 mg to 1200 mg. Inter subject variability in the pharmacokinetics of vandetanib are marked, but intra subject variability is small.
- Food had not significant affects on the bioavailability of vandetanib following a single 300 mg oral dose administered to healthy volunteers (Study 24). The geometric least squares (gLS) means mean Cmax following administration of vandetanib with food was 11% lower relative to fasted administration, and there were was no difference between fasting and fed gLS means mean $AUC_{0\text{-inf}}$. The ratios (fed:fasted) for the gLS means for the Cmax and the $AUC_{0\text{-inf}}$ were entirely enclosed within the standard bioequivalence limits of 0.8 to 1.25.
- Vandetanib has a large volume of distribution which indicates extensive tissue distribution. In the population pharmacokinetic analysis in patients with MTC (study

58), the apparent volume of distribution was approximately 7450 L (apparent initial and peripheral volume of distributions 2100 L (SE=104) and 5350 (SE=536) L, respectively). The estimate of inter individual variation in the total volume of distribution was 101%.

- Ex vivo studies showed that vandetanib protein binding is ~93-94%, and is unchanged by hepatic impairment, renal impairment, or advanced colorectal cancer with liver metastases (studies 15, 22, 50). In an *in vitro* protein binding study (KPJ010), vandetanib protein binding was independent of concentration over the range 0.05 µg/mL to 6 µg/mL, and showed that vandetanib binds to serum albumin (independent of concentration) and α-1 acid glycoprotein (dependent on concentration).
- In the mass balance study in healthy volunteers (Study 25), the total radioactivity recovered over the 21 day collection period was 69% of the total dose of radioactivity, with ~44% being excreted in faeces and ~25% recovered in urine. The elimination of radioactivity was very slow with a total of between 1% and 3% of the dose being excreted daily from Day 8 to Day 21. This is consistent with both the slow apparent oral plasma clearance of vandetanib (estimated mean 13.2 L/h) and the long apparent plasma half life (estimate mean 19 days) in patients with MTC (population pharmacokinetic analysis Study 58). The percentage of the dose excreted daily (Day 8 to Day 21) was similar in urine and faeces indicating that both renal and hepatic excretion contribute to the elimination of vandetanib.
- There were no satisfactory data in the submission on renal clearance in patients. Data from the mass balance study (Study 25) indicates that ~ 25% of the administered dose was eliminated in the urine in the 21 day collection period indicating that renal excretion is significant. However, it was not possible to quantify the contributions of unchanged vandetanib and vandetanib metabolites to the total radioactivity excreted in the urine.
- In the mass balance study (Study 25), unchanged vandetanib and two known metabolites (vandetanib-N-oxide and N-desmethyl-vandetanib) were detected in plasma, urine and faeces following an oral radiolabelled dose of vandetanib (800 mg). An additional minor metabolite of vandetanib was found in both urine and faeces (glucuronide conjugate). N-desmethyl-vandetanib was the major circulating metabolite, and exposure to the metabolite relative to the parent compound was about 7% to 10% (Studies 16, 22, 26). Vandetanib-N-oxide was the minor circulating metabolite, and exposure to the metabolite relative to the parent compound was about 1.4% to 1.8% (Studies 16, 22, 26).
- *In vitro* data showed that the formation of N-desmethyl-vandetanib from vandetanib was mediated primarily by CYP3A4 (study KMX038), and that the formation of N-oxide-vandetanib from vandetanib was mediated by FMO1 and FMO3 (KMX046). N-desmethyl-vandetanib and vandetanib have similar pharmacology activity, while N-oxide-vandetanib has markedly lower pharmacological activity than vandetanib.
- Hepatic impairment (mild, moderate, and severe) had no significant affects on exposure to vandetanib as assessed by AUC values, while Cmax values were non-clinically significantly lower in patients with hepatic impairment relative to healthy subjects (Study 16).
- In moderate and severe renal impairment, a doubling in exposure to vandetanib relative to subjects with normal renal function based on $AUC_{0\text{-}inf}$ values could not be ruled out following a single oral 800 mg dose (Study 22). The starting dose of vandetanib should be reduced in patients with moderate or severe renal impairment, while no adjustment to the starting dose appears to be required for patients with mild renal impairment.

- In the pharmacokinetic interaction study with itraconazole (a CYP3A4 inhibitor), co administration with vandetanib (single dose 300 mg) did not affect exposure to vandetanib relative to vandetanib alone as assessed by the Cmax and $AUC_{0\text{-}504h}$ (Study 15). These results suggest that vandetanib can be co administered with CYP3A4 inhibitors without dose modification.
- In the pharmacokinetic interaction study with rifampicin (a CYP3A4 inducer), co administration with vandetanib (single dose 300 mg) reduced exposure to vandetanib by 40% relative to vandetanib alone as assessed by the AUC0-504h (Study 26). This result suggests that co administration of vandetanib with CYP3A4 inducers should be avoided.
- *In vitro* data indicated that vandetanib can induce CYP1A2, CYP2C9 and CYP3A4 activity (Study KMX067). However, *in vivo* data in patients with malignant disease suggest that vandetanib at steady state (100 mg or 300 mg once daily) does no significantly affect the pharmacokinetics of docetaxel (Study 06) or irinotecan (Study 38). Both docetaxel and irinotecan are metabolised by CYP3A4 and the *in vivo* data suggest that vandetanib does not significantly reduce the metabolism of these two drugs by CYP3A4 induction.
- *In vitro* data indicated that vandetanib is not or is only a low affinity substrate for the transporter protein MDR1 (Pgp) and is not a substrate for the transporter proteins BCRP and MRCPI (Study KMN070). However, *in vitro* data indicated that vandetanib is an inhibitor of MDR1 and BCRP at IC50 levels greater than 10 fold the estimated steady state Cmax levels in patients with MTC treated with vandetanib up to 300 mg daily. *In vitro* data indicated that vandetanib is not a substrate of the OCT2 transporter but is an inhibitor at IC50 levels about 2.5 fold greater than the estimated steady state Cmax levels in patients with MTC treated with vandetanib 300 mg daily (KMX083). Consequently, increased plasma creatinine concentrations observed in patients treated with vandetanib might be due to inhibition of OCT2 mediated excretion of creatinine.
- The population pharmacokinetic analysis in patients with MTC (Study 58) showed that age and gender had no significant effects on vandetanib clearance or volume of distribution. The studies in Western, Chinese and Japanese patients showed that exposure was greater in the Asian patients than in the Western patients, probably due to greater oral apparent clearance in the Western patients.

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included pharmacodynamic and pharmacokinetic/pharmacodynamic data from the three studies.

- Pharmacokinetic/Pharmacodynamic data in the population pharmacokinetic analysis of patients with MTC from the pivotal Phase III efficacy and safety study (Study 58). The data relate to QTc interval prolongation, CTC ≥ grade 3 adverse events (AEs), and efficacy outcomes.
- Pharmacodynamic data from Study 21 in healthy volunteers primarily investigating the effect on QTc prolongation of vandetanib (700 mg single oral dose) administered in combination with ondansetron (32 mg IV infusion over 15 minutes).
- Pharmacodynamic data from Study 50 investigating the effect of vandetanib on vascular permeability assessed by dynamic contrast enhanced magnetic resonance

imaging (DCE-MRI) in patients with advanced colorectal cancer and liver metastases treated with vandetanib 100 mg or 300 mg once daily for 56 days.

Summary of pharmacodynamics

- The pharmacokinetic/pharmacodynamic data from Study 58 showed that at predicted steady state vandetanib plasma concentrations following 300 mg daily, increases in the mean QTc interval from baseline of ~26 ms (QTcB) and 34 ms (QTcF) were observed. The PD data from Study 21 showed that vandetanib and ondansetron in combination had an additive effect on QTcB prolongation compared with ondansetron alone. There was no "thorough QT/QTc" study in the submission complying with the TGA adopted guideline.[8] This considered to be a deficiency in the data, given the potential for vandetanib to significantly increase the QT interval.
- The pharmacokinetic/pharmacodynamic data from Study 58 showed no correlation between plasma concentration at Progression Free Survival (PFS) at the time of progression, and no correlations between PFS or Overall Survival (OS) and vandetanib trough plasma concentration at day 56, or total exposure up to day 56. In addition, the data showed no correlations between rash, diarrhoea, hypertension and QTc related AEs for Common Terminology Criteria for Adverse Event (CTCAE) grade ≥ 3 events and predicted vandetanib plasma concentrations. There was evidence from the pharmacokinetic/pharmacodynamic analysis that calcitonin concentrations decrease with increasing vandetanib plasma concentrations, but no evidence that changes in carcinoembryonic antigen concentration are related to vandetanib plasma concentration.
- The pharmacodynamic data from Study 50 showed that vandetanib (100 mg or 300 mg od) did not significantly reduce vascular permeability in patients with advanced colorectal cancer with liver metastases as assessed by DME-MRI.

Dose selection for the pivotal studies

The submission included no formal dose ranging studies. In the pivotal Phase III efficacy and safety study (Study 58), vandetanib 300 mg was selected as the dose with which to begin treatment, with permitted dose reductions to 200 mg and 100 mg in the event of CTCAE grade ≥ 3 events. The rationale for the use of the 300 mg dose in the pivotal study was based primarily on:

1. preclinical data which demonstrated that the greatest benefit (in terms of maximising inhibition against key targets) was seen when vandetanib was used at the maximum tolerated dose (MTD);
2. the MTD of 300 mg identified from data in the Phase I ascending dose study in Western patients (Study 01) and the corresponding Phase I study in Japanese patients (Study 43); and
3. data from Study 08, a Phase II study therapeutic exploratory study of vandetanib in hereditary MTC patients showing that the 300 mg dose was associated with an ORR of 20%, and that the regimen which allowed for dose reductions to 200 mg and 100 mg based on the occurrence CTCAE grade ≥ 3 events was safe and well tolerated.

[8] European Medicines Agency, "ICH Topic E 14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, Step 5: Note for Guidance on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (CHMP/ICH/2/04)", November 2005, Web, accessed 12 July 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002879.pdf>.

Efficacy

Evaluator's conclusions on clinical efficacy

The submission included one pivotal Phase III (therapeutic confirmatory) study supporting the efficacy of vandetanib 300 mg for the treatment of unresectable locally advanced or metastatic MTC (Study 58). The study randomised 231 patients to vandetanib and 100 patients to placebo. The study is considered to provide meaningful clinical evidence for the efficacy of vandetanib compared with placebo as assessed by the primary outcome of PFS, and supported by the secondary outcomes of Overall Response Rate (ORR), Disease Control Rate (DCR), Calcitonin (CTN) response, Carcinoembryonic Antigen (CEA) response, and Time to Worsening of Pain (TWP). However, there was no statistically significant difference between the two treatment arms in OS, but the survival data were immature at the data cut off date. The submission also included two, small, Phase II, open label, single arm studies which are considered to be exploratory as regards the efficacy of vandetanib rather than pivotal or supportive.

The TGA adopted EU "points to consider" document[9] provides guidance on applications supported only by one single Phase III study. While acknowledging the "general demand" for replication of scientific studies the document recognises that clinical drug development differs from the situation applying to strictly experimental studies. The document notes that "where the confirmatory evidence is provided by only one pivotal study, this study will have to be exceptionally compelling", and outlines a number of factors which should be taken into account in the regulatory evaluation of such studies. These factors have been applied to the pivotal Phase III study (Study 58) and the conclusions are summarised as follows:

1. the study is internally valid;
2. the study is externally valid;
3. the difference in PFS between the vandetanib and placebo treatment arms is clinically relevant;
4. the statistical significance difference in PFS between the vandetanib and placebo treatment arms as assessed by the primary analysis in the Full Analysis Set (FAS) is robust and supported by the PFS sensitivity analyses;
5. the sponsor's quality assurance and internal quality control procedures in conjunction with independent auditing procedures provide reassurance that the data were of good quality;
6. the assessment of the PFS was internally consistent with vandetanib being superior to vandetanib in most of the subgroup analyses;
7. the tested hypothesis was plausible.

The only factor which needs to be taken into account on which there were no data relates to centre effects. No data could be identified on whether there was a difference in PFS between the two treatment arms among the study centres. However, this is not considered to be critical in this multinational study from 63 centres where the number of patients from each centre was too small to allow for meaningful outcome comparisons to be made between the two treatment arms.

In Study 58, the primary PFS analysis was performed using the log rank test (unadjusted) based on all available centrally assessed modified Response Evaluation Criteria in Solid

[9] European Medicines Agency, "Committee for Proprietary Medicinal Products (CPMP): Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99)", 31 May 2001, Web, accessed 12 July 2013 <www.tga.gov.au/pdf/euguide/ewp233099en.pdf>.

Tumors (RECIST) data, including assessments performed during open label vandetanib treatment in patients initially randomised to placebo who decided to continue treatment with open label vandetanib following unblinding. Following protocol Amendment 6, investigators had the option to unblind subjects remaining on randomised therapy, whether or not disease progression had occurred. It was stated in the submission that the amendment was "made as a consequence of the analysis results, rather than before the data were analysed". The sponsor will be asked to clarify this rather confusing statement.

The decision to base the primary analysis on modified RECIST data from both the randomised and the open label phases is considered to be unusual. It appears to have been undertaken because central assessment of RECIST data specified for the primary analysis was not performed in real time. Consequently, in some patients initially randomised to placebo central assessments were undertaken after switching to vandetanib. The patient's decision to switch from placebo to vandetanib following unblinding was based on disease progression determined by the site read of the modified RECIST data. Sensitivity analysis of the PFS based on central assessment of RECIST data prior to open label treatment, with imputation of data for those patients in whom a central assessment had not occurred at this time point, showed that the outcome statistically significantly favoured vandetanib relative to placebo. In addition, a PFS sensitivity analysis based on site assessment of modified RECIST data also showed that the outcome statistically significantly favoured vandetanib relative to placebo.

The key efficacy findings in the pivotal Phase III study (Study 58) are summarised below:

- The median duration of follow up at the date of data cut off was 102 weeks in the vandetanib treatment arm and 106 weeks in the placebo treatment arm. There was a statistically significant difference in favour of vandetanib compared with placebo in PFS based on all available centrally assessed modified RECIST data (HR [Hazard Ratio] = 0.46 [95% CI: 0.31, 0.69]; p=0.0001). The HR represents a 54% reduction in the rate of progression in the vandetanib arm relative to the placebo arm. Progression events were reported in 31.6% (73/231) of patients in the vandetanib arm and 51.0% (51/100) of patients in the placebo arm. There were 23 (10.0%) patients in the vandetanib arm who received open label vandetanib before centrally determined progression and 26 (26%) patients in the placebo arm. These patients were included in the primary analysis of PFS in the FAS (that is, the Intention To Treat [ITT] population) in the treatment arms to which they were initially randomised.
- The median time to PFS in the vandetanib arm could not be derived from the KM analysis because an insufficient number of events had occurred in this treatment arm at the date of data cut off. Therefore, the median time to PFS for the vandetanib arm was estimated using a Weibull survival model. This model predicted a median time to PFS of 30.5 months in the vandetanib arm and 19.2 months in the placebo arm (consistent with 19.3 months derive from the Kaplan-Meier analysis). There were a number of sensitivity analyses of the PFS and all supported the primary PFS analysis.
- There was no statistically significant difference between vandetanib 300 mg and placebo as regards the secondary efficacy outcome of OS in the FAS (HR = 0.89 [95% CI: 0.28, 2.85]; p = 0.7121). In the OS analysis, death occurred in 13.9% (32/231) of patients in the vandetanib arm and 16.0% (16/100) of patients in the placebo arm. The OS data were immature with only 48 (14.5%) deaths at the time of the analysis compared with 166 (50.2%) specified for the final analysis. Furthermore, the long median time of PFS in the placebo arm in this study (19.3 months) suggest that the natural history of the disease in patients in the study is slowly progressive. Consequently, if there are differences in OS between the two treatment groups then it is likely that these will be slow to emerge and might only do so after prolonged treatment. However, future analysis of OS in Study 58 is unlikely to be conclusive due

to patients randomised to blinded placebo choosing to switch to open label vandetanib following protocol permitted unblinding.

- The secondary efficacy outcomes of ORR, DCR, CTN response, and CEA response all statistically significantly favoured vandetanib relative to placebo. No statistical adjustment was made for the multiple pairwise comparisons, and the nominal significance level for each of the analyses was $\alpha = 0.05$. However, the results were consistent for the secondary efficacy endpoints, and the statistical analyses based on the odds ratios with 95% CIs are considered to be robust.
- TWP was the only patient reported outcome (PRO) pre specified as a secondary efficacy outcome, and all other PRO's were considered to be exploratory. There was a statistically significant improvement in TWP for vandetanib compared with placebo (HR 0.61 [95% CI 0.43, 0.87], p=0.0062); log-rank test with treatment as the only factor in the FAS. In the vandetanib arm, 49.4% (114/231) of patients had worsening pain compared with 57.0% (57/100) in the placebo arm. The median time to deterioration in worsening of pain was 7.9 months in the vandetanib arm, compared with 3.3 months in the placebo arm.

The efficacy results from the two Phase II studies (exploratory therapeutic) for the primary endpoint of ORR are as follows:

- In Study 8, the ORR with vandetanib 300 mg was 20.0% (6/20), and the median duration of the response from onset until progression or death was 310.5 (95% CI: 254.0, 402.2) days.
- In Study 68, the ORR with vandetanib 100 mg was 15.8% (3/10), and the median duration of the response from onset until progression of death was 168 (95% CI: 158.0, 245.0) days.
- In the absence of a control arm it is difficult to meaningfully interpret the efficacy outcomes in Studies 8 and 68.

Safety

Studies providing evaluable safety data

The submission included key safety data on vandetanib from the following studies:

- Study 58 (vandetanib 300 mg): pivotal Phase III study in patients with locally advanced and metastatic MTC;
- Studies 8 (vandetanib 300 mg) and 68 (vandetanib 100 mg): exploratory Phase II studies in patients with locally advanced and metastatic hereditary MTC; and
- Pooled monotherapy data on vandetanib 300 mg from 11 studies (1, 2, 3, 7, 8, 39, 43, 44, 50, 57, and 58) in patients with various malignant tumours (primarily NSCLC).

Evaluation of the safety data in this clinical evaluation report focuses primarily on the pivotal Phase III data in patients with MTC (Study 58), supplemented by the data from two exploratory Phase II studies in patients with hereditary MTC (Studies 8 and 68), and the pooled data from 11 monotherapy Phase I/II/III studies with the 300 mg dose of vandetanib in patients with various malignant tumours (primarily NSCLC). The submission also included safety data from two studies in which vandetanib 100 mg was combined with chemotherapy in patients with NSCLC (Studies 32 and 36). The safety data from these two vandetanib combination studies are not considered to be directly relevant to the proposed vandetanib monotherapy 300 mg dose for the proposed indication and have not been evaluated.

Evaluator's overall conclusions on clinical safety

General comments

The safety profile of vandetanib is derived primarily from patients in the safety analysis set in the randomised period of the pivotal Phase III study (n=58). The relevant safety analysis set included 231 patients in the vandetanib arm and 99 patients in the placebo arm. The mean duration of total and actual exposure was notably longer in the vandetanib 300 mg arm than in the placebo arm (total exposure 74.9 and 53.9 weeks; actual exposure 73.5 and 53.7 weeks).

In the pivotal Phase III study (randomised period), there were 194 patients treated with vandetanib for at least 6 months, 162 treated for least 12 months, and 51 treated for at least 24 months. The 6 month exposure (194 patients) is less than that specified in the TGA adopted ICH guideline[10] relating to the extent of exposure for non-life threatening conditions (300 to 600 patients), while the 12 month exposure (162 patients) is consistent with the guidelines (at least 100 patients). However, these guidelines are considered not relevant to the proposed indication as unresectable locally advanced or metastatic MTC is considered to be a life threatening condition. The exposure data from the pooled vandetanib 300 mg monotherapy studies in various malignant conditions included 491 patients treated with vandetanib for at least 6 months, 174 treated for at least 12 months and 84 treated for at least 24 months. Overall, exposure to vandetanib in the randomised period of the pivotal Phase III study is considered adequate, particular as vandetanib has been designated as an orphan drug.

The pivotal Phase III study included an open label period in which 102 patients were treated with vandetanib in addition to the randomised period in which 231 patients were treated with the drug. The safety profile of vandetanib in the open label period has been examined and is considered to be consistent with that in the randomised period. In addition, the safety profiles of vandetanib in the two, Phase II studies in 54 patients with hereditary MTC (Studies 8 and 68) are considered to be consistent with the safety profile of the drug in the pivotal Phase III study (randomised period).

The safety profile of vandetanib in the pivotal Phase III study (randomised period) differed in some respects from the drug's safety profile in the pooled monotherapy vandetanib 300 mg studies (n=1839). The differences appear to be primarily due to the different patient populations in the two datasets, with the majority of patients in the pooled monotherapy vandetanib 300 mg studies being treated for NSCLC. Consequently, the safety profiles of vandetanib from the two datasets are not directly comparable. However, examination of the safety data from the pooled monotherapy vandetanib 300 mg studies does not give rise to additional or unexpected concerns.

Optimal dose

The dose reduction data suggest that a lower vandetanib dose than 300 mg once daily might be more appropriate for treatment of patients for the proposed indication. Of the 231 patients randomised to vandetanib in the pivotal Phase III study, 114 (49.4%) required dose reductions and/or interruptions primarily for the management of AEs compared with 15 (15.2%) patients in the placebo arm. The mean duration of dose interruption was 21.3 days in the vandetanib arm (n=109) and 11.5 days in the placebo arm (n=15). The mean total exposure to vandetanib was 74.9 weeks and the median actual

[10] European Medicines Agency, "ICH Topic E 1Population Exposure: The Extent of Population Exposure to Assess Clinical Safety, Step 5. Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95)" June 1995, Web, accessed 12 July 2013 <www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002747.pdf>.

exposure was 73.5 weeks (exposure accounting for dose interruptions), suggesting that dose interruptions did not markedly reduce total exposure to vandetanib.

In the vandetanib arm, 83 (35.9%) patients required dose reductions and 81 (35.1%) of these patients had a dose reduction directly to 200 mg daily and 2 (0.9%) patients had a reduction directly to 100 mg. Of the 81 patients initially reduced to 200 mg once daily, 30 required subsequent reductions (29 to 100 mg once daily and 1 to non protocol specified 200 mg every other day).

Dose reductions due to AEs were required by 54 (23.4%) patients in the vandetanib arm (28 [12.1%] for CTCAE < grade 3 events and 26 [11.3%] for CTCAE ≥ 3 events), and 1 (1.0%) patient in the placebo arm for a CTCAE < grade 3 event. Dose interruptions due to AEs were required by 79 (34.2%) patients in the vandetanib arm (33 [14.3%] for CTCAE grade < 3 events and 46 [19.9%] for CTCAE grade ≥ 3 events), and 11(11.1%) patients in the placebo arm (7 [7.1%] for CTCAE grade < 3 events and 4 [4.0%] for CTCAE grade ≥ 3 events). In the vandetanib arm, dose reductions and interruptions occurred most commonly due to QTc prolongation, rash and diarrhoea.

The design of the pivotal Phase III study did not allow for direct comparison of the safety profile of the 300 mg, 200 mg, and 100 mg doses.

Overall AE profile

In the pivotal Phase III study (randomised period), most patients in both the vandetanib and placebo treatment arms experienced at least 1 AE (99.6% and 90.9%, respectively). However, the incidence of CTCAEs ≥ grade 3 was notably higher in patients in the vandetanib arm (55.4%) than in the placebo arm (24.2%). Furthermore, SAEs also occurred notably more frequently in patients in the vandetanib arm (30.7%) than in the placebo arm (13.1%), but the incidence of death associated with SAEs was similar in the two treatment arms in the randomised period (2.2% and 2.0%, respectively). Discontinuations due to AEs also occurred more frequently in patients in the vandetanib arm (12.1%) than in the placebo arm (3.0%). Treatment related AEs (investigator defined) occurred notably more frequently in patients in the vandetanib arm (96.1%) than in the placebo arm (59.6%).

Most commonly occurring AEs

In the pivotal Phase III study (randomised period), the most commonly reported System Organ Class (SOC) disorders in patients in the vandetanib arm (versus placebo) were "skin and subcutaneous tissue disorders" (90.5% versus 30.3%) followed by "gastrointestinal disorders" (80.5% versus 56.6%). The 10 most commonly occurring AEs (Preferred Terms [PT]) occurring in the vandetanib arm (versus placebo) were:

- diarrhoea (55.4% versus 26.3%);
- rash (45.0% versus 11.1%);
- nausea (33.8% versus 17.2%);
- hypertension (31.6% versus 5.1%);
- headache (26.0% versus 9.1%);
- fatigue (23.8% versus 23.2%);
- decreased appetite (21.2% versus 12.1%);
- acne (19.9% versus 5.1%);
- dry skin (15.2% versus 5.1%); and
- dermatitis acneiform (15.2% versus 2.0%).

All of the 10 most commonly occurring AEs reported in the vandetanib arm occurred more frequently in patients in this arm compared with placebo.

Death and other serious AEs

In the pivotal Phase III study, the Safety Analysis Set (SAS) included 47 (14.2%) deaths: 32 (13.9%) in the vandetanib arm and 15 (15.2%) in the placebo arm. There was no difference in the percentage of deaths occurring in patients in the vandetanib and placebo arms in the randomised period (2.2% and 2.0%, respectively). In the 5 patients in the vandetanib arm with an SAE resulting in death, the events were:

- respiratory failure in 1 patient;
- respiratory arrest in 1 patient;
- acute cardiac failure/arrhythmia in 1 patient;
- disseminated intravascular coagulation/sepsis in 1 patient;
- pneumonia/aspiration in 1 patient; and
- staphylococcal sepsis in 1 patient.

In the 2 patients in the placebo arm with an SAE resulting in death, the events were gastrointestinal haemorrhage in 1 patient and gastroenteritis in 1 patient. Overall, of the 7 deaths associated with SAEs in the randomised period there was 1 death that was considered by investigators to be related to the study drug (that is, acute cardiac failure/arrhythmia in 1 vandetanib treated patient).

In the pivotal Phase III study (randomised period), SAEs occurred notably more frequently in patients in the vandetanib arm (30.7%) than in the placebo arm (13.1%). The following SAEs were the most common in the vandetanib arm, but did not occur in the placebo arm:

- pneumonia (2.2%);
- diarrhoea (2.2%);
- decreased appetite (1.7%);
- hypertensive crisis (1.7%);
- urinary tract infection (1.3%);
- abdominal pain (1.3%);
- hypercalcaemia (1.3%); and
- depression (1.3%).

Discontinuations due to AEs

In the pivotal Phase III study (randomised period), treatment discontinuation due to AEs occurred notably more frequently in the vandetanib arm (12.1% [n=28]) than in the placebo arm (3.0% [n=3]). AEs resulting in discontinuation in the vandetanib arm occurring in ≥ 1.0% of patients (versus placebo) were: asthenia (1.7% [n=4] versus 0%) and rash (1.3% [n=3] versus 0%).

Safety issues of particular interest

Vandetanib is a selective inhibitor of VEGF vascular dependent angiogenesis, with additional activity against both the EGFR and RET dependent tumour growth. Consequently, there are important risks associated with the drug arising from effects on both the VEGF and EGF downstream signalling pathways. These include diarrhoea, hepatic failure, proteinuria, rash and other skin reactions, QT prolongation, hypertension, heart failure, abnormal/delayed wound healing, posterior leukoencephalopathy syndrome, GI

perforation, haemorrhage and thrombosis, and hypothyroidism[11] (Sponsors Global Risk Management Plan, 7 September 2011). Relevant data relating to these risks of special interest associated with vandetanib in the submitted safety data are discussed below.

Rash and other skin reactions

Rash and other skin reactions including acne, dry skin, dermatitis acneiform, photosensitivity reaction, and pruritus occurred very commonly in patients in the vandetanib arm, but dose reductions and treatment discontinuations due to these AEs were uncommon.

"Skin and subcutaneous tissue disorders" (SOC) were reported in 90.5% (n=209) of patients in the vandetanib arm and 30.3% (n=30) in the placebo arm. The most commonly reported AEs (PT) occurring in ≥ 10% of patients in the vandetanib arm (versus placebo) were rash (45.0% versus 11.1%), acne (19.9% versus 5.1%), dry skin (15.2% versus 5.1%), dermatitis acneiform (15.2% versus 2.0), photosensitivity reaction (13.4% versus 0%), and pruritus (10.8% versus 4.0%).

However, most patients in the vandetanib arm with "skin and subcutaneous tissue disorders" (SOC) did not require either dose reduction or treatment discontinuation. In the vandetanib arm, these disorders resulted in dose reduction in 4.3% (10) of patients and treatment discontinuation in 1.7% (n=4) of patients. In the vandetanib arm, dose reductions and treatment discontinuation were reported (respectively) for rash in 3 (1.3%) and 3 (1.7%) patients, dermatitis acneiform in 2 (0.9%) and no patients, photosensitivity reactions in 1 (0.4%) and 1 (0.4%) patients, pruritus in no and 1 (0.4%) patient, and acne in no patients. In the placebo arm, no "skin and subcutaneous tissue disorders" (SOC) resulted in dose reduction or discontinuation.

The grouped event term "rash" occurred notably more commonly in the vandetanib arm than in the placebo arm (89.2% versus 23.2%, respectively). The majority of patients with grouped "rash" in the vandetanib arm and all patients in the placebo arm experienced CTCAE grade 1 or 2 events (82.2% versus 23.2%). CTCAE Grade ≥ 3 events were reported in 6.9% of patients in the vandetanib arm and 1 (0.4%) of these patients had a CTCAE grade 4 event.

In the pooled vandetanib 300 mg monotherapy data (n=1839), there were rare reports of serious skin conditions including erythema multiforme (8 [0.4%] patients), Stevens-Johnson syndrome (6 [0.3%] patients), and toxic skin eruption (1 [0.3%] patient). There were no cases of these serious skin conditions in the pivotal Phase III study.

Diarrhoea, nausea, vomiting and GI perforation

Diarrhoea, nausea and vomiting occurred very commonly in patients treated with vandetanib 300 mg, but dose reductions and discontinuations due to these AEs were uncommon.

The AE (PT) of diarrhoea was reported in 55.4% (n=128) of patients in the vandetanib arm and 26.3% (n=26) of patients in the placebo arm. In the vandetanib arm, 4 (1.7%) patients had a dose reduction due to diarrhoea compared with 1 (1.0%) patient in the placebo arm. Discontinuations due to diarrhoea occurred in 2 (0.9%) patients in the vandetanib arm compared with 1 (1.0%) patient in the placebo term. There was no marked difference in the incidence of diarrhoea (PT) and the incidence of diarrhoea (grouped event).

The AE (PT) of nausea was reported in 33.8% (n=78) of patients in the vandetanib arm and 17.2% (n=17) of patients in the placebo arm. In the vandetanib arm, there was 1

[11] Kamba T, McDonald DM. (2007) Mechanisms of adverse effects of anti-VEGF therapy for cancer. *Br J Cancer* 96: 1788-1795.

(0.4%) patient who discontinued due to nausea compared with no patients in the placebo arm. No patients in either of the two treatment arms required dose reductions due to nausea.

The AE (PT) of vomiting was reported in 14.7% (n=34) of patients in the vandetanib arm and 7.1% (n=7) of patients in the placebo arm. In the vandetanib arm, 1 patient (0.4%) discontinued treatment due to vomiting compared with no patients in the placebo arm. No patients in either of the two treatment arms required dose reductions due to vomiting.

The grouped event of "nausea/vomiting" was reported in 36.8% (n=85) of patients in the vandetanib arm compared with 20.2% (n=20) of patients in the placebo arm, and CTCAE grade 1 or 2 accounted for 81/85 events in the vandetanib arm and 20/20 events in the placebo arm.

Intestinal perforation (small bowel) was reported as an SAE in 1 (0.4%) patient with diverticulitis in the vandetanib arm, and this event was considered to be causally related to treatment. The event was graded CTCAE ≥ 3 and resulted in treatment discontinuation.

Hypertension

Hypertension occurred very commonly in the vandetanib arm, but dose reductions and discontinuations due to this AE were uncommon.

Hypertension (PT) was reported as an AE in 31.6% (n=73) of patients in the vandetanib arm and 5.1% of patients in the placebo arm, and CTCAE ≥ 3 events were reported in 7.4% (n=17) and 0% of patients, respectively. Dose reductions due to hypertension and hypertensive crisis were reported in 2 (0.9%) and 1 (0.4%) patients respectively in the vandetanib compared with no patients in the placebo arm. Treatment discontinuation due to hypertension occurred in 2 (0.9%) patients in the vandetanib arm and no patients in the placebo arm. Blood pressure monitoring during the study showed that in patients taking no anti hypertensive drugs at baseline, elevated blood pressure developed in 59.7% (138/223) of patients in the vandetanib arm and 11.1% (11/92) of patients in the placebo arm.

Haemorrhage

Haemorrhage (grouped event) occurred very commonly in both the vandetanib (15.6% [n=36]) and placebo arms (11.1% [n=11]), with the absolute risk difference being 4.5%. The majority of haemorrhages (grouped event) in both treatment arms were CTCAE grade 1 or 2 events, and CTCAE grade ≥ 3 events were reported in 2 (0.9%) patients in the vandetanib arm compared with 3 (3.0%) in the placebo arm. Epistaxis was reported more frequently in vandetanib treated patients (7.8% [n=18]) compared with placebo (5.1% [n=5]), and all events of epistaxis were CTCAE grade 1 or 2. Haemoptysis was reported more frequently in patients in the vandetanib arm compared with the placebo arm (3.0% [n=7] versus 2.0% [n=2]). Intraventricular haemorrhage, intracranial haematoma and cerebral haemorrhage were each reported in 1 (0.4%) patient in the vandetanib arm. One (1) patient in the placebo arm died of a GI haemorrhage. Haemorrhage (grouped event) resulted in treatment discontinuation in 1 (1.0%) patient in the placebo arm and no patients in the vandetanib arm.

QTc prolongation

QTcB prolongation based on protocol defined ECG assessments occurred notably more frequently in patients in the vandetanib arm (8.2%) than in the placebo arm (0%). Two (0.9%) patients in the vandetanib arm discontinued treatment due to an AE of QTc prolongation or electrocardiogram QT prolonged, and both of these patients met the criteria for protocol defined QTc prolongation. In addition, 1 patient in the vandetanib arm had an AE of prolonged QTc that was CTCAE Grade 4, although the patient did not meet the criteria for protocol defined QTc prolongation. QT prolongation initially emerged most often in the first 3 months of treatment, but first occurrences were also observed after this

time. The maximum increase in QTcB from baseline in patients in the vandetanib arm was 27.6 ms (range: -27.6 to 135.7 ms) observed at Week 12, and the corresponding change from baseline in the placebo arm at this time point was 1.7 ms (range: -13.3 to 88.3 ms). During randomised treatment, 22 (9.5%) patients in the vandetanib arm had QTcB values of > 500 ms compared with 1 (1.0%) patient in the placebo group, and 63 (27.3%) patients in the vandetanib arm had an increase in QTcB from baseline of > 60 ms compared with 1 (1.0%) patient in the placebo arm.

QTc related AEs (grouped events) were reported more frequently in vandetanib treated patients (15.6%) than in placebo treated patients (4.0%). In the vandetanib arm, 16 (7.0%) patients had CTCAE grade 1 or 2 events compared with 1 (1.0%) patient in the placebo arm, and 20 (8.7%) patients had CTCAE grade ≥ 3 events compared with 3 (3.0%) patients in the placebo arm.

There were no reports of Torsade de Pointes (TdP) in the pivotal Phase III study. However, 2 cases of TdP (documented by ECG) have occurred in the vandetanib clinical program. The first case occurred in a patient with NSCLC enrolled in Study 57 who experienced TdP after 12 weeks of treatment with vandetanib 300 mg daily. The second case occurred in a patient with papillary thyroid cancer in Study 79 who experienced TdP after 5 weeks of treatment with vandetanib 300 mg daily. Both patients recovered. Only the TdP case from Study 59 was included in the pooled monotherapy studies as the data from Study 79 are preliminary and unvalidated. Therefore, in the pooled monotherapy vandetanib 300 mg studies (n=1839) TdP has been reported in 1 (0.1%) patient.

Cardiac failure

The available data suggest that cardiac failure is unlikely to be a significant risk with vandetanib therapy.

"Cardiac disorders" (SOC) were reported in 13.4% (n=31) of patients in the vandetanib arm and 13.1% (n=13) of patients in the placebo arm. The AEs (PT) occurring with an incidence of ≥ 1.0% in the vandetanib arm (versus placebo) were:

- palpitations (2.6% [n=6] versus 2.0% [n=2]);
- angina pectoris (1.7% [n=4] versus 1.0% [n=1]);
- bradycardia (1.7% [n=4] versus 0%); and
- sinus bradycardia (1.7% [n=4] versus 0%).

Cardiac failure (PT) was reported in 2 patients in the vandetanib arm compared with no patients in the placebo arm. The 2 patients in the vandetanib arm included 1 (0.4%) patient with CTCAE grade 1 cardiac failure (following a CTCAE grade 3 event of left ventricular failure), and 1 (0.4%) patient with acute cardiac failure/ventricular arrhythmia resulting in death with both events in this patient being considered to be related to the study drug.

Ischaemic heart disease (grouped event) was reported in 5 (2.2%) patients in the vandetanib arm (4 CTCAE grade 1 events and 1 CTCAE grade 3 event), and 2 (2.0%) patients in the placebo arm (both CTCAE grade 1 events).

In the pooled monotherapy vandetanib 300 mg data (n=1839), cardiac disorders (SOC) were reported in 180 (9.8%) patients and the only two events occurring in ≥ 1% of patients were palpitations (2.4% [n=44]) and atrial fibrillation (1.1% [n=44]).

Proteinuria and renal events

Newly developed dipstick proteinuria or deterioration of existing proteinuria was markedly higher in the vandetanib arm (90.9% [n=210]) than in the placebo arm (28.3% [n=28]). In addition, the frequency of newly developed dipstick haematuria or deterioration of existing haematuria was higher in the vandetanib arm (34.2% [n=79])

than in the placebo arm (22.2% [n=22]). The incidence of proteinuria reported as an AE was greater in the vandetanib arm (10.0% [n=23]) than in the placebo arm (2.0% [n=2]), while the incidence of haematuria reported as an AE was similar in the two treatment arms (1.7% [n=4] and 1.0% [n=1], respectively).

Among the patients in the vandetanib arm who developed dipstick proteinuria or had deterioration of existing proteinuria during randomised treatment, 23.4% (54/210) had concurrent or subsequent AEs of hypertension and 47.2% (109/220) had concurrent or subsequent elevation of blood pressure. Among the patients in the vandetanib arm who developed dipstick haematuria or had deterioration of existing haematuria, 6.9% (16/79) had concurrent or subsequent AEs of hypertension and 18.2% (42/79) had concurrent or subsequent elevated blood pressure.

In patients with a baseline observation and at least one follow up value, a higher percentage shifted from normal baseline (Grade 0) to elevated creatinine CTCAE grade ≥ 1 in the vandetanib arm (15.4% [35/228]) than in the placebo arm (0%). There were 9 (3.9%) patients in the vandetanib arm with an AE of blood creatinine increased compared with no patients in the placebo arm. There were 2 (0.9%) patients in the vandetanib arm who discontinued treatment due to AEs of blood creatinine increased.

Nephrolithiasis was reported in 4.3% (n=10) patients in the vandetanib arm and 2 (2.0%) patients in the placebo arm. Renal failure was reported in 4 (1.7%) patients in the vandetanib arm and 1 (1.0%) patient in the placebo arm.

Hypothyroidism

Hypothyroidism occurred commonly in patients in the vandetanib arm. Hypothyroidism was reported as an AE in 15 (6.5%) patients in the vandetanib arm and no patients in the placebo arm. All of the AEs of hypothyroidism were CTCAE grade 1 or 2. There were 114 (49.3%) and 17 (17.2%) patients in the vandetanib and placebo arms, respectively, who required an increase in thyroid hormone replacement therapy while on randomised treatment.

Embolic events

Venous embolic and thrombotic events were reported in 2 (0.9%) patients in the vandetanib arm and 4 (4.0%) patients in the placebo arm. Both patients in the vandetanib arm experienced CTCAE grade 2 events, while in the placebo arm CTCAE grades 1, 2, 3 and 4 events were each experienced by 1 patient.

Wound healing

There were no reports of wound dehiscence in the pivotal Phase III study. In the pooled monotherapy vandetanib 300 mg studies, wound complications were reported in 3 (0.2%) patients.

Reversible posterior leukoencephalopathy syndrome (RPLS)

There were no reported of RPLS in the pivotal Phase III study. However, 4 cases of RPLS have occurred in the vandetanib program. One case occurred in Study 32 in a patient who received vandetanib 100 mg daily in combination with chemotherapy for NSCLC. Two cases occurred in paediatric patients with primary brain tumours receiving vandetanib with concomitant radiotherapy in investigator sponsored Study IRUSZACT0051. One case occurred in a patient receiving vandetanib in combination with gemcitabine + oxaliplatin for transitional cell cancer in an investigator sponsored study IRUSZACT0070. There were no cases of RPLS in patients receiving vandetanib 300 mg monotherapy. However, there were 2 cases reported in patients receiving vandetanib in combination with chemotherapy.

Other relevant AEs

Visual impairment

Visual abnormalities identified by ophthalmological assessment were more common in the vandetanib arm than the placebo arm, with abnormalities in either eye being reported in 83.6% (n=133) of patients in the vandetanib arm and 61.5% (n=32) of patients in the placebo arm. The most notable difference between treatment arms was in abnormalities of the epithelium, which were observed in 49.7% (n=79) of patients in the vandetanib arm compared with 3.8% (n=2) of patients in the placebo arm. Independent consultant ophthalmoligical review of the data showed that 30.8% (49/159) of patients in the vandetanib arm who underwent ophthalmologic examinations had vortex keratopathy, compared with no patients in the placebo arm. The consultant considered that vortex keratopathy was related to vandetanib treatment.

Hepatic events

ALT elevations > 3x ULN (Upper Limit of Normal), > 5x ULN, and > 8x ULN while on randomised treatment were reported in 11 (4.8%), 4 (1.7%) and 1 (0.4%) patients in the vandetanib arm compared with no patients in the placebo arm. There were no patients in either arm with ALT elevations > 3x ULN and bilirubin elevations > 2x ULN while on randomised treatment. In the vandetanib arm, mean ALT values increased from baseline (23 U/L) to Week 12 (45 U/L), and then decreased to baseline levels by Week 120. In contrast, there were no changes in ALT levels in the placebo treatment arm over the course of the study. Hepatobiliary AEs were reported in 9 (3.9%) patients in the vandetanib arm and 1 (1.0%) patient in the placebo arm. There was one report of hepatic failure resulting in death in the placebo arm due to metastatic thyroid cancer.

Interstitial lung disease (ILD)

There were no reported cases of ILD (PT) in the randomised phase of the pivotal Phase III study, but there was 1 case in the open label period following administration of contrast material during cardiac catheterisation. In the pivotal Phase III study in the vandetanib arm there were 3 cases of pneumonitis (2 [0.9%] in the randomised period and 1 [2.3%] in the open label period). All 3 cases were CTCAE ≥ 3 events, and discontinuation due to pneumonitis occurred in 2 patients (1 in the randomised period and 1 in the open label period). In the pooled monotherapy vandetanib studies, pneumonitis was reported in 0.7% (n=13) patients.

List of questions

Efficacy

1. Why was it was decided to include all available “central read” RECIST assessments (randomised and open label) in the primary analysis of PFS in the pivotal Phase III study (Study 58)? Data from the open label period had the potential to bias the result due to patients randomised to placebo crossing over to vandetanib.
2. In Study 58, following protocol Amendment 6 investigators had the option to unblind subjects remaining on randomised therapy, whether or not disease progression had occurred. The rationale given for unblinding was “based on the results of the primary analysis for the study, which showed a significant benefit for subjects receiving vandetanib” (Protocol Amendment 006, Dated 13 January 2010). The results of the primary analysis of PFS provided in the protocol amendment showed a statistically significant improvement in PFS for subjects randomised to vandetanib compared to placebo (HR = 0.45; 95% CI = 0.30, 0.68; p<0.0001). Please explain the difference between the results provided for the primary analysis of PFS in the Clinical Study

Report (CSR) and in Protocol Amendment 6. Furthermore, please explain the somewhat confusing statement in the CSR that the amendment was "made as a consequence of the analysis results, rather than before the data were analysed".

3. It is stated that Study 58 was double blinded. Were investigators aware of calcitonin and CEA measurements for individual patients during the course of the study? If so, then it is unlikely that the study was truly double blinded given that vandetanib could potentially suppress levels of both of these biomarkers.
4. The primary analysis of PFS in the pivotal Phase III study (Study 58) was undertaken using a log-rank test unadjusted for baseline covariates. Why was it decided to undertake the primary analysis using a statistical method unadjusted for baseline covariates rather than a statistical method adjusted for baseline covariates?

Safety

1. Does the sponsor intend to investigate vandetanib doses lower than 300 mg once daily for the proposed indication? The submitted data included no dose ranging studies. The pharmacokinetic/pharmacodynamic modelling data showed no relationship between vandetanib plasma concentration and PFS or OS. The safety data showed that AEs associated with vandetanib 300 mg can be effectively managed by reducing the dose to 200 mg and/or 100 mg once daily.
2. Why do the patient numbers and percentages from the pooled vandetanib 300 mg monotherapy studies relating to AEs, most commonly occurring AEs, SAEs, deaths, and discontinuations due to AEs described in the Summary of Clinical Safety differ from those in the source tables provided on the CD. The relevant tables are: Table 2.7.4.2.1.1.1; Table 2.7.4.2.1.1.2; Table 2.7.4.2.1.6; Table 2.7.4.2.1.3.1; Table 2.7.4.2.1.3.2; and Table 2.7.4.2.1.4. The data provided in the Summary of Clinical Safety are "hyperlinked" directly to the relevant tables.
3. Why was Bazett's method rather than Fridericia's method was used to correct the QT interval in the pivotal Phase III study (Study 58)? The mean heart rate in the pivotal study was consistently about 4 to 6 bpm below baseline levels in the vandetanib arm, and bradycardia/sinus bradycardia was reported as an AE in 8 (2.4%) patients in the vandetanib arm. Bazett's correction is known to under correct at heart rates lower than 60 bpm, and heart rates were consistently lower than baseline in the vandetanib arm. Consequently, Fridericia's method might have been a more appropriate QT interval correction method. Furthermore, the pharmacokinetic/pharmacodynamic data from Study 58 showed that vandetanib (300 mg daily) at the predicted steady state Cmax increased the mean QT interval to a greater extent when corrected by Fridericia's method compared with Bazett's method (34 ms and 26 ms, respectively).

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The pivotal Phase III study showed that vandetanib 300 mg once daily resulted in a statistically significant predicted median increase in PFS of approximately 11.2 months compared with placebo as assessed by centrally reviewed modified RECIST criteria (30.5 months versus 19.3 months, respectively). The risk of experiencing an event (disease progression or death) at the date of data cut off was 54% lower in the vandetanib arm relative to the placebo arm (HR = 0.46 [95% CI: 0.31, 0.69], p=0.0001). The results for PFS are considered to be clinically meaningful.

The primary analysis of the PFS was supported by a number of sensitivity analyses. In particular, sensitivity analyses of the PFS excluding events occurring in the open label period and a Cox proportional hazards model adjusting for pre specified baseline covariates supported the primary analysis. The primary analysis of the PFS was also supported by the secondary efficacy endpoints of ORR and DCR, both of which statistically favoured vandetanib compared with placebo. In addition, the biomarker responses (CTN and CEA) both favoured vandetanib compared with placebo. There was no statistically significant difference in OS between the vandetanib and placebo treatment arms, but the data are considered to be immature. However, future assessments of OS are unlikely to satisfactorily discriminate between vandetanib and placebo due to the significant bias introduced into the analysis by crossover of patients from randomised placebo to open label vandetanib.

There were limited data in the pivotal Phase III study on patient reported outcomes (PROs). Time to worsening of pain (PRO) was pre specified as a secondary efficacy endpoint, and patients in the vandetanib arm had a statistically significantly longer time to worsening of pain compared with patients in the placebo group (median time 7.9 versus 3.3 months, respectively). All other PROs were considered to be exploratory.

First round assessment of risks

In the pivotal Phase III study (randomised period), nearly all patients (99.6%) in the vandetanib arm experienced at least 1 AE. However, most of these AEs were manageable by symptomatic treatment and/or dose reduction and/or dose interruption rather than treatment discontinuation.

The most commonly reported risks associated with vandetanib (versus placebo) were:

- diarrhoea (55.4% versus 26.3%);
- rash (45.0% versus 11.1%);
- nausea (33.8% versus 17.2%);
- hypertension (31.6% versus 5.1%);
- headache (26.0% versus 9.1%);
- fatigue (23.8% versus 23.2%);
- decreased appetite (21.2% versus 12.1%);
- acne (19.9% versus 5.1%);
- dry skin (15.2% versus 5.1%); and
- dermatitis acneiform (15.2% versus 2.0%).

SAEs occurred notably more frequently in patients in the vandetanib arm (30.7%) than in the placebo arm (13.1%). In addition, visual impairment assessed by ophthalmological assessment occurred frequently in both the vandetanib (83.6%) and placebo (61.5%) treatment arms, with 30.8% of patients in vandetanib arm having vortex keratopathy compared with no patients in the placebo arm. Also, the risk of hypothyroidism was more common in the vandetanib arm (6.5%) compared with the placebo arm (0%). Discontinuations due to AEs occurred notably more frequently in the vandetanib arm (12.1% [n=28]) than in the placebo arm (3.0% [n=3]). It was notable that female patients were at a greater risk of AEs associated with vandetanib treatment than male patients.

The most significant and potentially life threatening risk associated with vandetanib treatment relate to QT prolongation. QTcB prolongation based on protocol defined ECG assessments occurred notably more frequently in patients in the vandetanib arm (8.2%) than in the placebo arm (0%). In the randomised study period, the maximum increase in

QTcB from baseline in patients in the vandetanib arm was 27.6 ms (range: -27.6 to 135.7 ms) observed at Week 12, and the corresponding change from baseline in the placebo arm at this time point was 1.7 ms (range: -13.3 to 88.3 ms). During randomised treatment, 22 (9.5%) patients in the vandetanib arm had QTcB values of > 500 ms compared with 1 (1.0%) patient in the placebo group, and 63 (27.3%) patients in the vandetanib arm had an increase in QTcB from baseline of > 60 ms compared with 1 (1.0%) patient in the placebo arm.

There was 1 death in the vandetanib arm due to acute cardiac failure/arrhythmia, which raises the possibility that this death might have been related to QT prolongation. While no cases of TdP were reported in the pivotal Phase III study, 1 case was reported in the pooled monotherapy studies (0.1%) and 1 additional case was reported in Study 79 (preliminary unvalidated data). In the pooled monotherapy vandetanib 300 mg studies, sudden death was reported in 1 (0.1%) patient, cardio respiratory arrest in 3 (0.2%) patients, and cardiac arrest in 2 (0.2%) patients. In the population pharmacokinetic analysis (Study 58), the mean ± SD increase in QTcB was 26.5 ± 9.6 ms (range: 12.8 to 64.5 ms) and in QTcF was 33.9 ± 7.24 ms (range: 19.6 to 70.1 ms) in 230 patients assuming steady state vandetanib Cmax concentrations of 800 ng/mL.

Other serious but uncommon risks that have been reported with vandetanib in the clinical trial program include: pneumonitis (2 [0.9%] cases in the randomised period and 1 [2.3%] case in the open label period of the pivotal Phase III study [Study 58]; all 3 cases CTCAE ≥ grade 3 events; discontinuation in 2 of the cases); and rare reports in the pooled monotherapy vandetanib 300 mg studies of erythema multiforme (8 [0.4%] patients), Stevens-Johnson syndrome (6 [0.3%] patients), and toxic skin eruption (1 [0.3%] patient).

Laboratory abnormalities of note occurring in the pivotal Phase III study (randomised period) included: CTCAE Grades 1-4 occurring with an incidence of ≥ 10% in the vandetanib group and ≥ 5% more frequently than in the placebo group – hypocalcaemia (57.1% versus 25.3%), ALT increased (51.1% versus 18.2%), AST increased (28.9% versus 12.1%), creatinine increased (16.5% versus 1%), hypoglycaemia (22.1% versus 8.1%); and CTCAE grade 3 or 4 events occurring more commonly in the vandetanib arm than in the placebo arm - ALT increased (1.7% versus 0%), hypocalcaemia (5.6% versus 3.0%), hypomagnesaemia (0.4% versus 0%), hypokalaemia (0.4% versus 0%), hypernatraemia (1.7% versus 0%), and hyperglycaemia (1.7% versus 1.0%). Elevated thyroid stimulating hormone (TSH) levels were also observed more frequently in the vandetanib arm (18.6%) than in the placebo arm (1.0%). Urinalysis (dipstick) showed a greater incidence of proteinuria in the vandetanib arm than in the placebo arm (90.9% versus 28.3%, respectively), and haematuria was also observed more commonly in the vandetanib arm than in the placebo arm (34.2% versus 22.1%, respectively).

In the US, the FDA approved vandetanib for the treatment of MTC with a Risk Evaluation Mitigation Strategy (REMS) aimed at reducing the risk of QT prolongation. Elements of the strategy include medication guides, communication strategies, certification of healthcare professionals permitted to prescribe vandetanib, certification of pharmacies permitted to dispense vandetanib, and a boxed warning on the prescribing information (label) highlighting the association between vandetanib and QT prolongation, TdP and sudden death. Health Canada has also adopted a similar approach to the FDA, and the Canadian sponsor recently distributed a “Dear Health Care Professional” letter drawing attention to the association between vandetanib and QTc interval prolongation and cases of TdP and sudden death, and stating that vandetanib was only available through a Restricted Distribution Program. If the TGA approves vandetanib for the proposed indication, then it might like to consider a similar approach to the Australian supply of vandetanib to that adopted by the US and Canadian regulators. The approach adopted by the USA and Canadian regulators appears to be due to the particularly high incidence of QTcB prolongation observed in the pivotal Phase III study (Study 58) in patients treated with

vandetanib compared with placebo and the associated potential risks of TdP and sudden death.

In addition to restricting the supply of vandetanib, one of the other approaches adopted by the US and Canadian regulators to mitigating the risks of vandetanib was to limit the indication to the treatment of symptomatic or progressive MTC in patients with unresectable locally advanced or metastatic disease. The restriction of the indication is presumably due the indolent and slowly progressive nature of unresectable locally advanced or metastatic MTC. If the TGA approves vandetanib, then it might like to consider a similar approach to limiting the indication to patients with symptomatic of progressive disease. However, it is considered that that this approach might unnecessarily hinder the prescribing of vandetanib to patients with unresectable locally advanced or metastatic MTC. Consequently, it is recommended that the proposed indication should remain general, particularly as vandetanib will be prescribed for the proposed indication by medical practitioners who are expert in the treatment of cancer.

First round assessment of benefit-risk balance

The benefit-risk balance of vandetanib, given the proposed usage, is favourable. The median predicted increase in time to progression or death of 11.2 months in patients treated with vandetanib is considered to provide an important clinical benefit, given that there are no other approved treatments for unresectable locally advanced or metastatic MTC. The risks of treatment with vandetanib for the proposed usage are significant, but are considered to be manageable by appropriated symptomatic treatment, dose reductions, and dose interruptions. In addition, it is considered that the potentially life threatening risk of QT prolongation can be managed by judicious patient selection, careful attention to known risk factors and appropriate ECG monitoring.

First round recommendation regarding authorisation

It is recommended that the submission to register vandetanib 300 mg once daily for the treatment of patients with unresectable locally advanced or metastatic MTC be approved.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a RMP that was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 6.

Table 6: Summary of Ongoing Safety Concerns for Caprelsa.

Important identified risks	Diarrhoea
	Heart failure
	Hypertension
	QTc prolongation and torsades de pointes
	Rash and other skin reactions
Important potential risks	Abnormal/delayed wound healing
	Hepatic failure
	Interstitial lung disease (ILD)
	Renal toxicity
	Reversible posterior leukoencephalopathy syndrome (RPLS)
Important missing information	Long-term use
	Use during pregnancy
	Use in elderly patient population
	Use in paediatric patient population
	Use in patients with hepatic impairment
	Use in patients with cardiac impairment
	Use in patients with moderate to severe renal impairment

OPR reviewer's comments

It is noted that the version of the EU RMP that was most recently reviewed and published by the European Medicines Agency (EMA) included the following additional safety concerns:

- Important identified risks:
  - Appetite decreased: this is listed in the "Adverse Effects" section of the draft Australian PI,
  - Cerebrovascular events: this is listed in the "Precautions" section of the draft Australian PI,
  - Cholelithiasis: this is listed in the "Adverse Effects" section of the draft Australian PI,
  - Dysphagia: this is listed in the "Adverse Effects" section of the draft Australian PI,
  - Hypocalcaemia: this is listed in the "Adverse Effects" section and a recommendation is included to monitor serum calcium in the "Precautions – QTc Prolongation" section of the draft Australian PI,
  - Infections: several terms associated with infections are listed in the "Adverse Effects" section of the draft Australian PI,
  - Intestinal perforation and/or obstruction: these are listed in the "Adverse Effects" section of the draft Australian PI,
  - Pancreatitis: this is listed in the "Adverse Effects" section of the draft Australian PI,
  - Phototoxicity: this is listed in the "Precautions (Skin reactions)" and "Adverse Effects" sections of the draft Australian PI, and a targeted follow up questionnaire for skin reactions is already proposed in the RMP,
  - Pneumonia: this is listed in the "Adverse Effects" section of the draft Australian PI,
  - Weight decreased: this is listed in the "Adverse Effects" section of the draft Australian PI,
- Important potential risks:
  - Drug-drug interactions: information is included in the "Interactions with other medicines" section of the draft Australian PI,

  - Reproductive toxicity: information is included in the "Effects on fertility and Use in Pregnancy" sections of the draft Australian PI,

- Important missing information:
  - Use in non Caucasian patient population: no risk minimisation activities proposed in the EU RMP.

This EU RMP has indicated that the use of routine pharmacovigilance and risk minimisation activities are proposed for all of these safety concerns except for the important potential risks "drug-drug interactions" and "reproductive toxicity". As no other pharmacovigilance and risk minimisation activities beyond those that are considered to be routine activities are proposed for most of these additional safety concerns, and the fact that relevant safety information is already provided in the draft Australian PI as stated above is considered acceptable. However, it is expected that the sponsor provides an assurance that an updated RMP (the EU RMP) and/or Australian specific Annex will be provided to the TGA in the future, with the inclusion of all these relevant safety concerns or be accompanied by an acceptable justification for any safety concern omitted.

Pursuant to the evaluation of the nonclinical and clinical aspects of the Safety Specification (SS) and the above summary of the Ongoing Safety Concerns, it is also recommended that "haemorrhage" and "hypothyroidism" be included as identified risks, and "use in breast feeding women", be included as an area of missing information for the following reasons:

- "haemorrhage" and "hypothyroidism": both of these AEs were observed in clinical studies and the relevant information already were included under the "Precautions" section of the draft PI, as per the clinical evaluator's request,
- "use in breast feeding women": breast feeding women were excluded in the pre authorisation clinical studies (Global RMP) and the potential risk of reduced post natal growth and development due to excretion of vandetanib in breast milk was identified based on observation in rodent studies.

Pharmacovigilance plan

Proposed pharmacovigilance activities

Routine pharmacovigilance activities are proposed for all safety concerns. In addition, additional PV activities in the form of 7 targeted questionnaires to collect follow up information will be used for the following safety concerns: heart failure, QTc prolongation and TdP, rash and other skin reactions (including phototoxicity events), ILD, renal toxicity, RPLS and hepatic failure.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The proposed use of routine pharmacovigilance for all safety concerns and enhanced pharmacovigilance (targeted follow up questionnaires) for the important identified risks: heart failure, QTc prolongation and TdP, rash and other skin reactions, and important potential risks: ILD, renal toxicity, RPLS and hepatic failure, are considered acceptable at this stage. A copy of each targeted questionnaire is provided in the Global RMP. The information requested in each of the questionnaires includes details of the event, the patient's medical and medication histories, and relevant laboratory or diagnostic test results, which are considered appropriate to monitor these safety concerns.

As stated in this report, an updated RMP (the EU RMP) and/or Australian specific Annex with the inclusion of the relevant additional safety concerns should be provided to the TGA. It is expected that the updated RMP and/or Australian specific Annex should also include details of any relevant additional pharmacovigilance activities proposed for each of the additional safety concerns, including the following as identified in the EU RMP5,

unless an acceptable justification can be provided as to why any of these activities may not be relevant to the Australian market:

- Important potential risk: Drug-drug interactions (all the following studies are expected to be completed in June 2013):
  - Study to evaluate co administration of vandetanib with digoxin,
  - Study to evaluate co administration of vandetanib with metformin,
  - Study to evaluate co administration of vandetanib with omeprazole (proton pump inhibitor) or ranitidine (histidine antagonist),
  - Study to evaluate co administration of vandetanib with midazolam.

  A search on ClinicalTrials.gov website on 10 September 2012 has identified the following studies, which should be confirmed by the sponsor as to whether they are the corresponding studies as listed in the EU RMP:
  - a recently completed study entitled "Study in Healthy Volunteers to Assess the Pharmacokinetics of Digoxin Administered Alone and in Combination with Vandetanib"; NCT01561781
  - a recently completed study entitled "A Phase I Study to Assess the Pharmacokinetics of Metformin When Administered Alone and in Combination with Vandetanib"; NCT01551615
  - an ongoing study (anticipated completion in August 2012) entitled "Study in Healthy Volunteers to Assess Effect of Omeprazole and Ranitidine on the Pharmacokinetics of Vandetanib"; NCT01539355
  - a recently completed study entitled "Study in Healthy Volunteers to Assess the Pharmacokinetics of Midazolam Administered Alone and in Combination with Vandetanib"; NCT01544140
- Reproductive toxicity:
  - Targeted follow up on pregnancy outcome
- The EU RMP5 also listed Study D4200C00097 as an additional pharmacovigilance activity but it is unclear if this study is designed specifically to evaluate any specific safety concerns identified in the EU RMP or not:
  - Study D4200C00097: an international, double blind, two arm study to evaluate the safety and efficacy of vandetanib 150 mg and 300mg/day in patients with unresectable locally advanced or metastatic medullary thyroid carcinoma with progressive or symptomatic disease (anticipated completion in October 2015).

It is also recommended that the sponsor comments on the relevance of the studies being conducted as part of the FDA's post marketing requirements in context of this Australian submission and provide an acceptable justification if any of these studies will not be considered relevant in Australia. The sponsor should provide an assurance that the results from any relevant studies will be provided to the TGA when available, which can be submitted as part of a future submission, Periodic Safety Update Reports (PSURs) or updated RMP.

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The Australian specific Addendum to the Global RMP stated that risk minimisation activities for Australia will be conducted in accordance with the Global RMP and that no additional risk minimisation activities will be proposed for Australia. It is stated in the

Global RMP that additional risk minimisation activities are proposed. However, it is noted that the Global RMP indicated that only routine risk minimisation activities are proposed for all important identified and potential risks.

OPR reviewer's comments

It is unclear whether additional risk minimisation activities will be implemented in Australia. It is noted that strategies consistent with additional risk minimisation activities have been implemented in the US and EU, with a strong focus on mitigating risks associated with QT prolongation. The US FDA has imposed a Risk Evaluation and Mitigation Strategy (REMS) with the primary focus to inform prescribers and patients about the risks particularly those associated with QT prolongation, and to educate prescribers of the appropriate monitoring and management of QT prolongation. The EMA has requested that educational materials directed at healthcare professionals and patient alert cards are supplied to inform of the risks particularly those associated with QT prolongation and RPLS and the appropriate management strategy. In addition, the US FDA has also imposed a restricted distribution program for the supply of Caprelsa with the requirement that only prescribers and pharmacies certified through this program are able to prescribe and dispense this drug. The sponsor was requested to clarify in the s31 request for information if similar additional risk minimisation activities will be implemented in Australia or if not, to provide an appropriate justification.

Potential for medication errors

Although it is not explicitly discussed in the Global RMP, the potential for medication error is expected to be minimised by the distinguishing features between the two tablet strengths:

- 100 mg tablet: round shape with "Z100" embossed on one side of tablet,
- 300 mg table: oval shape with "Z300" embossed on one side of tablet.

As discussed in the Global RMP, the potential for misuse is not anticipated due to the properties of vandetanib. The Global RMP discussed the potential for off label use as expected to be very small, including in paediatric population. It is acknowledged that the off label use outside of the approved indication, such as in paediatric MTC patients or in combination with other drugs for the treatment of MTC might occur. However, it is expected that spontaneous AE reporting in the post market will further informed of these events.

OPR reviewer's comments

This is considered acceptable if the use of Caprelsa is only to be initiated and managed under the supervision of a healthcare professional experienced in cancer therapy. It is recommended that the following or a similar statement be included in the Dosage and Administration section of the PI:

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

Toxicity in overdose

The "Potential for overdose" section of the Global RMP and the "Overdosage" section of the draft Australian PI stated that no specific treatment for overdose is available. It is noted that an increase in the severity and frequency of certain AEs have been observed when multiple doses at and above 300 mg were taken. The potential for QT prolongation and TdP in context of an overdose is also noted. It is recommended in the draft Australian PI that:

> *"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 AE has not occurred, that is, an ECG within 24 hours to determine QTc prolongation."

Instruction is included in the draft Australian Consumer Medicine Information (CMI) to contact Poisons Information Centre (with contact details provided) for advice, or to seek emergency medical attention at the nearest hospital in case of overdose.

OPR reviewer's comments

This is considered acceptable.

Summary of recommendations

The OPR provides the recommendation in the context that the submitted RMP is supportive to the application, with the amendments as requested below:

- the implementation of the RMP identified as the Global RMP Edition 1, (dated 7 September 2011) with RMP Addendum 1 – Australian Risk Minimisation Activities (dated 7 September 2011), and any subsequent versions, is imposed as a condition of registration.

Safety concerns

If this application is approved, it is recommended that the Delegate considers requesting the sponsor to provide an updated RMP and/or Australian specific Annex to the OPR within 6 months post registration, with the inclusion of all the relevant safety concerns and accompanied by appropriate and acceptable pharmacovigilance and risk minimisation activities. Notably, the following additional safety concerns are noted in the version of the EU RMP5, which was reviewed by the EMA, but are not currently included in the RMP provided for this submission:

- Important identified risks:
  - Appetite decreased
  - Cerebrovascular events
  - Cholelithiasis
  - Dysphagia
  - Hypocalcaemia
  - Infections
  - Intestinal perforation and/or obstruction
  - Pancreatitis
  - Phototoxicity
  - Pneumonia
  - Weight decreased
- Important potential risks:
  - Drug-drug interactions
  - Reproductive toxicity
- Important missing information:
  - Use in non Caucasian patient population

It is also recommended that "haemorrhage" and "hypothyroidism" be included as identified risks, and "use in breast feeding women" be included as an area of missing information, and these be accompanied by appropriate and acceptable pharmacovigilance and risk minimisation activities, for the following reasons:

- "haemorrhage" and "hypothyroidism": both of these AEs were observed in clinical studies and the relevant information were already included under the Precautions section of the draft PI, as per the clinical evaluator's request,
- "use in breast feeding women": breast feeding women were excluded in the pre authorisation clinical studies (Global RMP) and the potential risk of reduced post natal growth and development due to excretion of vandetanib in breast milk was identified based on observation in rodent studies.

As recommended by the nonclinical evaluator, the sponsor should also include the relevant information on the reduced post natal pup growth, delayed physical and sexual development as observed in rats dosed with vandetanib during late gestation and lactation, in the nonclinical safety specification of the RMP. In addition, the relevant information on phospholipidosis should be included in the nonclinical safety specification of the RMP and further information be provided on whether this potential risk will be further monitored (and how) or if not, why further monitoring will not be required.

Other pharmacovigilance activities

If this application is approved, it is recommended that the Delegate considers requesting the sponsor to provide an assurance that the results from the studies being conducted as part of the FDA's post marketing requirements that may be relevant to this Australian submission, will be provided to the TGA when available.

Risk minimisation activities – education programmes

If this application is approved, it is recommended that the Delegate considers imposing as a condition of registration the proposed education programmes to inform prescribers and patients of the important risks associated with vandetanib, in particular the risk of QT prolongation (including associated TdP and sudden death). It is recommended that the proposed Australian educational (including the Patient alert card) and assessment materials (questionnaires to evaluate knowledge on risks) be provided to the OPR for approval prior to marketing. The format and content of all the educational and assessment materials must be consistent with the educational objectives and should be adequate and appropriate to measure effectiveness and minimise the risks.

In addition, the following should be clarified by the sponsor:

- Prescribers will be certified prior to prescribing. However, it is unclear if there is an intention to make this a restriction for supply or how this will be enforced i.e. will the supply be linked to certified prescribers only (how will this be checked by dispensing pharmacists)? Will recertification be required, and if so at what intervals?
- The stated success criteria to measure the effectiveness of the proposed education programme are not clearly defined enough to ascertain whether they are acceptable or not.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no objection to registration on quality grounds.

Nonclinical

There was no objection to registration if clinical studies adequately addressed safety.

Clinical

The clinical evaluator recommended **approval** of the application. There was no second round evaluation.

Overview of data

Study 58 was pivotal. It was a Phase III, randomised, double blind, placebo controlled trial in patients with unresectable locally advanced or metastatic MTC. This trial has been published[12] and a copy of the publication is included in the agenda papers.

Smaller efficacy studies 8 and 68 were supportive. Clinical pharmacology was also studied.

Pooled safety data were also available from 11 Phase I-III studies of vandetanib 300 mg in patients with various malignant tumours (primarily NSCLC) ("pooled monotherapy studies"), with a data cut off date of 19 October 2009 (that is, >3 years ago). The evaluator considered safety information from several vandetanib 100 mg studies in NSCLC to be too indirectly relevant for consideration.

The sponsor also referred to ongoing Study IRUSZACT0113 (vandetanib in combination with bortezomib in MTC; Phase I/II dose ranging) and ongoing Study IRUSZACT0098 (vandetanib in paediatric hereditary MTC; Phase I/II) but no data were evaluated from these studies. Preliminary results of Study 79 (a placebo controlled Phase II study in differentiated thyroid cancer) were included in the dossier but are not considered directly relevant.

Pharmacokinetics

The evaluator considered the population pharmacokinetic analysis from Study 58 to be the main source of pharmacokinetic data for patients with MTC.

Absorption, distribution, metabolism, excretion

The tablets are immediate release. Absorption is relatively slow; estimates of Tmax varied from 4-8 h.

Although the evaluator discusses dissolution as the rate limiting step for absorption, the sponsor notes that:

> *"absorption of the 300 mg vandetanib dose from the tablet or by oral solution gave similar [Cmax] and [Tmax] values indicating that absorption across the gut-wall is the rate limiting step rather than dissolution from the tablet".*

This is relevant since vandetanib tablets can be dispersed in water and given as a 'slurry'.

Vandetanib has increased solubility at low pH. There were no interaction studies between vandetanib and drugs affecting gastric pH. A study of interactions with omeprazole and

[12] Wells SA Jr, *et al.* (2012) Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol.* 30: 134-141.

ranitidine may be reported by June 2013. Possibly, lowering of gastric pH (for example, after cessation of pH raising medicine) could increase Tmax or Cmax.

There was **no food effect** in single dose cross over Study 24. In pivotal Study 58, vandetanib was given with no food restrictions.

There are 100 mg and 300 mg tablets. There was no formal dose proportionality study. In two of four studies there was a suggestion of more dose adjusted exposure with 300 mg than with 100 mg doses at steady state (Study 04) although at steady state (Day 29) in Study 01 in patients with malignancy, the opposite impression was given.

An absolute bioavailability study was not done. Volume of distribution was around **7450 L** in the population pharmacokinetic part of Study 58, with high inter individual variability. In animals, vandetanib penetrated into the brain. Vandetanib is 93-94% protein bound, with binding unchanged by hepatic or renal impairment.

Clearance from plasma after oral administration was ~13.2 L/h, but relative contributions of renal and non renal clearance were not quantified.

Two major metabolites were identified, but exposure was <10% relative to vandetanib for each. N-desmethyl-vandetanib (as potent as vandetanib) was formed after metabolism of vandetanib via **CYP3A4**. N-oxide-vandetanib was not as potent and its formation was not mediated by CYP enzymes, but rather by **flavin-containing monoxygenase isoforms 1 and 3** (FMO1 is found in adult kidney and intestine; FMO3 is found in the liver).

In a mass balance study (Study 25), radioactivity recovered by Day 21 was 69% of the total dose (44% in faeces and 25% in urine). Enterohepatic recirculation may occur. Recovery of radioactivity was incomplete due to the long plasma half life of vandetanib and the low dose administered.

Half life is long at around 19 days, consistent with slow clearance and large volume of distribution.

Special populations

A single 800 mg dose **hepatic impairment** study (Study 16) showed a modest decrease in vandetanib AUC and a moderate decrease in Cmax in severe impairment, along with a moderate increase in half life. Impact on metabolite pharmacokinetic was also assessed.

A single 800 mg dose **renal impairment** study (Study 22) showed that even mild renal impairment resulted in higher AUC and lower oral clearance, with increased exposure with worsening renal function. Similar trends emerged for assayed metabolites. For vandetanib, results are shown in Table 7.

Table 7: Pharmacokinetic parameters for vandetanib.

Parameter (units)	Statistic	Mild/Normal	Moderate/Normal	Severe/Normal
AUC (ng.h/mL)	GLS mean ratio (90% CI)	1.46 (1.24, 1.72)	1.62 (1.31, 1.99)	1.79 (1.39, 2.31)
C_{max} (ng/mL)	GLS mean ratio (90% CI)	1.07 (0.89, 1.29)	1.09 (0.86, 1.38)	1.11 (0.83, 1.48)
CL/F (L/h)	GLS mean ratio (90% CI)	0.68 (0.58, 0.81)	0.62 (0.50, 0.76)	0.56 (0.43, 0.72)

The sponsor focused on doubling of exposure as an indicator of concern (based on tolerability data for vandetanib from earlier patient studies in which daily doses of 100 to 300 mg were relatively well tolerated while daily doses of 500 to 600 mg were poorly tolerated).

There was a suggestion from cross study comparison of higher exposure in **Chinese and particularly Japanese populations**.

Drug interactions

Study of vandetanib (Day 4) with itraconazole (CYP3A4 **inhibitor**; Days 1-24) showed no major effect of concomitant use on vandetanib pharmacokinetics. Exposure to vandetanib was 40% lower with concomitant CYP3A4 **inducer** rifampicin, and exposure to the active N-desmethyl metabolite increased 2-3-fold.

Based on *in vitro* data, vandetanib may induce CYP1A2, CYP2C9 and CYP3A4; there were no formal *in vivo* studies. Drug interaction studies with digoxin, metformin, omeprazole, ranitidine and midazolam are being or have been conducted but have not been submitted for evaluation.

An interaction study with the CYP3A4 **substrate** docetaxel (in Study 06, NSCLC) revealed a marked decrease in docetaxel Cmax (but not AUC). This suggests a potential for interaction with CYP3A4 substrates, but this was not seen in an interaction study with Folfiri, where irinotecan is a CYP3A4 substrate.

In vitro experiment KMX083 showed vandetanib to inhibit OCT2. The sponsor used this to explain the increase in plasma creatinine in patients given vandetanib.

In Study 58, 15.9% of vandetanib subjects and 6.3% of placebo arm subjects had International Normalised Ratio (INR) >2x ULN, suggesting the possibility of a warfarin interaction, however the *in vitro* data above pointed to induction rather than inhibition of CYP2C9.

Pharmacodynamics

Study 58 provided population pharmacokinetic data relating to efficacy outcomes.

CTN levels fell at predicted vandetanib concentrations >500 ng/mL, plateauing at vandetanib concentrations >1500 ng/mL. No clear relationship between changes in vandetanib exposure and changes in **CEA** levels was established.

Best response was found to correlate with an increase in predicted **steady state exposure**. The model found that a predicted steady state AUC of ≥20.77 μg.hr/mL is required for the probability of partial response to be ≥50%. This modelling suggested that 10% of patients are non responders irrespective of exposure achieved, and that increases in exposure beyond 20-30 μg.hr/mL do not result in marked improvements in best response.

Study 50 studied tumour perfusion and vascular permeability using dynamic contrast enhanced MRI, in 24 patients with colorectal cancer and liver metastases, given vandetanib (100 mg or 300 mg) orally once daily for 56 days. Reduction in perfusion was expected, but changes from baseline were <5% (negligible), with no dose effect.

Efficacy

Study 58

Design and conduct

This was a randomised, double blinded, placebo controlled study. Adults with unresectable locally advanced or metastatic MTC were enrolled. They were required to have measurable tumour at baseline and a CTN level of ≥500 pg/mL to indicate advanced disease at study entry. To justify use of a placebo control, the sponsor noted that there is no agreed standard therapy for the condition (this view seems accurate).

After an interim analysis, the protocol was amended so patients could be unblinded and enter an open label phase. The data cut off date was 31 July 2009.

Inclusion criteria included WHO Performance status 0-2, and life expectancy of ≥12 weeks. **A total of 330 subjects were randomised** (~2 to 1) to daily oral vandetanib 300 mg (n=231) or placebo (n=99). The randomisation ratio of 2.33 to 1 was attributed to block randomisation and play of chance. The study had a superiority design.

Study subjects

Mean age was lower in the vandetanib arm at 50.7 years than in the placebo arm at 53.4 years. 21.6% of vandetanib subjects and only 10% of placebo arm subjects were aged 18 to <40 years. There was a similar fraction of subjects aged ≥65 in each arm (~21%).

Consistent with this imbalance, Table 8 shows that ~12% of vandetanib subjects and 5% of placebo subjects had hereditary disease and/or a syndrome.

Table 8: Family history of MTC or associated syndrome of vandetanib subjects.

		Number (%) of patients		
		Vandetanib 300mg (N=28)	Placebo (N=5)	Total (N=33)
Family history of MTC	Yes	12 (42.9)	4 (80.0)	16 (48.5)
	No	12 (42.9)	1 (20.0)	13 (39.4)
	Unknown	4 (14.3)	0	4 (12.1)
Associated syndrome	FMTC	4 (14.3)	1 (20.0)	5 (15.2)
	MEN2a	14 (50.0)	3 (60.0)	17 (51.5)
	MEN2b	7 (25.0)	0	7 (21.2)
	None	2 (7.1)	1 (20.0)	3 (9.1)
	Unknown	1 (3.6)	0	1 (3.0)

Among all subjects **with a determined mutation status**, RET mutation status was positive in 98.6% (137/139, vandetanib) and 89.3% (50/56, placebo). Many subjects had indeterminate status; mutation status was assessed by sequencing the 6 most commonly mutated exons in MTC and by evaluating for the M918T mutation. Mutation was generally at position 918 in sporadic cases (142/155 RET mutation positive sporadic or "background unknown" cases), but often at position 634 in hereditary cases (13/32 RET mutation positive hereditary cases).

In keeping with the age imbalance, WHO Performance Status was better in the vandetanib arm (67% with Status 0, that is, normal activity) than in the placebo arm (58%).

There was no requirement for prior chemotherapy (it is not widely used in MTC); ~20% of subjects had received any. There was a history of thyroidectomy in 90%, lymphadenectomy in 74-80%; radical neck dissection in ~10%; radiotherapy in ~80% and radioimmunotherapy in ~4%. It was noted that 22% had received therapy specified as "other".

The percentage of subjects with distant metastases (commonly to liver, lymph nodes, lungs and bone) was 93.5% of vandetanib and 97% of placebo subjects. All subjects had multiple organ involvement (typically 3-5). Only 1 and 2 subjects respectively had "only Stage III" disease.

Efficacy evaluation

Tumour response was assessed using RECIST. All scans were assessed for progression by central imaging review.

The primary endpoint was PFS in the ITT population based on "central read" RECIST assessments. The primary analysis included assessments in patients randomised to placebo who chose to **switch to open label** vandetanib. Duration of follow up was ~104 weeks across arms. Mean duration of exposure (in the randomised phase) was 73.5 weeks for vandetanib and 53.7 weeks for placebo.

Results

Progression free survival

Disease progressed in 73/231 vandetanib subjects (31.6%) and 51/100 placebo subjects, with a hazard ratio of 0.46 (95% CI, 0.31-0.69) favouring vandetanib. Median PFS in the placebo arm was 19.3 months. Weibull model predicted median PFS in the vandetanib arm was 30.5 months. Sensitivity analyses for PFS were supportive; with exclusion of data from the open label phase the hazard ratio improved to 0.27.

12.1% of vandetanib subjects but 22% of placebo subjects developed new liver lesions. New liver lesions can be due to necrosis/cystic change rather than disease progression; presumably the protocol specified confirmation of new liver lesions occurred.

Primary analysis of PFS indicated that 51/100 placebo arm subjects progressed. Sensitivity analysis excluding open label phase data indicated that 59/100 had progression, so at least 8 patients who had progressed in the randomised phase must have responded in the open label phase well enough to "reverse" documented progression. A total of 58/100 placebo subjects switched to open label vandetanib; this could occur "whether or not disease progression had occurred".

Primary analysis of PFS indicated that 73/231 vandetanib subjects progressed. Sensitivity analysis excluding open label data indicated that 64/231 had progression. A total of 44/231 vandetanib subjects switched to open label vandetanib.

Results in the randomised phase were better than primary efficacy results; but both supported vandetanib. The FDA assessed the primary efficacy endpoint using data from the randomised period, and also redefined endpoints and efficacy analysis methodologies.

Fewer females in either arm progressed. In those with hereditary/germline mutation, 7/28 vandetanib subjects progressed (25%) versus 2/5 placebo subjects (40%): roughly in keeping with the overall results. In subjects with no objective response to prior systemic anti cancer therapy results were less compelling than in the overall analysis, with similar progression across arms.

Overall survival (OS)

An initial OS analysis was shown (another is planned when more mature data are available). The initial results show that 13.9% of vandetanib subjects and 16% of placebo subjects had died; the HR was 0.89 (95% CI 0.28-2.85). Subgroup analysis was not performed. Final assessment will be biased by switching of subjects to open label vandetanib.

Objective response rate (ORR)

The partial response rate was 45% for vandetanib (104/231) and 13% for placebo (13/100), with an odds ratio of 5.5 (95% CI 3.0-10.8). There were no complete responses. In an ad hoc analysis, ORR was calculated excluding open label assessments, and in this case the OR rose to 76.9 (most partial responses in the placebo arm were after crossing to vandetanib).

Quality of life

Time to worsening of pain was assessed. This factored in opioid use and worst pain item of the BPI (CER1 page 64). Outcomes favoured vandetanib, for example, median time to worsening of pain was 7.85 months for vandetanib but 3.25 months for placebo.

Other patient reported outcomes were considered exploratory and not well reported.

Diarrhoea is a symptom of MTC. There were twice as many reports of diarrhoea as an AE in the vandetanib arm than the placebo arm (indeed diarrhoea was the most common severe AE for vandetanib). Stool frequency over time was generally higher in the vandetanib arm.

Global quality of life was assessed using the Functional Assessment of Cancer Therapy-General Questionnaire (FACT-G) questionnaire. There was little change from baseline in either arm.

Other efficacy endpoints

Disease control rate was better in the vandetanib arm.

CTN and CEA fell substantially in the vandetanib arm but not the placebo arm. Most CTN responses were partial (that is, at least a halving of CTN from baseline) but 3/231 vandetanib subjects (and no placebo arm subjects) had complete normalisation of CTN. There were similar results for CEA.

Study 8

This was a Phase II, **open label, uncontrolled** study of vandetanib **300 mg daily** in 30 adults with locally advanced or metastatic **hereditary** MTC. Mean age was 48.7 yrs (range 20-77); 21/30 were female; 21/30 had multiple endocrine neoplasia type 2 (MEN2A); 29/30 had metastases. The main objective was to assess ORR (based on computed tomography/magnetic resonance imaging [CT/MRI] scans using RECIST criteria). **ORR** was 20% (6/30 partial responses), that is, lower than the 45% in Study 58 (ORRs are not specified for Study 58's vandetanib hereditary or germline subgroup, but PFS was lower at 25% for this group, compared to the vandetanib 'sporadic or unknown' subgroup at 32.5%). **Median PFS** was 27.9 months, similar to that in Study 58.

Study 68

This was a Phase II, **open label, uncontrolled** trial of vandetanib **100 mg daily** in adults with locally advanced or metastatic **hereditary** MTC. On progression, increase in dose to 300 mg was optional. A total of 19 patients received vandetanib (13/19 male; mean age 44.7 years, range 22-79; 17/19 with MEN2A; 18/19 with metastatic disease). **Partial response rate** was 15.8% (3/19), with no complete responses. There was insufficient follow up to assess median PFS. Three subjects had a partial CTN biochemical response.

Safety

Vandetanib was embryotoxic and teratogenic in rats. Pregnancy category D is appropriate and consistent with categorisation for other tyrosine kinase inhibitors.

Vandetanib inhibits VEGFR, EGFR and RET. Consequently, there are important risks associated with the drug arising from effects on both the VEGF and EGF downstream signalling pathways. These include diarrhoea, hepatic failure, proteinuria (VEGF modulates glomerular permeability), rash and other skin reactions, QT prolongation, hypertension, heart failure, abnormal wound healing, posterior leukoencephalopathy syndrome, GI perforation, haemorrhage, thrombosis and hypothyroidism.

Effects on RET downstream signalling are less well characterised. The sponsor states: "there are no known class effects of RET specific inhibitors, as all RET inhibitors that have been tested in the clinic also have other molecular targets".

Clinical exposure

In Study 58, n=231 patients received ≥1 dose of randomised vandetanib and n=99 ≥1 dose of randomised placebo; there was further exposure to vandetanib in the open label phase.

In the randomised phase, 162/231 vandetanib subjects (70.1%) received ≥12 months of vandetanib, and 42/99 (42.4%) received ≥12 months of placebo. Total treatment years were **331.7 patient years** for randomised vandetanib and **102.3 patient years** for randomised placebo.

Safety data were reported for the open label phase of Study 58. One patient had an acute myocardial infarction resulting in discontinuation of vandetanib, as well as acute renal failure and interstitial lung disease. Otherwise, results were unremarkable.

Safety data were reported for Study 8 and Study 68. In Study 8 (n=30), dose reduction from 300 mg or dose interruption was prominent.

In pooled vandetanib 300 mg monotherapy studies, most subjects were treated for <6 months. The focus in Table 9 is on pivotal Study 58.

Table 9: Summary of patients in Study 58 who had at least 1 AE in any category while on randomised treatment (Safety Analysis set).

	--Vandetanib 300 mg (N=231)--	--Placebo (N=99)--	
AE category	Number (%) of patients [a]	Number (%) of patients [a]	Total number (%) of patients (N=330)
Any AEs	230 (99.6)	90 (90.9)	320 (97.0)
Any vandetanib causally [b] related AE	222 (96.1)	59 (59.6)	281 (85.2)
Any AEs of CTCAE grade 3 and higher	128 (55.4)	24 (24.2)	152 (46.1)
Any SAEs (including events with outcome = death)	71 (30.7)	13 (13.1)	84 (25.5)
Any SAEs with outcome = death	5 (2.2)	2 (2.0)	7 (2.1)
Any AEs leading to discontinuation of randomised treatment	28 (12.1)	3 (3.0)	31 (9.4)

[a] Patients with multiple events in the same category are counted only once in that category.
[b] As assessed by the Investigator.
Note: No other AEs were considered by the sponsor to be significant that were not already included in one of the other categories.

Deaths and serious AEs in Study 58

13.9% of vandetanib subjects and 15.2% of placebo arm subjects died as of 31 July 2009. Most deaths were attributed to MTC, but 8/32 vandetanib deaths and 1/15 placebo arm deaths were considered unrelated to MTC. In one male vandetanib patient, acute cardiac failure at Day 431 followed in 8 days by arrhythmia was considered treatment related. In this patient, QTc prolongation had been observed while the patient was on vandetanib and in the interval of ~1 week between stopping vandetanib and death, however amitriptyline and amiodarone were confounding medications. Otherwise, fatal SAEs were considered unrelated to study drug.

The following SAEs were common in the vandetanib arm, but did not occur in the placebo arm: pneumonia (2.2%); diarrhoea (2.2%); decreased appetite (1.7%); hypertensive crisis (1.7%); urinary tract infection (1.3%); abdominal pain (1.3%); hypercalcaemia (1.3%); and depression (1.3%).

Common AEs in Study 58

Skin disorders (for example, rash, photosensivity reaction), GI disorders (for example, diarrhoea, nausea, vomiting), hypertension, headache, decreased appetite, QT prolongation and hypocalcaemia were all reported very commonly (>10%) and at a distinctly higher exposure adjusted incidence in the vandetanib arm.

Some other AEs were reported very commonly and at a distinctly higher exposure adjusted incidence in the placebo arm: fatigue; back pain; arthralgia; pain in extremity and dyspnoea.

According to population pharmacokinetic/pharmacodynamic assessment, females were at greater risk of AEs than males.

Cardiovascular effects

QT prolongation

Mechanism

Vandetanib and to a lesser extent its metabolites inhibit the KIR (hERG) channel. Inhibition of RET kinase (and perhaps other kinases) by vandetanib is likely to suppress the PI3K signalling pathway. Inhibition of PI3K signalling has been suggested as an alternative mechanism for drug-induced QT prolongation, particularly tyrosine kinase inhibitor induced QT prolongation.[13] Therefore, there are several plausible mechanisms by which vandetanib delays cardiac repolarisation.

Extent of QT prolongation in clinical studies

There was no thorough QT study in the submission.

In Study 58, maximum mean increase in QTcB from baseline occurred at Week 12, and was 27.6 ms (range: -27.6 to 135.7 ms). The corresponding change from baseline in the placebo arm was 1.7 ms (range: -13.3 to 88.3 ms).

During randomised treatment, 9.5% of vandetanib subjects and 1.0% of placebo subjects had QTcB >500 ms. QTcB prolongation was particularly prominent in females.

Regarding **population pharmacokinetic data** from Study 58, the evaluator wrote that "mean ± SD increase in QTcB was 26.5 ± 9.6 ms (range: 12.8 to 64.5 ms) and in QTcF was 33.9 ± 7.24 ms (range: 19.6 to 70.1 ms) in 230 patients assuming steady state vandetanib Cmax concentrations of 800 ng/mL." Modelling suggested a maximum change in QTc within 1 month, with little increase after 6 weeks.

Whether the Bazett or Fridericia correction is more appropriate is discussed; both corrections reveal a very substantial effect.

Study 21 in 28 healthy volunteers studied QTc prolongation with vandetanib (single oral dose of 700 mg), administered in combination with ondansetron 32 mg IV.[14] The study showed that concomitant use of both agents slightly increased ondansetron Cmax (by around 26-36%) and produced an additive effect on QTc prolongation.

AEs related to QT prolongation with vandetanib

For Study 58, protocol defined QT prolongation is defined. There were complex criteria for dose interruption due to QT prolongation.

In Study 58, Grade 3 or higher QT prolongation - related AEs occurred in 8.6% of vandetanib subjects and 3% of placebo subjects. Most AEs of any grade in this category were 'QT prolongation', but in the vandetanib arm one patient had grade 2 ventricular tachycardia, two patients lost consciousness and one had syncope. There were no reports of TdP, however the FDA Medical (Clinical) Review notes that two patients died from sudden death and cardio respiratory failure after data cut off but within 30 days of the last vandetanib dose.[15]

There have been 2 reports of TdP in the vandetanib clinical programme: in a NSCLC patient after 12 weeks, and in a papillary thyroid cancer patient after 5 weeks. Both

[13] Lu Z, *et al.* (2012) Suppression of phosphoinositide 3-kinase signaling and alteration of multiple ion currents in drug-induced long QT syndrome. *Sci Transl Med.* 4: 131ra50.
[14] Recently the maximum recommended IV dose for ondansetron has been reduced from 32 mg to 16 mg because of QTc prolongation concerns.
[15] <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022405Orig1s000MedR.pdf>

patients recovered. In pooled monotherapy vandetanib 300 mg studies, sudden death was reported in 1 (0.1%) patient, cardio respiratory arrest in 3 (0.2%) patients, and cardiac arrest in 2 (0.2%) patients.

The diarrhoea seen in MTC is exacerbated with vandetanib. Vomiting is also seen. In Study 58, grade 3 or higher hypokalaemia was reported in 1.3% (vandetanib) versus 0% (placebo). These changes may affect risk of arrhythmias.

Hypertension and cardiac failure

Hypertension is seen with VEGF pathway inhibitors. Also, there was systolic and diastolic hypertension in rats given vandetanib.

In Study 58, hypertensive crisis of grade 3 or higher was reported in 1.7% versus 0%; grade 3 or higher hypertension was reported in 7.4% versus 0%. Also, elevated blood pressure developed commonly in those taking no anti hypertensives at baseline (138/223 or 61.9% of vandetanib subjects and 11/92 or 12% of placebo arm subjects), with diastolic increases peaking at week 12 and systolic increases peaking at Week 24.

Cardiac failure was reported in 2 vandetanib patients (one grade 1, but following grade 3 left ventricular [LV] failure; one acute and followed by grade 5 arrhythmia as noted above under 'Deaths') and no placebo arm patients. Thus while there was no signal of a major increase in cardiac failure on vandetanib, at least one patient died as a result of cardiac failure considered treatment related.

There was no RPLS reported in Study 58, but there have been 4 reports across the vandetanib clinical programme (2/4 in paediatric patients with primary brain tumours).

Ischaemic heart disease

In Study 58, 2.2% of vandetanib subjects and 2% of placebo arm subjects had related AEs.

Ischaemic cerebrovascular conditions

In Study 58, 1.3% of vandetanib subjects and no placebo arm subjects had such AEs.

Venous embolic and thrombotic events

In Study 58, there were more such events in the placebo arm.

Pneumonitis / interstitial lung disease

In Study 58, pneumonitis (grade 3) was reported in 2/231 vandetanib subjects and no placebo subjects in the randomised phase, with a further case in the open label phase. ILD was reported in 1 placebo subject taking vandetanib in the open label phase (after administration of contrast material during cardiac catheterisation). In pooled monotherapy studies, pneumonitis was reported in 0.7% (n=13). Causality is often unclear in patients being treated for NSCLC. Many cases were in Japanese patients.

Rash

In Study 58, there was a clear increase in skin and subcutaneous tissue AEs in the vandetanib arm versus the placebo arm (90.5% versus 30.3%). 6.9% versus 0% of rashes were grade 3 or higher but there were no cases of toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson Syndrome or toxic skin eruptions. Rash did not account for much dose reduction. Mean time to onset of grade 3 rash was 103.1 days for vandetanib (range 10-316). Folliculitis and alopecia were also observed, more commonly in females.

The sponsor notes:

> *In many cases, this rash is similar to the rash seen with other EGFR inhibitors, and there have been several publications providing guidance on the management of these rashes. One type of rash that is idiosyncratic for vandetanib is a photosensitivity reaction, with some patients developing a rash only in sun exposed areas. Patients*

who are taking vandetanib should be cautioned to avoid sun exposure, and to use protective clothing or sunscreen when outside.

In the pooled 300 mg monotherapy data (n=1839), there were 8 reports of erythema multiforme, 6 reports of Stevens-Johnson Syndrome, and 1 report of a toxic skin eruption. This suggests a **high incidence of serious skin reactions**.

GI effects

In rats, there was inhibition of gastric emptying/intestinal transit, suggesting an effect on GI motility. AEs consistent with this have been seen in vandetanib clinical studies (for example, diarrhoea, nausea, vomiting, dysphagia, intestinal obstruction).

In Study 58, diarrhoea of grade ≥3 was reported in 10.8% of vandetanib subjects but 2% of placebo subjects; dehydration was reported in 2.6% versus 0%, respectively. Mean time to onset of grade 3 diarrhoea was 151.1 days for vandetanib (range: 9 to 415 days).

In Study 58, nausea or vomiting of grade ≥3 was reported in 1.7% of vandetanib subjects and no placebo subjects.

Visual effects

In Study 8 (n=30), 4 patients reported visual changes (for example, glare) and had corneal cloudiness or other corneal changes on ophthalmological examination.

In Study 58, visual abnormalities were more common in the vandetanib arm (83.6%) than the placebo arm (61.5%), with most differences ascribed to corneal pathology (49.7% versus 3.8%). **Vortex keratopathy** was common with vandetanib. This is also called cornea verticillata, a generally innocuous condition. It was considered that ≥3 months of dosing were (usually) required to develop this condition.

Clinical chemistry

Liver tests

In Study 58, despite an effect on liver function test results (ALT and AST elevations were more common), there were no Hy's Law cases (that is, ALT elevation >3x ULN and bilirubin elevation >2x ULN) with vandetanib.

Renal tests

Despite an effect of vandetanib on serum creatinine (increased in 16.5% versus 1%), there were no grade 3-4 elevations. Two vandetanib subjects discontinued treatment due to creatinine elevation. Vandetanib may inhibit the renal organic cation transporter 2 (OCT2). Also, new or worse dipstick proteinuria was much more common in the vandetanib arm (90.9% versus 28.3%), and the AE of proteinuria was reported in 10% versus 2%. Patients with this proteinuria often had raised blood pressure, but raised blood pressure was apparently even more frequent in subjects without proteinuria. In Study 58, new or worse dipstick haematuria was seen in 34.2% (vandetanib) versus 22.2% (placebo). Urine microscopy was not discussed.

Thyroid tests

Vandetanib affects thyroid function, elevating TSH in a median time of 57 days. Hypothyroidism was reported in 6.5% of vandetanib subjects and no placebo subjects, although all cases were grade 1-2. MTC patients will typically be on thyroid replacement therapy, and 49.3% of vandetanib subjects (but only 17.2% of placebo arm subjects) need an increase in replacement dose.

Electrolytes

Vandetanib provoked hypocalcaemia (57.1% of vandetanib and 25.3% of placebo subjects had the biochemical abnormality; 10.8% and 3.0% reported the AE), and to a lesser extent hypomagnesaemia and hypokalaemia. Hypercalcaemia was also reported as a serious AE.

Glucose

Decreased glucose was more common in the vandetanib arm than the placebo arm (22.1% versus 8.1%). α2 blockers may increase insulin secretion.

Other

Wound healing

Cutaneous wound healing was impaired in an *in vivo* mouse model.

There was a report of small bowel perforation in a patient with diverticulitis in the vandetanib arm, considered related to treatment.

Bleeding

In Study 58, AEs describing haemorrhage were reported at a similar rate across arms, with 2/231 (vandetanib) and 3/99 (placebo) reporting grade ≥3 AEs. Epistaxis and haemoptysis were the main types of bleeding, but in 3/231 vandetanib patients bleeding was intracranial (whereas in the placebo arm, one patient died after GI haemorrhage).

In Study 12 (Phase 1 dose escalation), 3/6 healthy male subjects given 300 mg vandetanib experienced haematuria. In Study 58, new or worse dipstick haematuria was seen in 34.2% (vandetanib) versus 22.2% (placebo).

Haemoglobin

In Study 58, haemoglobin rose within several weeks of starting vandetanib. Mean increase peaked at 1.4 g/dL at Week 8 (versus -0.1 in the placebo arm). The maximum individual increase was 5.6 g/dL at Week 24. Erythrocyte volume (presumably MCV) also rose on vandetanib compared to placebo. This suggests stringent VEGF blockade. VEGF inhibition enhances erythropoiesis in animal models.[16] The sponsor states that in another study where patients crossed from vandetanib to gefitinib, the increase in haemoglobin reversed quickly. A patient with an increase in haemoglobin of >1.8 g/dL had a TIA.

Risk management plan

In the US and EU, approval of vandetanib in MTC was linked to risk mitigation programmes. The FDA REMS aimed to reduce the risk of QT prolongation. It mandated medication guides, communication strategies, certification of doctors allowed to prescribe vandetanib, certification of pharmacies allowed to dispense vandetanib, and a boxed warning on the PI (label) highlighting the association between vandetanib and QT prolongation, TdP and sudden death.

In Australia, the sponsor has told the TGA that "prescribers will be required to be certified prior to prescribing vandetanib" (RMP Evaluation). Details of this provision need to be explained by the sponsor (see RMP Evaluation), and need the approval of the TGA's RMP Section. Otherwise, the RMP was considered acceptable by the TGA's Office of Product Review, although various amendments have been requested.

[16] Tam BY, *et al.* (2006) VEGF modulates erythropoiesis through regulation of adult hepatic erythropoietin synthesis. *Nat Med.* 12: 793-800. There was induction of hepatic EPO transcription.

Risk-benefit analysis

Delegate considerations

Optimal dose

There were no formal dose-ranging clinical studies.

The sponsor noted that based on nonclinical studies, inhibition of molecular targets and anti tumour effect increased with increasing vandetanib concentration, "indicating that efficacy in the clinic will be greatest at the maximum tolerated dose".

A maximum tolerated dose of 300 mg was established in Phase I studies using doses in the range 50-600 mg. Dose limiting toxicities were diarrhoea, skin rash and hypertension; QTc prolongation was seen at all dose levels.

In Study 58, 49.4% of vandetanib subjects had dose reductions/interruptions (compared with 15.2% of placebo arm subjects). Dose reduction to 200 mg or 100 mg occurred in 35.9%. Reduction was generally to 200 mg but 32/231 subjects ended up on 100 mg daily. Commonly this was due to QTc prolongation, rash or diarrhoea.

The evaluator interpreted this as indicating that dose reductions and interruptions were an effective means of managing AEs while keeping patients on therapy. Another interpretation is that a starting dose of 300 mg daily is high.

Study 68 was conducted in parallel with Study 58, in an effort to provide evidence of efficacy and tolerability at 100 mg, but dose was selected in the pivotal study before Study 68 results were available. Efficacy outcomes were lower in Study 68 than in Studies 8 and 58, but dose was not the only variable to differ across studies.

The US application was discussed at the Oncologic Drug Advisory Committee meeting on 2 December 2010. The committee voted unanimously to require the applicant to evaluate additional doses as a post marketing requirement to determine the optimal dose. A Phase IV trial (D4200C00097) was mandated by the FDA to explore a 150 mg versus 300 mg starting dose. Completion is anticipated by October 2015 (RMP Evaluation).

The sponsor's view is that:

> *Adjusting the dose for tolerance should be encouraged, as it allows those patients who do not develop significant side effects to stay on the highest dose of vandetanib and thereby derive the maximum potential benefit, and permits patients who develop toxicity to control it by changing to a lower dose. The data from Study 58 show that patients who dose reduced to 200 mg or 100 mg were able to stay on the lower dose for a median of 23 weeks or 29 weeks, respectively. This strategy is effective in allowing patients to stay in the drug even with chronic dosing.*

RET status

The EU indication states in part:

> *For patients in whom RET mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.*

In the CSR for Study 58, it was noted that within the "RET mutation status positive" subgroup there was disease progression in 34.3% of vandetanib subjects (47/137) and 54% of placebo subjects (27/50). Within the small "RET mutation status negative" subgroup there was disease progression in 50% of vandetanib subjects (1/2) but 83.3% of placebo subjects (5/6). Within the "unknown RET mutation status" subgroup there was disease progression in 27.2% of vandetanib subjects (25/92) versus 43.2% of placebo subjects (19/44). Based on these results, the Delegate sees no need for a qualifying statement in the indication regarding RET status.

Indolent and asymptomatic disease

The US indication promotes use in symptomatic, quickly progressing disease in patients with unresectable locally advanced or metastatic MTC. The EU indication requires symptomatic and aggressive disease in patients with unresectable locally advanced or metastatic MTC. With the proposed Australian indication, treatment would be indicated in asymptomatic, indolent disease as long as that disease was unresectable and locally advanced, or metastatic. The clinical evaluator supported the sponsor's proposal.

The sponsor notes that the prognosis of MTC is generally favourable if the disease is treated at an early stage, but in patients presenting with metastases the median overall survival is 2-3 years.[17] Also, about 35% of patients present with tumours extending beyond the thyroid with regional lymph node involvement, and 13% have metastatic disease at presentation. About 90% of patients with metastatic disease die of progressive cancer.

Patients may be symptomatic due to tumour location (for example, with local disease: dysphagia, neck pain, horseness, dyspnoea) or humoral factors (MTC cells secrete CTN, CEA, and several biogenic amines; symptoms include diarrhoea and flushing). Measurement of CTN is used in clinical practice to monitor progression, as levels are associated with tumour burden. Elevation of CTN need not mean the whereabouts of solid tumour is known. The major protocol deviation "no measurable tumour at baseline" occurred in 9/231 vandetanib subjects (3.9%) and 5/100 placebo subjects.

An editorial[18] accompanying the publication of the pivotal Phase III study notes:

> *The potential toxicity associated with long term administration of vandetanib highlights the importance of appropriate selection of patients for treatment with this agent. The relatively indolent tempo of disease in some patients with MTC who were enrolled onto this trial, which did not require demonstration of progression before entry, is evident from the time to progression of 19.3 months in patients who received the placebo. The risk-benefit ratio of treatment is likely to be unfavourable in asymptomatic patients or patients with a low disease burden who experience slow progression. These patients may be appropriately monitored while not receiving therapy by assessment of the tempo of disease radiologically and through measurement of calcitonin doubling time. In contrast, patients who are symptomatic, have a high disease burden, or have rapidly progressing disease stand to benefit the most from treatment with vandetanib.*

CTN or CEA doubling times have been suggested as proxies for aggressive disease. There was analysis of efficacy in patients sub grouped according to CTN and CEA doubling time. There was an indication of additional benefit of vandetanib in aggressive disease (Figure 4).

[17] Modigliani E, *et al.* (1998) Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. The GETC Study Group. Groupe d'étude des tumeurs à calcitonine. *Clin Endocrinol (Oxf).* 48: 265-273; Roman S, et al. (2006) Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. *Cancer* 107: 2134-2142.

[18] Solomon B, Rischin D. (2012) Progress in molecular targeted therapy for thyroid cancer: vandetanib in medullary thyroid cancer. *J Clin Oncol.* 30: 119-121.

Figure 4: CTN and CEA doubling times.

CTN doubling time <=24mths	V=39/124(31.5%)	P=27/46(58.7%)
CTN doubling time > 24mths	V=23/83(27.7%)	P=19/43(44.2%)
Unknown CTN doubling time	V=11/24(45.8%)	P=5/11(45.5%)
CEA doubling time <=24mths	V=25/69(36.2%)	P=26/33(78.8%)
CEA doubling time > 24mths	V=28/119(23.5%)	P=14/48(29.2%)
Unknown CEA doubling time	V=20/43(46.5%)	P=11/19(57.9%)

Figures refer to fractions and percentages for disease progression.

Benefit was preserved in patients with longer CTN doubling times (and Solomon and Rischin[19] refer to CTN doubling time as a means of monitoring tempo of disease), although consideration of CEA doubling times would raise concerns about benefit in indolent disease. The Delegate agrees with the clinical evaluator that the proposed indication is – in this regard – acceptable.

Use in locally advanced disease

In Study 58, 95% of patients had metastatic disease, although patients with locally advanced (unresectable) disease could enrol. The sponsor speculated this was due to:

- aggressive surgical techniques resulting in fewer "unresectable" locally advanced tumours;
- the requirement for CTN ≥500 pg/mL and clearly measurable tumour, favouring patient with metastatic disease; and
- the investigator preference to select patients with metastatic disease.

Efficacy of vandetanib in patients with metastatic disease was established (progression in 30.9% of vandetanib patients [67/217] and 52.6% of placebo patients [51/97]) but not in patients with only locally advanced disease (42.9% [6/14] versus 0% [0/3], respectively).

Given:

- the small number of patients enrolled with only locally advanced disease;
- the lack of a trend towards a treatment benefit in these patients;
- a plausible mechanism explaining benefit in metastatic disease but not locally advanced disease (inhibition of angiogenesis required for metastatic growth, etcetera, by VEGFR inhibition); and
- the distinct toxicity of the agent (for example, potential for sudden cardiac death)

the Delegate thinks **the indication should be restricted to those with metastatic disease**. While vandetanib may confer a benefit in locally advanced MTC, this has not been demonstrated in the Dossier provided.

Another option is restriction to "metastatic MTC or aggressive and symptomatic, unresectable locally advanced MTC" based on the conjecture that local disease with these characteristics is more likely to metastasise and that vandetanib is therefore more likely to confer a benefit; but this option is not clearly supported by evidence in the dossier.

[19] Solomon B, Rischin D. (2012) Progress in molecular targeted therapy for thyroid cancer: vandetanib in medullary thyroid cancer. *J Clin Oncol.* 30: 119-121.

Resistance

In inhibition assays, some RET mutations conferred resistance (for example, V804L, V804M)[20] while others – activating mutations – conferred sensitivity (for example, L858R).

EGFR signalling is a significant determinant of the activity of vandetanib against cancer cells. Also, RET signals through RAS amongst other pathways.[21] However, mutant constitutively active K-RAS does not seem prominent in MTC.[22]

The significance of acquired resistance in this potentially long term treatment is unclear.

Risk mitigation for QT prolongation

QT prolongation is considerable with vandetanib, and in some patients causes life threatening arrhythmias. Overseas, this has been addressed via strong PI warnings and restricted access/prescriber education. Given the strong signal in a limited clinical dataset, the Delegate suggests the PI include a black box warning and suitable contraindications, precautions and Clinical Trials text. Although prescribing will be from specialists, access should be restricted to those educated about this safety risk, via a certified prescriber scheme.

Serious skin disorders

The vandetanib trial programme saw multiple cases of serious skin reactions (erythema multiforme, Stevens-Johnson Syndrome) and there is an argument for including a black box warning about these, too. However, the Delegate considers the updated Precaution regarding "Skin reactions" to be sufficient.

Proposed action

The Delegate proposes to approve the application but change the indication to: **treatment of patients with metastatic MTC**.

The Delegate proposes the following conditions of registration:

- Prior to marketing, the sponsor implements a workable scheme of prescriber education and certification, acceptable to the TGA's RMP Section.
- The sponsor implements the Global RMP dated 7 September 2011, with Australian Risk Minimisation Activities (same date), and any subsequent version.
- The sponsor provides to the TGA Study D4200C00097, when any interim or final study report is complete.
- The sponsor provides to the TGA the reports of vandetanib drug interaction studies with digoxin, metformin, omeprazole, ranitidine and midazolam.

The advice of the ACPM is requested. In particular:

- Does the Committee consider the benefit of vandetanib in the indicated population to outweigh its risks?
- Does the Committee have any suggestions about how best to minimise risk of arrhythmia/sudden cardiac death, and other serious safety risks?

[20] Found in 1-2% of MTC, as discussed on page 202 of Houvras Y. (2012) Completing the Arc: targeted inhibition of RET in medullary thyroid cancer. *J Clin Oncol.* 30: 200-202.
[21] Houvras Y. (2012) Completing the Arc: targeted inhibition of RET in medullary thyroid cancer. *J Clin Oncol.* 30: 200-202.
[22] Schulten HJ, *et al.* (2011) Mutational screening of RET, HRAS, KRAS, NRAS, BRAF, AKT1, and CTNNB1 in medullary thyroid carcinoma. *Anticancer Res.* 31: 4179-4183.

- What is the Committee's view regarding an appropriate scope for the indication, given issues around RET mutation status, indolent/asymptomatic disease, and lack of data in locally advanced MTC?

Response from sponsor

The sponsor received the Delegate's Request for ACPM Advice (DRA) for the above submission on 2 November 2012. Our comments in relation to the DRA are provided below.

Indication

The ability to precisely define a population of patients with advanced MTC having the greatest need for treatment, where vandetanib has the greatest benefit/risk, and at the same time not excluding patients with an urgent need for treatment, is difficult. The sponsor recognises the views expressed by the Delegate concerning the toxicity of vandetanib and note the proposal to restrict the indication to only those MTC patients with metastatic disease. However, the sponsor believes that limiting the indication to patients with metastatic disease will exclude patients in great need of treatment and who may receive benefit from vandetanib.

The Delegate considers that there is a plausible mechanism of action explaining benefit in metastatic, but not locally advanced, disease (that is, inhibition of angiogenesis required for metastatic growth etc by VEGFR inhibition). The sponsor considers that the following factors are important in understanding the likely mechanism of action in locally-advanced, disease:

- As a potent inhibitor of VEGFR2, vandetanib inhibits endothelial proliferation and cell migration *in vitro*, and angiogenesis *in vivo*. Inhibition of angiogenesis will be expected to impact on locally advanced disease.
- As an inhibitor of the EGFR tyrosine kinase, vandetanib also inhibits EGF driven endothelial cell proliferation and will have also inhibit EGFR mediated tumour cell proliferation and tumour growth.
- Similarly, by virtue of its activity against RET tyrosine kinase, vandetanib would be expected to attenuate signalling pathways that contribute to tumour cell proliferation, as has been demonstrated for MTC, PTC and NSCLC tumour cells.

Thus, there are plausible mechanisms, supported by preclinical data, to anticipate a direct effect on locally advanced tumour growth in addition to restricting the vascular supply of primary tumours.

Although there were only 14 patients (5%) with unresectable locally advanced disease randomised to receive vandetanib in Study 58, 3 patients had objective tumour responses indicating that vandetanib has activity in this subgroup of patients. MTC very often spreads to the relatively confined anatomic areas of the neck or mediastinum where complete surgical resection is sometimes extremely difficult and preservation of speech, swallowing or vascular integrity is impossible with resection. When MTC becomes unresectable, whether the disease is locally advanced or metastatic, there are no effective treatment options available to patients beyond experimental therapies, or as a last resort, cytotoxic chemotherapy that are all relatively ineffective. Patients with unresectable disease in the neck that is progressing or causing symptoms are in particularly urgent need for treatment because of the small area of the neck and the many vital anatomic structures located within this small area. Small volume asymptomatic disease that is progressing is likely to become symptomatic in these areas; for example, an enlarging lesion compressing the oesophagus, trachea, nerves or vessels that is not yet causing symptoms is a lesion that would very likely require treatment.

There are many clinical scenarios in which MTC is progressing but not yet symptomatic. A physician caring for an MTC patient with a progressing unresectable tumour compressing the carotid artery would not elect to wait to begin treatment until the patient had a stroke. Treating physicians need to have the option to initiate treatment in the face of progressing disease without symptoms, rather than having to wait for symptoms to occur. Therefore, physicians need to have the ability to initiate treatment in MTC that is either progressing without symptoms, or already symptomatic regardless of progression status.

The sponsor therefore proposes the following indication to try to ensure that the use of vandetanib is restricted to those MTC patients with the most urgent need for treatment and gives physicians the option to treat patients with progressive or symptomatic locally advanced disease:

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

The sponsor considers that this indication will ensure that the use of vandetanib is restricted to those MTC patients with the most urgent need for treatment. The sponsor notes that the Delegate had also considered a similar indication in his assessment of the file, and trust that the proposed wording above will be considered acceptable.

Safety

The sponsor agrees to the Delegate's proposal to include a black box warning on the prescribing information and is in agreement with most of the text suggested for this section of the PI, with the exception of the text pertaining to sudden cardiac death. The sponsor recognises that QT prolongation and TdP can lead to sudden cardiac death. However, the actual term "sudden cardiac death" has not been reported in the vandetanib studies; the term that has been reported is "sudden death". Although the sponsor accepts the term "sudden death" should be included in the same sentence as ventricular arrhythmias, there are no cases received that conclusively link QT prolongation as causing sudden death. Therefore, the sponsor proposes the term "sudden cardiac death" be replaced with the term "sudden death" in this section. The proposed change to the black box warning is shown below (changes shown in strikethough).

> ***Vandetanib (Caprelsa) may cause fatal or life-threatening ventricular arrhythmias (including torsades de pointes) or sudden ~~cardiac~~ death. These outcomes may be more likely in patients in whom vandetanib significantly prolonges 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 >480ms.
> - 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.

Sponsor's comments on the questions to APCM

The sponsor would like to make the following comments and observations on the Delegate's questions to APCM.

1. Does the Committee consider the benefit of vandetanib in the indicated population to outweigh the risks?

Sponsor comment: Given that locally advanced or metastatic MTC is an incurable disease with no other approved therapies and is associated with considerable morbidity, the benefit risk assessment for Caprelsa is strongly positive.

The pivotal MTC study (Study 58) demonstrated a statistically significant improvement in PFS for vandetanib compared with placebo (HR=0.46; 95% CI: 0.31, 0.69; p=0.0001), representing a 54% reduction in the rate of progression in the vandetanib arm. Results of the sensitivity analysis to determine whether the methodology used or the derivation of PFS had an impact on the results were supportive of the primary analysis. In addition, subgroup analyses for PFS identified no specific subgroup that did not benefit from vandetanib treatment.

The median PFS in the placebo group was 19.3 months; the median PFS in the vandetanib group could not be calculated because an insufficient number of PFS events had occurred in the vandetanib group at the time of data cut off, but it is predicted to be 30.5 months.

The risks associated with vandetanib treatment have been well described and are mostly treatable. These most commonly include rash, phototoxicity, diarrhoea, and hypertension. More serious toxicities have also been well described and occur less commonly. These include TdP, posterior reversible leukoencephalopathy syndrome, heart failure, Stevens-Johnson syndrome and other serious skin reactions. The sponsor acknowledges that some of the more serious toxicities associated with treatment with Caprelsa have ultimately caused death; however, this has been uncommon.

The sponsor also notes, and concur with, the first round assessment of benefit-risk balance in the report of the TGA clinical evaluator (received by the sponsor on 12 October 2012) which concluded that vandetanib provides an important clinical benefit, and whilst there are recognised risks, these are manageable. The sponsor also notes that the clinical evaluator also considered a restriction of the indication but did considered this to be unnecessarily restrictive, given the product would be used by experts in the treatment of cancer.

In conclusion, the benefit of vandetanib in MTC is clinically significant and there is no alternative therapeutic option. Risks have been identified but these can be mitigated, for example, through education, monitoring, patient selection or dose modification. When used in accordance with proposed product information, the benefits of vandetanib outweigh its risks in patients with advanced MTC.

2. Does the Committee have any suggestions about how best to minimise risk of arrhythmia/sudden death and other serious safety risks?

Sponsor comment: The side effect profile of vandetanib, while significant, still allows for positive benefit risk. The major risk is QT prolongation and TdP, which can lead to sudden cardiac death. QT prolongation is a very common AE in patients receiving vandetanib for MTC; however, its risks may be mitigated by regular ECG monitoring and maintenance of electrolyte balance. Other known risks (for example, Stevens-Johnson Syndrome, ILD, RPLS, and heart failure) are expected to be infrequent events when vandetanib is used as monotherapy in MTC, even at a 300 mg daily starting dose. Information on the

management of these risks is included in Australian Prescribing Information and in the Australian RMP and this will be supplemented by the proposed physician education.

3. What is the Committee's view regarding an appropriate scope for indication, given issues around RET mutation status, indolent/asymptomatic disease and lack of data in locally advanced disease?

The sponsor has already commented on the need for the indication to cover patients with locally advanced disease, in addition to patients with metastatic disease, as proposed by the Delegate. The sponsor has suggested a modification to the indication proposed by the Delegate.

For indolent/asymptomatic disease, the sponsor recognises that even advanced cases of MTC may take a clinically indolent course and therefore patients may not require immediate treatment for their advanced disease. Thus a period of watchful waiting without treatment may be acceptable in some patients. Given that vandetanib will be prescribed for the proposed indication by medical practitioners who are expert in the treatment of cancer, the sponsor considers that a more general indication which does not include any specific text relating to indolent/aymptomatic disease is preferable, as this will allow physicians to use their clinical judgment to decide when the appropriate time is to initiate treatment with vandetanib.

As vandetanib inhibits RET along with VEGFR and EGFR, the sponsor acknowledges that vandetanib could have greater activity in MTC patients with an activating RET mutation. An activating mutation of the RET receptor is clearly an important pathway in the development and progression of MTC; however, there are other important molecular aberrations important in MTC as approximately 50% of sporadic MTC cases are RET mutation negative. The sponsor agrees with the Delegate that there is no need for a qualifying statement on RET mutation status in the indication based on the following factors:

- There was clear evidence of vandetanib anti tumour activity in 2 of 7 confirmed RET mutation negative patients on Study 58, and supportive evidence for vandetanib benefit in the RET mutation negative patients based on activity in the RET mutation unknown population (of whom ~50% are likely to be RET mutation negative, based on literature reports).
- Because vandetanib is also a potent inhibitor of EGFR and VEGFR, there is also a plausible molecular biologic rationale for vandetanib activity in RET mutation negative patients.

4. Does the Committee have any recommendations for improving vandetanib's PI?

The proposed Australian Prescribing Information is similar to that approved for Caprelsa in the EU, US and Canada. Caprelsa has been on the market since April 2011 but because MTC is a rare disease, most of the most of the safety data to date has come from randomised clinical trials. Inclusion and exclusion criteria and monitoring methods in the clinical trials are closely reflected in product labelling, which suggests that the marketed experience will not differ appreciably from the clinical trial experience.

As of September 2012, the estimated cumulative market exposure to Caprelsa is estimated at 488 patient years. The safety profile remains under constant surveillance for new findings or trends but this has not changed significantly since first marketing authorisation.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered these products to have an overall positive benefit-risk profile for the revised indication:

> *For the treatment of patients with symptomatic or progressive, metastatic or locally advanced unresectable medullary thyroid cancer (MTC).*

In making this recommendation, the ACPM agreed with the Delegate on the matter of the black box warning for the QTc interval prolongation; and did not support the inclusion of skin toxicity in this warning statement.

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- A statement in the "Precautions" section of the PI and relevant sections of the CMI to ensure awareness of the risk of photosensitivity.
- A statement in the "Clinical Trials" section of the PI to emphasise the limitation of the data in determining the response in patients with MTCs with the differing mutations.
- A statement in the "Dosage and Administration" and "Drug Interactions" sections to strengthen awareness of the safety risks associated with the significant potential interaction with other drugs involved in CYP3A4 metabolism, noting the absence of clear evidence.

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Prior to marketing, the sponsor implements program of prescriber education, acceptable to the TGA's RMP Section.
- The sponsor implements the Global RMP, with Australian Risk Minimisation Activities, and any subsequent versions agreed with the Office of Product Review.
- The sponsor provides to the TGA Study D4200C00097, when any interim or final study report is complete.
- The sponsor provides to the TGA the reports of drug interaction studies with digoxin, metformin, omeprazole, ranitidine and midazolam.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Caprelsa tablets containing vandetanib 100 mg and 300 mg. The approved indication reads as follows:

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

Specific conditions of registration applying to these therapeutic goods:

1. The implementation in Australia of the vandetanib Risk Management Plan (RMP) identified as the Global Risk Management Plan Edition 1, dated 7 September 2011 with Risk Management Plan Addendum 1 – Australian Risk Minimisation Activities

(dated 7 September 2011), included with submission PM-2011-03002-3-4, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

2. The sponsor is requested to provide updated RMP and/or Australian specific annex to the TGA's Office of Product Review within six months post registration, with the inclusion of all relevant safety concerns and accompanied by appropriate pharmacovigilance and risk minimisation activities. In providing this update, please take into account the RMP Evaluation for this application.
3. Prior to supply, the sponsor is requested to implement a workable scheme of prescriber education and certification, acceptable to the TGA's RMP section.
4. The sponsor is requested to provide to the TGA Study D4200C00097, when any interim or final study report is complete.
5. The sponsor is requested to provide to the TGA the reports of vandetanib drug interaction studies with digoxin, metformin, omeprazole, ranitidine and midazolam.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au