



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for Lenvatinib mesilate

Proprietary Product Name: Lenvima

Sponsor: Eisai Australia Pty Ltd

**August 2016**

**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 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 <<https://www.tga.gov.au>>.

## About AusPARs

- An Australian Public Assessment Report (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; it provides 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.

### Copyright

© Commonwealth of Australia 2016

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <[tga.copyright@tga.gov.au](mailto:tga.copyright@tga.gov.au)>.

# Contents

<b>About AusPARs</b>	<b>ii</b>
<b>Common abbreviations</b>	<b>5</b>
<b>I. Introduction to product submission</b>	<b>7</b>
Submission details	7
Product background	7
Regulatory status	9
Product information	10
<b>II. Quality findings</b>	<b>10</b>
Introduction	10
Drug substance (active ingredient)	11
Drug product	12
Biopharmaceutics	13
Quality summary and conclusions	18
<b>III. Nonclinical findings</b>	<b>20</b>
Introduction	20
Pharmacology	20
Pharmacokinetics	21
Toxicology	23
Nonclinical summary and conclusions	29
<b>IV. Clinical findings</b>	<b>31</b>
Introduction	31
Pharmacokinetics	34
Pharmacodynamics	37
Dosage selection for the pivotal studies	39
Efficacy	41
Safety	41
First round benefit-risk assessment	45
First round recommendation regarding authorisation	45
Clinical questions	45
Second round evaluation	46
Second round benefit-risk assessment	46
Second round recommendation regarding authorisation	46
<b>V. Pharmacovigilance findings</b>	<b>47</b>
Risk management plan	47
<b>VI. Overall conclusion and risk/benefit assessment</b>	<b>54</b>

Quality	55
Nonclinical	55
Clinical	55
Risk management plan	59
Risk-benefit analysis	60
Outcome	62
<b>Attachment 1. Product Information</b>	<b>63</b>
<b>Attachment 2. Extract from the Clinical Evaluation Report</b>	<b>63</b>

## Common abbreviations

Abbreviation	Meaning
AE	adverse event
ASA	Australian Specific Annex
AUC	area under the plasma drug concentration-time curve
AUC <sub>t1-t2</sub>	area under the plasma drug concentration-time curve from t1 to t2
BID	bis in die (twice daily)
C <sub>max</sub>	maximum serum concentration of drug
CMI	Consumer Medicines Information
DTC	differentiated thyroid cancer
ED50	effective dose 50%
EMA	European Medicines Agency
ER	Exposure Ratio
FDA	Food and Drug Administration (US)
FGF	fibroblast growth factor
GI	gastrointestinal
IC50	inhibitory concentration 50%
ORR	objective response rate
OS	overall survival
MTD	maximum tolerated dose
P-gp	P-glycoprotein
PD	pharmacodynamic(s)
PDGF	platelet derived growth factor
PFS	progression free survival
PI	Product Information
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency

Abbreviation	Meaning
PO	per os (oral)
PR	Partial Response
QD	quaque die (once daily)
QoL	quality of life
RAI	radioactive iodine
RMP	Risk Management Plan
RPSFT	rank preserving structural failure time
RR	radioiodine refractory
SD	Stable Disease
SmPC	Summary of Product Characteristics
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
Tmax	Time taken to reach the maximum concentration (Cmax)
TSH	thyroid stimulating hormone
VEGF	vascular endothelial growth factor

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	21 January 2016
<i>Date of entry onto ARTG</i>	28 January 2016
<i>Active ingredient:</i>	Lenvatinib mesilate
<i>Product name:</i>	Lenvima
<i>Sponsor's name and address:</i>	Eisai Australia PO Box 33004 Melbourne VIC 3004
<i>Dose forms:</i>	Hard capsules
<i>Strengths:</i>	4 mg, 10 mg
<i>Container:</i>	Blister Pack, PA/Al/PVC/Al (polyamide-aluminium foil-polyvinylchloride/aluminium foil)
<i>Pack size:</i>	30
<i>Approved therapeutic use:</i>	Lenvima is indicated for the treatment of patients with progressive, locally advanced or metastatic, radioactive iodine refractory differentiated thyroid cancer.
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	Recommended 24 mg taken once daily
<i>ARTG numbers:</i>	233425 (4 mg), 233426 (10 mg)

## Product background

This AusPAR describes the application to register lenvatinib mesilate (trade name: Lenvima) for the treatment of patients with progressive, radioactive iodine refractory differentiated thyroid cancer (DTC). Commerical Eyes Pty Ltd is the appointed agent for Eisai Australia Pty Ltd for this application.

Lenvatinib is a synthetic, orally available inhibitor of vascular endothelial growth factor receptor 2 (VEGFR2)<sup>1</sup> tyrosine kinase. Lenvatinib inhibits multiple tyrosine kinases, including VEGFR2. Lenvatinib blocks VEGFR2 activation by VEGF; the rationale is that inhibiting of VEGFR2 activation by VEGF should reduce the VEGF receptor signal transduction pathway, which in turn decreases vascular endothelial cell migration and

---

<sup>1</sup> Also known as KDR/FLK-1.

proliferation, and enhances vascular endothelial cell apoptosis. The precise mechanism of action is not known but anti-angiogenesis is likely to be prominent.

Current treatment of choice for primary DTC is surgery, then usually I-131 ablation and thyroxine. About 5-20% of patients develop locoregional recurrence. About 15% of patients either present with metastases or develop them after initial treatment. A third of metastatic cancers lose the ability to concentrate iodine, and radioiodine treatment may be not as effective; these are 'radioiodine refractory' (RR) tumours. Such tumours are more aggressive.

Tuttle notes that papillary and follicular cancers (the two subtypes of DTC<sup>2</sup>) are treated similarly, despite their biological differences.<sup>3</sup> Prognosis also differs. Risk of recurrence after initial surgery can be gauged, for example, with the American Thyroid Association (ATA) risk stratification tool.

Tuttle outlines the use of radioiodine therapy post thyroidectomy for DTC: adjuvant ablation of residual thyroid tissue and possible microscopic residual cancer; imaging for possible metastatic disease; and treatment of known residual or metastatic cancer. Post-operative radioiodine ablation is recommended by Tuttle for: known distant metastases; gross extrathyroidal extension; or primary tumours >4 cm. Sometimes it is used in patients with 1-4 cm tumours confined to the thyroid, if there are high risk features (for example, lymph node metastases; vascular invasion; aggressive histology).

Levothyroxine is used after initial thyroidectomy in patients to prevent hypothyroidism and to minimise potential thyroid stimulating hormone (TSH) stimulation of tumour growth.

External beam radiation may be useful in patients with metastatic DTC that is refractory to radioiodine or in patients whose tumours do not concentrate radioiodine.

Management of persistent or recurrent disease (minimal versus extensive) is also discussed. A subset of patients has radioiodine negative, serum thyroglobulin positive disease; of these, some with progressive macrometastatic disease unresponsive to radioiodine are considered (by Tuttle) for systemic therapy with tyrosine kinase inhibitors, or a clinical trial. The role of bisphosphonates and denosumab in reducing skeletal related events is noted, for those with bone metastases.

Sherman notes that tyrosine kinase inhibitors (TKIs) targeting angiogenesis in this context are tumouristatic and that improved overall survival has not been established:

*In addition, these newer 'targeted therapies' have significant toxicities and, therefore, it is important to limit the use of systemic treatments to patients at significant risk for morbidity or mortality due to progressive metastatic disease.<sup>4</sup>*

DTC can occur in children, and radiation exposure is a risk factor, but incidence is low and prognosis is better than in adults.<sup>5</sup>

The submission proposes registration of lenvatinib 4 mg and 10 mg (as mesilate) hard capsules. The recommended dose is 24 mg taken once daily. The daily dose is recommended to be titrated as needed according to the dose/toxicity management plan, which is specified in the submission. If a dose is missed and cannot be taken within 12

---

<sup>2</sup> A third subtype, Hurthle cell, is sometimes referenced as a variant of follicular carcinoma

<sup>3</sup> Tuttle RM. Differentiated thyroid cancer: overview of management. Up-to-date Topic 7838 Version 14.0 Topic last updated Sep 17, 2014.

<sup>4</sup> Sherman SI. Differentiated thyroid cancer refractory to standard treatment: chemotherapy. Up-to-date Topic 2191 Version 18.0 Topic last updated Mar 04, 2015.

<sup>5</sup> LaFranchi S. Thyroid nodules and cancer in children. Up-to-date Topic 5835 Version 14.0 Topic last updated Nov 04, 2015.



hours, that dose should be skipped and the next dose taken at the usual time of administration. Treatment should continue as long as there is clinical benefit.

### **Orphan status**

Lenvatinib has the following orphan designation in Australia:

*treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer*

Designation was on 27 November 2014.

### **Other registered products**

There are few other medicines on the Australian Register of Therapeutic Goods (ARTG) with a formal indication to treat DTC. Sorafenib is indicated as follows:

*Nexavar is indicated for the treatment of patients with locally advanced or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine.*

Sorafenib is also a multikinase inhibitor and its targets include VEGFR2. Sorafenib was approved based on one Phase III study in RR-DTC that had progression free survival (PFS) as a primary endpoint. Median PFS was 10.8 months (sorafenib) versus 5.8 months (placebo). There was no clear overall survival (OS) benefit with sorafenib. Toxicity of sorafenib was significant, with 65% of sorafenib subjects reporting grade 3-4 adverse events (AEs), versus 30% of placebo subjects. Dermatological AEs (such as palmar plantar erythrodysesthesia and rash) were prominent.

Other TKIs do not have specific indication in DTC, for example, pazopanib, axitinib, vandetanib, sunitinib. Some papillary thyroid cancers harbour BRAF V600 mutations, but BRAF or MEK inhibitors are not approved for treatment of such tumours. Of note, thyroid cancers with an activated MAPK pathway are typically radioiodine refractory.

Doxorubicin has sometimes been used to treat patients with progressive, symptomatic thyroid cancer unresponsive or not amenable to surgery, radioiodine therapy or external radiotherapy. Thyroid carcinoma is mentioned in this product's Product Information (PI) 'Indications' section.

### **Regulatory status**

#### **USA: FDA**

Lenvatinib is approved in the US with the following indication:

*Lenvima is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).*

Lenvatinib was also given orphan status for use in various conditions, including follicular thyroid cancer and metastatic or locally advanced papillary thyroid cancer on 27 December 2012.

Approval, on 13 February 2015, was standard (that is, not accelerated), and the drug was not considered by an advisory committee. The Food and Drug Administration (FDA) required the following:

*2865-1 Conduct a clinical trial to evaluate the incidence of serious and severe (i.e.  $\geq$  Grade 3) adverse reactions of an oral starting dose of 20 mg or of 14 mg daily*

*compared to the 24 mg starting dose, with a comparable objective response rate. Safety assessments will include evaluations for all severe or life-threatening ( $\geq$  Grade 3) and serious adverse reactions and should also include assessments of all adverse reactions.*

Trial completion is scheduled for mid-2019 and clinical study report (CSR) submission for mid-2020.

#### **EU: EMA**

Lenvatinib is approved in the EU with the following indication:

*Lenvima is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hurthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).*

Approval was via accelerated assessment. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) requested a study to investigate the most appropriate starting dose (compared to the US situation). The Summary of Product Characteristics (SmPC) also carries a 'black triangle' signalling that the product is subject to additional monitoring, to allow quick identification of new safety information.

#### **Product information**

The approved PI current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **II. Quality findings**

### **Introduction**

Lenvatinib is an oral, multiple TKI that selectively inhibits the kinase activities of VEGF receptors (VEGFR1 [FLT1], VEGFR2 [KDR] and VEGFR3 [FLT4]), in addition to other proangiogenic and oncogenic pathway related RTKs including fibroblast growth factor (FGF) receptors FGFR1-4, platelet derived growth factor (PDGF) receptor PDGFR $\alpha$ , KIT, and RET. VEGF has been identified as a crucial regulator of both physiologic and pathologic angiogenesis, and increased expression of VEGF is associated with a poor prognosis in many human tumours. Elevated levels of VEGF have been found in thyroid tumours, and the intensity of VEGF expression has been correlated with a higher risk of metastasis and shorter disease free survival in patients with papillary thyroid cancer.

Lenvima is indicated for the treatment of patients with progressive, radioactive iodine refractory differentiated thyroid cancer.

The recommended maximum adult dose is 24 mg taken once daily.

Lenvatinib mesilate is not subject to British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.) or United States Pharmacopoeia (USP) monographs.

Lenvatinib mesilate has the chemical structure shown below in Figure 1.

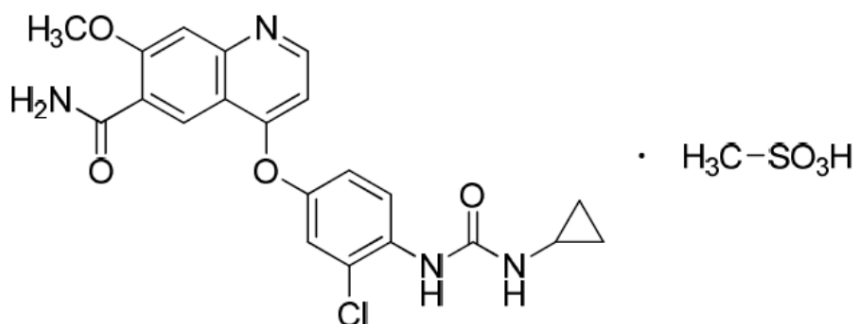
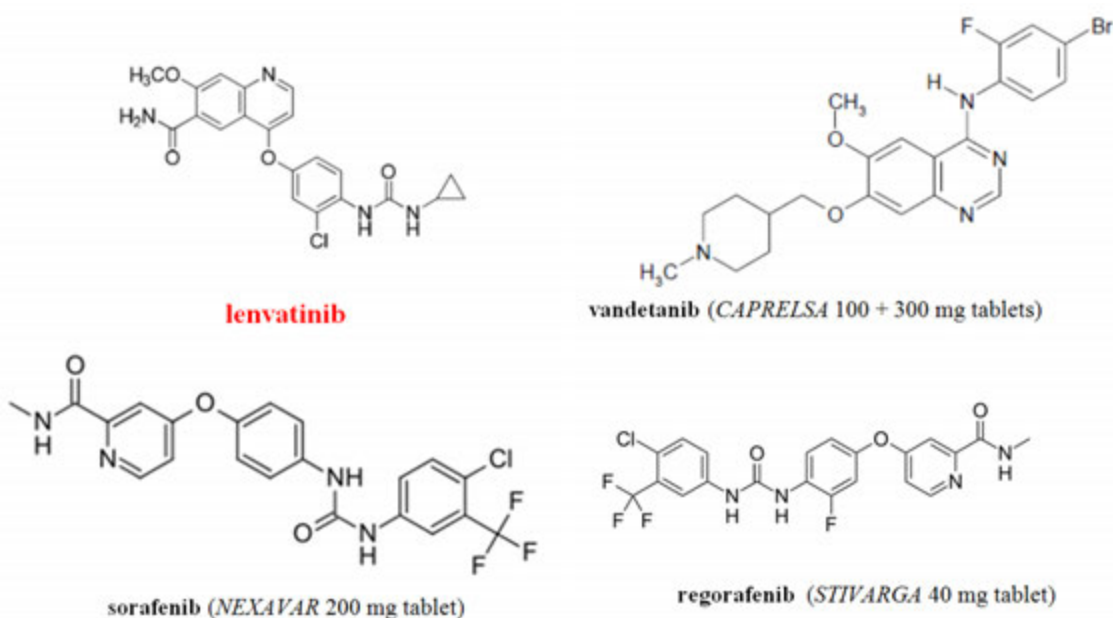
**Figure 1. Structure of lenvatinib mesilate.**

Figure 2 shows lenvatinib and related tyrosine kinase inhibitors. Lenvatinib is not very closely related to registered kinase inhibitors.

**Figure 2. Structure of lenvatinib and related tyrosine kinase inhibitors.**

The proposed tradename Lenvima is perhaps somewhat similar to Lanvis (40 mg thioguanine tablets used in the treatment of acute myeloblastic leukaemia).

### Drug substance (active ingredient)

Lenvatinib mesilate has the molecular formula  $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$ , molecular weight of 522.96 g/mol (mesilate) and 426.86 g/mol (free base). It is not chiral and has no enantiomer or diastereomer. It is a white powder and the disclosed synthesis involves 3 process steps.

The drug substance is stored in an inner polyethylene bag closed with a cable tie, which is heat sealed in an aluminium laminate bag. The polyethylene bag consists of a 60  $\mu$ m linear low density polyethylene (LLDPE) film on the inside and a 15  $\mu$ m nylon film on the outside. An alternate 100  $\mu$ m LDPE bag has also been described, and the applicant has indicated that stability data using the alternate bag is available on request.

A number of impurities were described, including genotoxic impurities. The discussion and justification based on the genotoxicity assessments conducted by the company are suitable from a chemistry and quality perspective; however, the suitability of the

genotoxicity assessment should be referred to the nonclinical evaluation unit. These controls are considered adequate if the nominated limits are toxicologically acceptable.

Based on the results presented, the drug substance is suitably stable when stored at 2-8°C in the proposed container closure system, and is unlikely to degrade significantly under normal storage conditions. The data presented supports a retest period of 30 months at 2-8°C. The drug substance was shown to be unaffected by light exposure, and no special storage conditions are required.

### Drug product

The lenvatinib capsules are described as hypromellose number 4 hard capsules each containing 100 mg of granules (Figure 3):

- 4 mg: A yellowish red body and a yellowish red cap, marked in black ink with “€” on the cap and “LENV 4 mg” on the body.
- 10 mg: A yellow body and a yellowish red cap, marked in black ink with “€” on the cap and “LENV 10 mg” on the body.

**Figure 3. Lenvatinib capsules (4 mg and 10 mg strengths).**



The capsules are packaged in cold formed polyamide and polyvinyl chloride laminated aluminium film blisters sealed by a push through aluminium foil.

A conventional immediate release formulation is used for the product, with direct replacement for the two strengths. Thus, the capsule contents are **not** scaled, but use a fixed excipient matrix except for mannitol which is adjusted to give the same fill mass.

Based on the presented data, the proposed shelf life for the unopened product in aluminium blisters of 36 months 'Store below 30°C' is suitable, subject to the responses to the above queries.

Based on the results presented, the bulk drug product is very stable and is unlikely to degrade significantly under normal storage and handling conditions. Shipping excursions of -20°C to 50°C have been shown to have no impact on the packed drug product quality over a 4 week period, and the bulk product has been shown to be suitably stable for 24 months at 30°C and 75% relative humidity (RH).

The directly exposed drug product was shown to be unaffected by light exposure, and no special storage conditions are required.

---

## Biopharmaceutics

### Rate and extent of absorption

Lenvatinib is rapidly absorbed after oral administration with  $T_{max}$  typically observed from 1 to 4 hours post dose. Food does not affect the extent of absorption, but slows the rate of absorption. When administered with food to healthy subjects, peak plasma concentrations are delayed by 2 h.

### Metabolism and distribution

In vitro, cytochrome P450 3A4 was the predominant (>80%) cytochrome isoform involved in the P450 mediated metabolism of lenvatinib. In vivo, inducers and inhibitors of CYP 3A4 had a minimal effect on lenvatinib exposure.

In human liver microsomes, the demethylated form of lenvatinib (M2) was identified as the main metabolite. M2' and M3', the major metabolites in human faeces, were formed from M2 and lenvatinib, respectively, by aldehyde oxidase.

In plasma samples collected up to 24 hours after administration, lenvatinib constituted 97% of the radioactivity in plasma radiochromatograms while the M2 metabolite accounted for an additional 2.5%. Based on  $AUC_{0-\infty}$ , lenvatinib accounted for 60% and 64% of the total radioactivity in plasma and blood, respectively.

Data from a human mass balance/excretion study indicate lenvatinib is extensively metabolised in humans. The main metabolic pathways in humans were identified as oxidation by aldehyde oxidase, demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (chlorbenzyl moiety), and combinations of these pathways followed by further biotransformations (for example, glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerisation). These in vivo metabolic routes align with the data provided in the in vitro studies using human biomaterials.

In vitro binding of lenvatinib to human plasma proteins was high and ranged from 98% to 99% (0.3-30  $\mu\text{g/mL}$ , mesilate). This binding was mainly to albumin with minor binding to  $\alpha$ 1-acid glycoprotein and  $\gamma$ -globulin.

In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1-10  $\mu\text{g/mL}$ , mesilate). Lenvatinib is a substrate for P-gp and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, or the BSEP.

### Mode, route and rate of elimination

Plasma concentrations decline bi-exponentially following  $C_{max}$ . The mean terminal exponential half-life of lenvatinib is approximately 28 h.

Following administration of radiolabelled lenvatinib to 6 patients with solid tumours, approximately two-thirds and one-fourth of the radiolabel were eliminated in the faeces and urine, respectively. The M2 metabolite was the predominant analyte in excreta (~5% of the dose) with lenvatinib the second most prominent (~2.5%).

### Dose response proportionality

In patients with solid tumours administered single and multiple doses of lenvatinib once daily, exposure to lenvatinib ( $C_{max}$  and AUC) increased in direct proportion to the administered dose over the range of 3.2 to 32 mg once daily (QD).

### Effects of age, gender and genetic polymorphism

Based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, age, sex, weight, or race (Japanese versus other, Caucasian versus other) had no significant effects on clearance

Paediatric patients have not been studied.

### Effects of food

Food does not affect the extent of absorption, but slows the rate of absorption. When given with food to healthy subjects, peak plasma concentrations are delayed by 2 h.

### Summary of bioavailability and bioequivalence studies

Three biopharmaceutic/bioavailability/bioequivalence studies have been presented in the dossier. Table 1 summarises the studies performed, and indicates which studies have been fully evaluated or summarised.

**Table 1. Summary of bioavailability and bioequivalence studies.**

Study Number	Primary objectives	Formulations	Evaluation
E7080-A001-001	To compare the bioavailability of a 10-mg capsule formulation with the 10-mg tablet formulation of E7080	E7080 10-mg capsule E7080 10-mg tablet	Summary only
E7080-A001-003	To determine the effect of food on the bioavailability of E7080 following administration of E7080 with and without a high fat meal	E7080 10-mg capsule	Full evaluation
E7080-A001-008	To determine whether two test lots of 10-mg capsules that vary by the level of lenvatinib crystal form were bioequivalent to a reference lot of 10-mg capsules.	E7080 10-mg capsules with low, medium and high crystal form	Summary only

The different formulations and their relation to the final proposed commercial formulation and the clinical study phases are summarised below in Table 2.

**Table 2. Different formulations and clinical study phases.**

Type of Study Study Number	Study Phase <sup>a</sup>	Strength	Study Objectives
<b>Relative Bioavailability</b>			
E7080-A001-001	1	10-mg capsule 10-mg tablet	Capsule vs tablet
<b>Absorption</b>			
E7080-E044-104	1	24-mg solution	Mass balance study with <sup>14</sup> C-lenvatinib
<b>Bioequivalence</b>			
E7080-A001-008	1	10-mg capsule	Low crystalline level vs Phase 3 clinical lot High crystalline level vs Phase 3 clinical lot
<b>Food Effect</b>			
E7080-A001-003	1	10-mg capsule	Food effect study
E7080-E044-101	1	1-and 10-mg tablets	Food effect study
a: The 4- and 10-mg capsules used in these Phase 1 studies were also used in the Phase 3 clinical trial E7080-G000-303, and they are the intended marketed formulations.			

E7080-A001-003 has been fully evaluated as it provides an estimate of the food effect for the capsules. Evaluation of crossover multiple dose PK Study E7080-E044-101 which included a food effect arm was not required as it was performed on tablets, which have had very limited use and were not used in pivotal studies.

E7080-A001-001 was a bridging bioequivalence study between the 10 mg capsule proposed for marketing and the 10 mg film coated tablet used in early clinical studies. Evaluation has not been performed due to the very limited tablet use.

E7080-A001-008 was a bioequivalence study comparing capsules that varied by the levels of crystalline lenvatinib. For both the high and low crystal level test formulations, the 90% confidence intervals for AUC<sub>0-∞</sub>, AUC<sub>0-t</sub>, and C<sub>max</sub> were within the 80% to 125% confidence interval, demonstrating bioequivalence. The study supports the justification for control of the level of the crystalline form in the capsules.

Mass balance Study E7080-E044-104 has been briefly discussed under the justification for not performing a BA study below.

#### ***Justification for not providing absolute bioavailability studies***

The sponsor argues that an absolute bioavailability study was not feasible because of the solubility limitations of the drug substance, making it difficult to formulate an intravenous preparation for human administration. In particular, the aqueous solubility was poor (water: slightly soluble, 0.1 M HCl: very slightly soluble, and Britton-Robinson buffer solutions pH 3, 5, 7, 9, and 11: practically insoluble).

Instead, a mass balance study was undertaken with an oral solution of lenvatinib to determine the metabolism and elimination of <sup>14</sup>C lenvatinib in an oral solution form (Study E7080-E044-104).

The radiolabelled oral solution was prepared by dissolving 24 mg of lenvatinib in 3 mM HCl (Table 3).

**Table 3. Solution preparations.**

	E7080	<sup>14</sup> C-E7080 dosing vehicle solution	E7080 drug substance
Dosage form	tablet	oral dosing solution	oral dosing solution
Dose	4 mg and 2 x 10 mg	2.14 mg/mL [quinoline-2- <sup>14</sup> C]E7080 solution 0.42 mL <sup>a</sup> E7080 drug substance 28.50 mg	24 mg
Other ingredients	Silica, colloidal anhydrous; Mannitol; Cellulose, microcrystalline Hydroxypropylcellulose; croscarmellose sodium; sodium stearyl fumarate; ethanol, anhydrous OPADRY 03F42069 YELLOW (hypromellose, talc, croscrogols, titanium dioxide, yellow ferric oxide) Water, purified	3 mmol/L hydrochloric acid 11.58 mL	-

Following oral administration of the solution containing <sup>14</sup>C lenvatinib, the median T<sub>max</sub> of radioactivity and lenvatinib in blood and plasma were 1.5 h (<sup>14</sup>C in blood and plasma) and 2.0 h (lenvatinib in blood and plasma).

The company has stated that:

- Lenvatinib exhibited good oral bioavailability in dogs (70.4%) and monkeys (78.4%).
- Lenvatinib is rapidly absorbed after oral administration, with T<sub>max</sub> typically observed from 1 to 4 h post dose.
- An absolute bioavailability study was not required by either the US FDA or EMA during scientific meetings.

The justification ignores the possibility of establishing absolute bioavailability via an intravenous microdose.<sup>6</sup>

*The justification should be referred to the clinical evaluator for assessment from a clinical perspective.*

#### **Justification for not providing biopharmaceutic studies for the 4 mg capsules**

Bioavailability studies have not been undertaken for the 4 mg capsules. The company has requested a biowaiver based on the following in relation to Australian Regulatory Guidelines for Prescription Medicines (ARGPM) Guideline 15:

- the nature of the dosage form;  
The 4 mg capsules are a hard hypromellose capsule intended for immediate release. The excipients and manufacturing process for the 4 mg capsule are identical to those used for the 10 mg capsule (although the capsule contents are not scaled).
- the solubility of the active ingredient(s);
- the comparative dissolution profiles across the physiological pH range (1-7.5) of the products being considered;

Comparative dissolution studies were performed using the following dissolution media:

<sup>6</sup> Boulton DW, et al Simultaneous oral therapeutic and intravenous <sup>14</sup>C-microdoses to determine the absolute oral bioavailability of saxagliptin and dapagliflozin. *Br J Clin Pharmacol.* 75: 763-768 (2013).



- JP Dissolution 1st Fluid (pH 1.2),
- Diluted McIlvaine buffer (pH 4.0),
- JP Dissolution 2nd Fluid (pH 6.8), and
- water.

The dissolution profiles of the 10 mg capsule and 4 mg capsule were similar, per the acceptance criteria for dissolution test. (Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms. Attachment 2 of Division-Notification 0229 No.10 of the Pharmaceutical and Food Safety Bureau, dated February 29, 2012, NIHS)

- the pharmacokinetic characteristics of the active ingredient(s), such as permeability (or absolute bioavailability), linearity or otherwise, first pass effect (if any) and its significance;

Oral lenvatinib is rapidly absorbed with a time to maximum concentration (T<sub>max</sub>) of 1 to 4 h. Following administration of single and multiple QD doses to subjects with solid tumours, exposure to lenvatinib (C<sub>max</sub> and AUC) increased dose proportionally over the range of 3.2 to 32 mg, indicating linear pharmacokinetics.

- the clinical consequences of any potential differences in bioavailabilities of the products under consideration (for example, increased dose leading to toxicity or decreased dose leading to lack of efficacy);

The proposed dosage regimen recommends a starting dose of 24 mg QD (2 x 10 mg capsules + 1 x 4 mg capsule). The daily dose may be modified as needed according to the dose toxicity management plan, a 3 step dose reduction plan of 20 mg, 14 mg and 10 mg. Lenvatinib has a predictable and manageable safety profile at 24 mg QD.

Clinical study data also indicates that whilst many patients did participate in dose reductions a significant clinical benefit was still observed. Therefore minor variation in the bioavailability of lenvatinib mesilate is not expected to significantly alter the safety nor the efficacy.

- the margin between the minimum effective and minimum toxic plasma concentration;

The recommended dose is 24 mg once daily, however with dose reductions the dose can range from 10 mg to 24 mg QD. The Maximum Tolerated Dose (MTD) was determined to be 25 mg QD. There have been reports of overdose with lenvatinib mesilate. The highest recorded overdose was 144 mg. The reported cases of overdose were associated with adverse events consistent with lenvatinib mesilate or no AEs.

- the similarities of, or differences between, the formulations being considered.

As shown in the Description and Composition of the Drug Product, formulation of the granulation mix of the 10 mg and 4 mg capsules is identical with the exception of the active ingredient quantity and the quantity of mannitol. Mannitol is added as a diluent. It is a non-hygroscopic material and therefore is less likely to contribute to increased water content in the drug product which may impact degradation of drug substance by hydrolysis. The amount of mannitol is varied to keep the granule weight encapsulated to 100 mg for lenvatinib capsules, therefore the 4 mg capsules contains more mannitol than the 10 mg capsule. The capsule shell and the printing ink of both the 4 mg and 10 mg capsules is identical.

The applicant has also addressed the following recommendations in the TGA adopted EU guideline,<sup>7</sup> in particular Section 4.1.6 – General Biowaiver Criteria:

- the pharmaceutical products are manufactured by the same manufacturing process  
All strengths are manufactured by the same manufacturing process at one manufacturing site.
- the qualitative composition of the different strengths is the same  
The qualitative composition is identical for both strengths; only the relative active and mannitol concentrations differ.
- the composition of the strengths are quantitatively proportional, that is, the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths  
The quantitative formulation of the granulation mix of the 10 mg and 4 mg capsules is identical with the exception of the active ingredient quantity and the quantity of mannitol. Mannitol is added as a diluent. The amount of mannitol is varied to keep the granule weight encapsulated to 100 mg for both capsule strengths. The capsule shell and the printing ink of both the 4 mg and 10 mg capsules are identical. This meets the criteria defined in the guideline.
- appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing  
Comparative dissolution data are discussed above, and demonstrate that the dissolution profile of the two strengths was similar across various dissolution media.

The justification meets the requirements of the ARGPM and is acceptable from a chemistry and quality perspective; however *the justification should be referred to the clinical evaluator for assessment from a clinical perspective.*

### Quality summary and conclusions

Toxicological advice has been sought on the proposed limit for the residual solvent DMI (1,3-dimethyl-2-imidazolidinone) in the drug substance and on impurity limits.

Toxicological advice has been sought on the genotoxicity and toxicological assessments of potential and actual impurities in the Active Pharmaceutical Ingredient (API) and the drug product.

The justification for not performing an absolute bioavailability study should be considered by the Delegate.

The justification for not providing biopharmaceutic studies for the 4 mg capsules should be considered by the Delegate.

Statistical details in Study E7080-A001-003A should be considered by the Delegate.

The following questions should be raised with the sponsor:

1. Please provide a copy of your response to the EMA's 'Rapporteur day 80 critical assessment report - Quality aspects'.
2. The proposed particle size method uses a MT3300 EX II (Microtrac) laser diffraction particle sizer, and states that laser diffraction instruments from other manufacturers may be used as required. Particle size readings are very dependent on the instrument

---

<sup>7</sup> European Medicines Agency, "Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr)", 20 January 2010.

make and model used; this statement has not been supported by validation for other instruments and should be removed from the analytical procedure.

3. Please confirm that the analytical procedure validations presented were all conducted at the Eisai Co., Ltd. Kashima Plant or give details.
4. Please provide the start dates for each of the primary stability studies.
5. Please cite or submit details of an assessment of the peak purity of the lenvatinib peak in stress degraded samples.
6. The stress stability studies are important as part of method validation. Please clarify whether the proposed control method was used in analysis of the stress samples. Please comment on differences in lenvatinib retention time as shown.
7. Please justify the choice of detection wavelength (252 nm).
8. You are requested to provide written assurance that the TGA will be notified immediately of any out of specification stability results or adverse trends in stability results in any ongoing or future trials.
9. Please provide the start dates for each of the primary stability studies.
10. Please cite or submit evidence of the stability indicating nature of the assay and related substances analytical procedures including mass balance and lenvatinib peak purity for stress degraded samples.
11. There are extensive inconsistencies in the report for Study E7080-A001-003. Please review and explain. Please comment on the validity of the other pharmacokinetic study reports.
12. The standardised meal for the fed treatment has been referenced in the protocol to the FDA guidance for food effect studies, however the actual composition of the meal used for the study has not been reported? Please cite or submit details of the composition of the standardised meal provided to applicant for the fed portion of Study E7080-A001-003.
13. Please cite or submit a tabulated summary of the demographic data for the study subjects, including height, weight and body mass index (BMI).
14. Please indicate where in the dossier the referenced report 'Additional Stability Testing of E7080 in Human Plasma during Frozen Storage. Sumika Chemical Analysis Service, Ltd. June 28, 2007' is located, or provide the report for evaluation of the validation stability studies.
15. Please provide assurance that all writing on the labels will be greater than 1.5 mm, with the exception of the registration number which should be greater than 1 mm.
16. The cartons and blisters all refer to the drug substance as lenvatanib, with the exception of the quantity statement on the front of the carton label, which states Each hard capsule contains (4 or 10) mg lenvatinib (as mesilate). All instances of lenvatanib on the labelling should be lenvatinib (as mesilate).

Approval is **not recommended**, with respect to the bioanalytical, pharmaceutical chemistry and quality control aspects, for the registration of the proposed capsules until satisfactory responses are provided to the questions raised in this report.

## III. Nonclinical findings

### Introduction

The submitted nonclinical dossier was compliant with the relevant International Conference on Harmonisation (ICH) guideline on the development of anti-cancer pharmaceuticals.<sup>8</sup> The overall quality of the dossier was high, with all pivotal safety studies conducted under Good Laboratory Practice (GLP) conditions.

In this evaluation report, all doses and concentrations on a weight basis are expressed in terms of the mesilate salt (Molecular Weight [MW] 522.96) same as in the sponsor's study reports, nonclinical summaries and the nonclinical overview, while the clinical dose and plasma drug concentrations are expressed as the base (MW 426.86).

### Pharmacology

#### Primary pharmacology

Lenvatinib is a receptor TKI. In vitro studies demonstrated that lenvatinib inhibited the tyrosine kinase activity of VEGF receptors -1 (Flt-1), -2 (KDR) and -3 (Flt-4), as well as the proto-oncogene RET, with IC<sub>50</sub> values <10 nM and K<sub>i</sub> values ≤1.5 nM. As the unbound C<sub>max</sub> for lenvatinib was ~20 nM, inhibition of these kinases is expected clinically. In addition, lenvatinib inhibited PDGF receptor α, FGF receptors FGFR1-4 and KIT with IC<sub>50</sub> values of <100 nM, indicating some inhibition of these kinases may also occur clinically. Lenvatinib did not inhibit or showed very low inhibition of other kinases including EGFR, BRK and BRAF.

Lenvatinib competitively inhibited VEGF and FGF receptors, as well as RET and KIT, with a structural study demonstrating lenvatinib bound to the ATP binding site of VEGFR-2. In addition to this binding, lenvatinib also interacts with the allosteric region in the kinase domain, the DFG region, of VEGFR-2. In contrast to sorafenib which binds the DFG region in its "out" conformation (closed), lenvatinib binds the DFG-in (open) conformation. This suggests that lenvatinib may belong to a new class of tyrosine kinase inhibitor, which has been termed type I½.<sup>9</sup> This type of kinase shows greater selectivity than Type I kinases which bind only the ATP binding site, but unlike type II inhibitors are able to bind to kinases in the "open" conformation.

In vitro, lenvatinib inhibited VEGF induced phosphorylation of VEGFR-2 (IC<sub>50</sub> 0.25 nM), tube formation (angiogenesis; IC<sub>50</sub> 2.1 nM) and proliferation (IC<sub>50</sub> 3.4 nM) in human umbilical vein endothelial cells (HUVECs). Three lenvatinib metabolites (M1, M2 and M3) were pharmacologically active. These compounds inhibited the proliferation of HUVECs in response to VEGF with IC<sub>50</sub> values of 57 nM (M1), 250 nM (M2) and 230 nM (M3). As these metabolites were not detected in plasma they are unlikely to contribute to the pharmacological activity of lenvatinib. Higher levels may occur locally, for example in liver and/or kidney, and may exert local activity in these tissues.

The efficacy of oral lenvatinib was assessed in vivo using tumour xenografts in athymic mice. Only those studies using thyroid cancer cell lines were evaluated. Lenvatinib dose-dependently inhibited the growth of papillary, follicular, medullary and anaplastic thyroid cancer cell line xenografts, as well as thyroid derived squamous cell cancer cell lines.

<sup>8</sup> International Conference on Harmonisation, "S9: Nonclinical evaluation for anticancer pharmaceuticals", 29 October 2009.

<sup>9</sup> Zuccotto F, et al. Through the "gatekeeper door": Exploiting the active kinase conformation. *J Med Chem.* 53: 2681-2694 (2010).

Lenvatinib significantly inhibited xenograft growth in all thyroid cancer cell lines ( $\geq 1$  mg/kg/day; estimated exposure ratio 0.2x based on body surface area, and 0.7x and 2x based on free fraction AUC and  $C_{max}$  extrapolated from a 3 mg/kg dose, respectively), with 50% reduction in tumour growth (relative to vehicle control) generally observed at  $\sim 10$  mg/kg and higher (exposure ratio  $\sim 2x$ , 11x and 32x based on dose, AUC and  $C_{max}$ , respectively). Inhibition of tumour angiogenesis was also demonstrated in an anaplastic thyroid cancer cell line xenograft model in mice that received  $\geq 3$  mg/kg/day lenvatinib (estimated exposure ratio 2x and 6x based on AUC and  $C_{max}$ ,<sup>10</sup> respectively) with 50% inhibition of microvessel density at around 30 mg/kg. Two studies compared the efficacy of lenvatinib and sorafenib in inhibiting the growth of papillary and follicular thyroid cancer cell lines. Both significantly inhibited thyroid cancer cell xenografts, but lenvatinib did so at lower doses compared to sorafenib (ED50 values of 5-7 mg/kg/day and 61-96 mg/kg/day, respectively), consistent with the difference in VEGFR2 binding affinity (KD 2.1 nM for lenvatinib and 33 nM for sorafenib).

### Secondary pharmacodynamics and safety pharmacology

A secondary pharmacodynamic pharmacology study revealed 10  $\mu$ M lenvatinib inhibited the serotonin 5-HT1A and 5-HT1B receptors, and noradrenaline transporter, by  $\sim 40$ -60%. This is unlikely to occur clinically as the unbound  $C_{max}$  is  $>500x$  lower than the lenvatinib concentration at which inhibition occurred. No other off target binding was observed.

Specialised safety pharmacology studies covered the cardiovascular, central nervous system (CNS) and respiratory systems. They revealed no adverse effects on lenvatinib on the respiratory or CNS systems in male SD rats at doses  $\leq 100$  mg/kg oral (PO) ( $\sim 150x$  unbound clinical  $C_{max}$ ).<sup>11</sup> In vitro studies found no effect of 10  $\mu$ M lenvatinib on the action potential in papillary muscles isolated from guinea pigs. Lenvatinib inhibited hERG tail currents with an IC50 of  $\sim 12$   $\mu$ M ( $>500x$  clinical unbound  $C_{max}$ ). There was no effect of lenvatinib on QTc in conscious dogs ( $\leq 30$  mg/kg; 33x unbound clinical  $C_{max}$ )<sup>12</sup> or in monkeys in the repeat dose toxicity studies at up to 3 mg/kg/day for 9 months ( $\sim 7x$  the unbound clinical unbound  $C_{max}$ ). The nonclinical study findings suggest low potential for QT prolongation in humans. Blood pressure was increased in dogs that received  $\geq 6$  mg/kg ( $9x$  unbound clinical  $C_{max}$ ), suggesting that hypertension is a potential risk in patients.

### Pharmacokinetics

Lenvatinib was absorbed rapidly in rodents ( $T_{max} \leq 1$  h, delayed at high doses), but more slowly in dogs, monkeys and humans ( $T_{max}$  1-8 h, 2 h in humans). Lenvatinib had good oral bioavailability in nude mice, SD rats, beagle dogs and cynomolgus monkeys (64-78%). Plasma half-life was moderate in laboratory animals (2-5h) and humans (6-7h). At high doses, exposure was generally higher in female compared to male rats and dogs, but there were no clear effects of gender on AUC in monkeys. In the pivotal studies, exposure to lenvatinib (as AUC) was approximately dose proportional in rats and monkeys.

Plasma protein binding was high in all species ( $\sim 98\%$  in rats and humans, 97% in mice, 96% in monkeys and 91% in dogs). The mean free fraction in plasma at the concentration range of 0.3-30  $\mu$ g/mL was 3.3% (mouse), 2.0% (rat), 8.9% (dog), 3.9% (monkey) and 1.7% (human). In human serum, lenvatinib was predominantly bound to albumin. The volume of distribution was small in rats and moderate in mice, dogs and monkeys. Tissue distribution studies in rats found high levels of lenvatinib and/or its metabolites in liver, kidneys and adrenal gland, with high levels of radioactivity also observed in the stomach

<sup>10</sup> Based on single 3 mg/kg PO dose in Study B03014.

<sup>11</sup>  $C_{max}$  in rats estimated from day 1  $C_{max}$  in male rats that received 100 mg/kg lenvatinib (Study S03016).

<sup>12</sup>  $C_{max}$  in dogs estimated from day 1  $C_{max}$  values in Study B-5108.

and GI tract. In monkeys lenvatinib and/or its metabolites distributed to liver, kidneys, gall bladder, kidney, renal cortex and renal medulla as well as to the iris, ciliary body and choroid, with retention in ocular tissues. Very high levels were detected in bile (in gall bladder), suggesting biliary excretion. Measurable and limited distribution to the brain and reproductive tissues (males) were observed.

Lenvatinib was extensively metabolised to over 70 metabolites by reactions including O-dearylation, demethylation, dealkylation, oxidation, hydroxylation, glutathione conjugation and/or combinations of these processes. The dominant circulating species was unchanged lenvatinib, and there were no major metabolites identified in plasma of humans, rats or monkeys when lenvatinib was radiolabelled on the quinolone moiety. One major plasma metabolite was identified in monkeys when lenvatinib radiolabelled on the chlorobenzene moiety was used (me50;<sup>13</sup> 13–39%). The in vitro metabolite profile was very similar in monkey and human liver microsomes, with 5 of 8 identified metabolites also observed in mouse, rat and dog liver microsomes. In humans, low levels of metabolite M2-glucuronide was observed in plasma (2.5%), with other minor plasma metabolites also observed in monkeys. Multiple metabolites were identified in urine and faeces, with the metabolite profile differing between species. Low levels of unchanged drug were detected in either excreta of monkeys and humans and rat urine, but high levels in rat faeces (44% of faecal radioactivity) and bile (16% of biliary radioactivity) were observed. Unique faecal and urinary metabolites were observed in humans, with me10 (quinolone GSH derivative) accounting for 6.8% of dose (30% of total urine radioactivity) and me46 (structure unidentified) 3.7% of dose (16% of total urine radioactivity). Metabolite me10 was also detected in monkey liver and kidneys, and me46 was not detected in animal species. CYP3A4 was the major CYP isoform responsible for metabolite formation, with aldehyde oxidase also involved in metabolite formation.

In studies using lenvatinib radiolabelled on the quinolone moiety the majority of radioactivity was excreted in the faeces (62-87%) with urinary excretion also observed (12-19%). Biliary excretion was demonstrated in rats and monkeys. A similar excretion profile was observed in humans (65% faeces, 23% urine). In monkeys that were administered <sup>14</sup>C-CB-lenvatinib the majority of radioactivity was excreted in the urine (80%) with lower levels of excretion via the faeces (14%). <sup>14</sup>C-CB-lenvatinib was not used in human studies. Together, the data indicate that lenvatinib is predominantly cleared by metabolism in monkeys, while biliary excretion also plays an important role, in addition to metabolism, in rats. Both the biliary/faecal and urinary excretion routes are likely to contribute to the excretion of lenvatinib and metabolites.

The pharmacokinetic profile in humans and monkeys were highly similar, with sufficient similarity in rodents and dogs to make these animal models suitable for assessing the toxicity profile of lenvatinib. The differences in metabolic profile in the urine and faeces of animals and humans are not considered problematic given the similarity of in vitro metabolites and the detection of one major human urine metabolite in monkey liver and kidney tissues. The plasma metabolite profile has not been fully established in humans or rats, but based on ICH guidance<sup>14</sup> this is not considered a major deficiency for an anti-cancer pharmaceutical for the treatment of advanced cancer.<sup>15</sup>

---

<sup>13</sup> Glucuronidated chloro-cyclopropylureido-phenol.

<sup>14</sup> International Conference on Harmonisation, "S9: Nonclinical evaluation for anticancer pharmaceuticals", 29 October 2009.

<sup>15</sup> ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals states that nonclinical qualification of metabolites is "generally not warranted". Therefore, the possibility of a major metabolite in humans does not significantly impact on the nonclinical evaluation.

## Pharmacokinetic drug interactions

Lenvatinib did not induce the expression or activity of CYP and UGT enzymes at concentrations that were clinically relevant. Lenvatinib inhibited CYP2C8 and CYP3A4 with  $K_i$  values of 11 and 106  $\mu\text{M}$ , respectively, and inhibited UGT1A1 and 1A4 with  $\text{IC}_{50}$  values of 10.6 and 14.0  $\mu\text{M}$ , respectively. As the anticipated unbound  $C_{\text{max}}$  at the MRHD is  $\sim 20$  nM, these effects are unlikely to occur clinically even when the increased distribution to liver is considered. No inhibition of other CYP (1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 2E1) or UGT (1A6, 1A9 and 2B7) enzymes was observed in in vitro assays. However, a pharmacokinetic modelling study predicted minor inhibition of CYP3A4. Lenvatinib also inhibited UGT1A1, 1A4 and 1A9, but with  $\text{IC}_{50}$  values  $>10$   $\mu\text{M}$ . This is unlikely to be clinically relevant.

Lenvatinib was a substrate for P-glycoprotein (P-gp) and BCRP, suggesting that its bioavailability may be altered by inhibitors or inducers of these transporters. However, it is noted that only minor changes in the bioavailability of lenvatinib were observed in clinical studies when co-administered with a P-gp inhibitor or inducer (Summary of Clinical Pharmacology Studies). Lenvatinib inhibited P-gp and BCRP with estimated  $\text{IC}_{50}$  values of  $>30$   $\mu\text{M}$ . The actual  $\text{IC}_{50}$  may be much higher as the maximum concentrations of lenvatinib tested were 10  $\mu\text{M}$  (P-gp) and 30  $\mu\text{M}$  (BCRP). The anticipated intestinal concentration of lenvatinib is 22  $\mu\text{M}$ .<sup>16</sup> As the estimated  $\text{IC}_{50}$  was higher than the anticipated intestinal concentration and  $>1000$  fold higher than the unbound clinical  $C_{\text{max}}$ , lenvatinib is not expected to have significant effects on the bioavailability of P-gp and BCRP substrates.

Lenvatinib was not a substrate for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP, but it inhibited these transporters with  $\text{IC}_{50}$  values ranging from 4  $\mu\text{M}$  to over 30  $\mu\text{M}$ . As the unbound clinical  $C_{\text{max}}$  was  $\sim 20$  nM, inhibition of these transporters is not expected clinically.

## Toxicology

### Acute toxicity

Acute oral toxicity was assessed in SD rats, beagle dogs and cynomolgus monkeys. The studies were of limited predictive value as the observation period was generally less than one week. The exception to this was a rat study which had an observation period of 4 weeks. In this study, mortality was observed in rats that received  $\geq 1000$  mg/kg, with mortality occurring between days 14 and 24. The maximum non lethal dose in rats was 500 mg/kg, which is associated with an estimated exposure of  $>240\times$  based on unbound  $C_{\text{max}}$ .<sup>17</sup> The estimated maximum non-lethal dose in dogs and monkeys was 1000 mg/kg, but this is expected to be lower had a longer observation period been used. These data indicated that lenvatinib has a low order of acute toxicity.

### Repeat dose toxicity

Studies of up to 6 months in SD rats, 4 weeks in beagle dogs and 9 months in cynomolgus monkeys were conducted to assess the toxicity profile of daily oral dosing with lenvatinib. Pivotal studies were GLP compliant, and the duration, species and number of animals

<sup>16</sup> Calculated according to: European Medicines Agency, "Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2\*\*)", 21 June 2012: 0.1x 24 mg/250 mL, with a 24 mg dose equivalent to 56  $\mu\text{mol}$  lenvatinib free base.

<sup>17</sup> In Study TKB02007, doses of 300 and 1000 mg/kg were associated with plasma  $C_{\text{max}}$  values of  $>130,000$  ng/mL on the first day of dosing.

addressed the requirements of ICH guideline S9.<sup>18</sup> In each species, there was a 4 week study with a 4 week recovery period to investigate the reversibility of effects.

### Relative exposure

Exposure ratios have been calculated based on animal: human plasma AUC<sub>0-24h</sub>, with both total and unbound ratios presented in Table 4. The unbound ratios are referred to in the discussion of observed toxicities. There was little effect of gender at the doses used in the pivotal studies, and therefore genders were combined for the calculation of exposure ratios. The exposure at the last time point was used in the animal studies. Moderate exposure ratios were achieved at the high dose in the pivotal repeat dose studies in rats and monkeys. Relative exposures in dogs were below that anticipated clinically.

**Table 4. Relative exposure in repeat dose toxicity and carcinogenicity studies.**

Species	Study duration [Study ID]	Dose (mg/kg/day)	AUC <sub>0-24 h</sub> (ng·h/mL)		Exposure Ratio (ER) #	
			Total	Unbound†	Total	Unbound
Rat (SD)	6 months [S08037]	0.4	3383	68	0.7	0.8
		2	17,612	352	3.5	4.1
		10	63,396	1268	13	15
Dog (Beagle)	4 weeks [S03077]	0.1	137	12	0.03	0.14
		0.5	563	50	0.1	0.6
Monkey (Cynomolgus)	9 months [SBL038-031]	0.1	235	9	0.05	0.1
		0.5	1418	55	0.3	0.6
		3	9778	381	1.9	4.4
Human (patients)	steady state [E7080-J081-105]	24 mg	5072*	86	–	–

# = animal:human plasma AUC<sub>0-24h</sub>; † Based on mean free fraction values of 2.0% (rat), 8.9% (dog), 3.9% (monkey) and 1.7% (human); \* Converted from 4104 ng·h/mL of the lenvatinib base to the mesilate salt.

### Major toxicities

The major target organs for lenvatinib were the kidney, GI tract (in particular duodenum and stomach), liver, gallbladder/common bile duct, reproductive organs and tissues, bone (including marrow), teeth and adrenals. Some effects also observed on pituitary, brain (choroid plexus), pancreas, spleen and other lymphoid tissues. Vascular lesions (arterial fibrinoid necrosis and/or medial arterial degeneration) were observed in all species at multiple anatomical sites and were responsible for the many of the target organ toxicities.

Mortality was observed in all species, at doses  $\geq 10$  mg/kg/day in rats (ER  $\geq 15x$ ) and  $\geq 3$  mg/kg/day in monkeys (ER  $\geq 4x$ ). In dogs, excessive toxicity led to early termination of

<sup>18</sup> International Conference on Harmonisation, "S9: Nonclinical evaluation for anticancer pharmaceuticals", 29 October 2009.



dosing, with subsequent mortality in a male dog that received 30 mg/kg/day. Mortality was frequently associated with severe duodenal lesions and/or renal toxicity. In rats, cholangitis and pancreatitis were also observed in premature decedents. In addition, bacterial infections and associated elevations in white blood cells were observed in rats that received  $\geq 10$  mg/kg/day lenvatinib.

Many of the observed toxicities were consistent with exaggerated pharmacological effects, and are considered class effects of receptor tyrosine kinase inhibitors. For example, similar findings have been reported for sunitinib, sorafenib, axitinib and regorafenib.<sup>19</sup> In particular, inhibition of angiogenesis through effects on VEGF signalling provides a mechanistic basis for many of the observed toxicities, including renal and gastrointestinal (GI) lesions, and effects on reproductive tissues. In the studies that included a recovery period (4 week studies in rats, dogs and monkeys) almost all lesions were shown to be reversible, except where indicated below. The observed class effects included:

- Vascular lesions were observed in all species at multiple sites including kidney, GI tract, spleen, testis, heart, liver, gallbladder, urinary bladder, ovaries, uterus, vagina, adrenals, sciatic and optic nerves, mammary gland and choroid plexus. The lesions were characterised as arterial fibrinoid necrosis, medial degeneration and haemorrhage. Lesions were observed at doses of  $\geq 10$  mg/kg/day in rats (ER 15x),  $\geq 0.5$  mg/kg/day in dogs (ER 0.6x) and  $\geq 3$  mg/kg/day in monkeys (ER 4x). Vascular lesions were reversible following cessation of dosing.
- Inflammation, atrophy, necrosis and/or hyperplasia were observed in the duodenum in rats ( $\geq 10$  mg/kg, ER 15x) and monkeys ( $\geq 3$  mg/kg/day, ER 4x). Similar lesions were reported at other intestinal sites at similar doses in rats, in dogs and at higher doses in monkeys, with oedema and autolysis also observed. Hyperplasia and inflammatory cell infiltration were observed in the stomach of rats that received  $\geq 10$  mg/kg/day lenvatinib. Vascular lesions were also observed in the stomach of rats and dogs. Severe GI lesions were commonly observed and considered the cause of death in premature decedents in all species. There were also increased blood neutrophil counts in rats, suggesting bacterial infection probably secondary to GI tract tissue damage. Clinical signs of abnormal faeces, vomiting and/or decreased food intake were also consistent with the observed microscopic GI toxicity. GI lesions were generally reversible, however in some rats and dogs there were incidences of mortality following cessation of dosing due to the severity of GI lesions.
- Glomerulopathy was observed in the kidney in rats ( $\geq 2$  mg/kg, ER 4x), dogs ( $\geq 0.5$  mg/kg/day, ER 0.6x) and monkeys ( $\geq 0.5$  mg/kg/day, ER 0.6x). Increased plasma BUN (all species) and, to a smaller extent, creatinine (monkeys) and proteinuria were observed at higher doses. Similar effects at or below anticipated clinical exposures have been reported for other tyrosine kinase receptor inhibitors, including regorafenib and sorafenib. The renal toxicity observed with lenvatinib was reversible.
- Hepatotoxicity was observed at higher doses in rats ( $\geq 10$  mg/kg/day, ER 15x), dogs ( $\geq 100$  mg/kg/day, ER  $\geq 60$ x) and monkeys ( $\geq 3$  mg/kg/day, ER 4x). Variable increases in ALT and/or AST, and in some cases, ALP and bilirubin were reported, with histological findings of hepatocyte necrosis, vacuolation and/or pigmentation, sinusoidal dilatation, Kupffer cell hypertrophy/ hyperplasia, cholangitis and/or inflammation. Vascular lesions were observed in the gallbladder (dogs and monkeys) and common bile duct (rats), as well as inflammation in the gallbladder (monkeys).

---

<sup>19</sup> Nonclinical evaluation reports for sunitinib, sorafenib, axitinib and regorafenib; Patyna S, et al. Nonclinical safety evaluation of sunitinib: A potent inhibitor of VEGF, PDGF, KIT, FLT3, and RET receptors. *Toxicol Pathol* 36: 905-16 (2008).

- Pancreatic toxicity was observed in all species, with decreased zymogen granules in rats ( $\geq 10$  mg/kg/day, ER 15x) and monkeys ( $\geq 3$  mg/kg/day, ER 4x) and acinar atrophy in dogs ( $\geq 2$  mg/kg/day, ER 3x). Pancreatitis was also observed in some premature decedent male rats (10 mg/kg/day).
- In bone, there was an increased epiphyseal growth plate in femur and/or increased epiphyseal cartilage in the sternum in rats ( $\geq 10$  mg/kg/day, ER 15x) and monkeys ( $\geq 0.5$  mg/kg/day, ER 0.6x). Hypocellularity was also observed in the bone marrow of these species at the same doses.
- Discolouration, weakness (broken or missing teeth) and microscopic abnormalities (dysplasia, inflammation in pulp and gingiva) were observed in the incisors in rats that received  $\geq 2$  mg/kg/day lenvatinib (ER 4x). These findings are likely secondary to the role of VEGF and FGF in the development of normal dentition. However, they are unlikely to be relevant to adult humans, as rat incisors are constantly growing and there were no adverse effects on teeth in the pivotal monkey study.
- In females, follicular atresia, atrophy of the vaginal epithelium and/or vaginal mucification were observed in rats ( $\geq 2$  mg/kg/day, ER 4x), dogs ( $\geq 2$  mg/kg/day, ER 3x) and monkeys ( $\geq 0.5$  mg/kg/day, ER 0.6x). Reduced menstruation was also observed in monkeys. In males, hypocellularity in the testes and desquamated seminiferous epithelial cells in the epididymides were observed in rats ( $\geq 10$  mg/kg/day, ER 15x), dogs ( $\geq 0.1$  mg/kg/day, ER 0.1x) and monkeys ( $\geq 30$  mg/kg/day, ER 14x).
- Lymphoid depletion or atrophy was observed in lymphoid tissues including spleen, thymus and mesenteric lymph node in rats ( $\geq 10$  mg/kg/day, ER 15x) and monkeys ( $\geq 3$  mg/kg/day, ER 4x). Lymphoid depletion/ necrosis was also observed in the jejunum of dogs that received 0.5 mg/kg/day lenvatinib (ER 0.6x).
- Eosinophilic exudate and perivascular mononuclear cell infiltration were observed in the choroid plexus in rats (10 mg/kg/day, ER 15x) dogs ( $\geq 2$  mg/kg/day, ER 3x) and monkeys (3 mg/kg/day, ER 4x). Vascular lesions were also observed in the choroid plexus in monkeys.
- In the adrenals, cortical hypertrophy, necrosis and/or vacuolation was observed in rats ( $\geq 2$  mg/kg/day ER 4x), dogs ( $\geq 2$  mg/kg/day, ER 3x) and monkeys ( $\geq 0.1$  mg/kg/day, ER 0.1x).
- Basophilic cell vacuolation was observed in the pituitary of rats ( $\geq 10$  mg/kg/day, ER 15x), dogs ( $\geq 2$  mg/kg/day, ER 3x) and monkeys ( $\geq 0.5$  mg/kg/day, ER 0.6x)

In summary, the toxicity profile of lenvatinib is consistent with its pharmacological effects and is comparable with other medicines in this class. Based on the low to moderate exposure ratios it is expected that many of the reported effects may be observed clinically. Importantly, the nonclinical studies demonstrated reversibility of these effects. The teeth and bone effects are unlikely to be clinically relevant in the proposed adult population.

## Genotoxicity

The genotoxicity of lenvatinib was assessed in in vitro mutagenicity assays in bacterial and mammalian cells (mouse lymphoma L5178Y cells), and in vivo using a micronucleus assay in rats. This testing strategy is consistent with ICH guideline S2 (R1),<sup>20</sup> and the studies were appropriately conducted and validated. Lenvatinib was not mutagenic in bacteria or mammalian cells, or clastogenic in mammalian cells or SD rats at doses  $\leq 2000$  mg/kg.

---

<sup>20</sup> International Conference on Harmonisation, "S2(R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use", 9 November 2011.

Estimated relative exposure at this dose level is >240x the exposure in humans based on unbound  $C_{max}$  in rats dosed with 1000 mg/kg PO.<sup>21</sup> Together, the data indicate a low genotoxic potential for lenvatinib.

### Carcinogenicity

No carcinogenicity studies were submitted, which is acceptable for a pharmaceutical for the treatment of advanced cancer.<sup>22</sup>

### Reproductive toxicity

Embryofetal development studies were conducted in SD rats and NZW rabbits. Studies of fertility, early embryo development and pre/postnatal development were not conducted which is acceptable.<sup>23</sup> The design and conduct of the embryofetal development studies was appropriate. Pregnant animals were exposed to lenvatinib during the period of organogenesis (gestation day [GD] 6-17/18), with appropriate numbers of animals exposed.

Toxicokinetic data were not collected in the embryofetal development data, so exposure ratios were estimated using body surface area. A conversion factor of 6 or 12 was applied for rats and rabbits, respectively. The estimated exposure ratios in the pivotal studies were all very low. Higher doses in the pilot studies were associated with total litter loss due to early resorptions. The exposures achieved were adequate to demonstrate the reproductive toxicity of lenvatinib.

### Relative exposure

Table 5 shows relative exposure.

**Table 5. Relative exposure in repeat-dose toxicity and carcinogenicity studies.**

Species	Study	Dose (mg/kg/day)	Dose (mg/m <sup>2</sup> )	ER <sup>#</sup>
Rat (SD)	Embryofetal development [Study S05152]	0.1	0.6	0.03
		0.3	1.8	0.09
		1	6.0	0.3
Rabbit (NZW)	Embryofetal development [Study S06009]	0.03	0.4	0.02
		0.1	1.2	0.06
		0.5	6.0	0.3
Human (patients)	steady state [Study E7080-J081-105]	24 mg	19.4*	–

# based on body surface area as toxicokinetic data were not collected; \* Dose converted to mesilate salt.

<sup>21</sup> Based on  $C_{max}$  132400 µg/mL in male rats receiving a PO dose of 1000 mg/kg.

<sup>22</sup> International Conference on Harmonisation, "S9: Nonclinical evaluation for anticancer pharmaceuticals", 29 October 2009.

<sup>23</sup> International Conference on Harmonisation, "S9: Nonclinical evaluation for anticancer pharmaceuticals", 29 October 2009.

Placental transfer of lenvatinib was very low following a single 3 mg/kg PO dose of lenvatinib on GD13 or GD18. The ratio of maternal plasma: tissue at the approximate Tmax (0.5h) was  $\leq 0.04$  in foetal plasma and tissues, with the highest level observed in fetal liver. Lenvatinib was excreted in the milk of lactating SD rats following a single 3 mg/kg PO dose on LD 9. The milk to plasma ratio was  $\sim 2$  based on AUC.

Fertility studies were not conducted. However, lenvatinib administration was associated with lesions in male and female reproductive organs in the repeat dose studies. It is expected that female fertility would be impaired by lenvatinib treatment based on decreased menstruation and follicular atresia observed in monkeys at clinically relevant doses (ER 0.6x). Angiogenesis mediated by VEGF is critical for the development and function of the corpus luteum.<sup>24</sup> Therefore, impaired female fertility is an expected effect of VEGF inhibition. Adverse effects in testes were observed in rats and dogs at exposures  $\geq 14x$  that expected at the Maximum Recommended Human Dose (MRHD). Impaired male fertility is also a plausible effect of VEGF inhibition based on its functional role in the testes.<sup>25</sup>

Lenvatinib administration during organogenesis caused increased early resorptions at doses  $\geq 1$  mg/kg/day PO in rats and  $\geq 0.5$  mg/kg/day PO in rabbits (relative exposure  $\leq 0.3x$  based on BSA). Total litter loss occurred at higher doses. Abortions were also induced in rabbits at doses  $\geq 0.5$  mg/kg/day (relative exposure 0.3x). Foetal malformations were observed at doses of  $\geq 0.1$  mg/kg/day in rats and rabbits (relative exposure  $< 0.1x$  for both species). In rats, external malformations (parietal oedema, cryptophthalmia and missing, bent, kinked or short tail), visceral malformations (retroesophageal subclavian artery) and skeletal malformations (discontinuous rib cartilage, hemicentric and/or split cartilage in the thoracic centrum/split vertebral centrum) were observed. Malformations observed in rabbits were short tail, retroesophageal subclavian artery, fused ribs, and vertebral anomalies (absent lumbar vertebra, fused cartilage/hemicentric thoracic centrum, misshapen lumbar arch, and thoracic hemivertebrae). Maternal toxicity (reduced weight gain and food intake) was observed at doses  $\geq 1$  mg/kg/day in rats and  $\geq 0.5$  mg/kg/day in rabbits.

### ***Pregnancy classification***

The sponsor has proposed Pregnancy Category D,<sup>26</sup> which is appropriate based on the teratogenic and embryofetal lethality observed in rats and rabbits. This category is also consistent with that of other multi TKIs.

### **Impurities**

The proposed specifications for impurities and/or degradants in the drug substance and product are acceptable based on ICH guidelines M7, Q3B and S9.<sup>27</sup>

---

<sup>24</sup> Ferrara N, et al., Vascular endothelial growth factor is essential for corpus luteum angiogenesis. *Nat Med.* 4: 336-340 (1998).

<sup>25</sup> Rudolfsson SH, et al. Hormonal Regulation and Functional Role of Vascular Endothelial Growth Factor A in the Rat Testis. *Biol Reprod.* 70: 340-347 (2004).

<sup>26</sup> Category D: "Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details."

<sup>27</sup> International Conference on Harmonisation, "M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk", 23 June 2014; International Conference on Harmonisation, "Q3B(R2): Impurities in new drug products", 2 June 2006; International Conference on Harmonisation, "S9: Nonclinical evaluation for anticancer pharmaceuticals", 29 October 2009.

## Paediatric use

Juvenile rats were more sensitive to lenvatinib compared to adult rats, despite similar or lower systemic exposure. In one week old rats, doses of  $\geq 1$  mg/kg/day PO lenvatinib caused mortality within 2 weeks, whereas doses of  $\leq 25$  mg/kg/day PO for 2 weeks were tolerated in 3 weeks old rats. The toxicity profile was similar in juvenile rats with duodenal lesions and GI toxicity associated with mortality, and similar lesions observed in the other target organs. When dosing was initiated at 3 weeks of age, mortality occurred more rapidly than in comparable doses given to adults (10 mg/kg/day). In addition, lenvatinib was associated with growth retardations and delayed physical and sexual development. Lenvatinib is not proposed to be used in children, but these studies demonstrate that an exacerbation of lenvatinib toxicity is likely to occur in this population. In addition, the observed effects on teeth and bones would be relevant to a paediatric population (see 'Repeat dose toxicity' section).

## Phototoxicity

The phototoxicity of lenvatinib was assessed in a validated in vitro assay (3T3 Neutral Red uptake). Minimal cytotoxicity was observed in the presence or absence of light at lenvatinib concentrations  $\leq 20$   $\mu\text{g/mL}$  (32x clinical total Cmax, and 1854x unbound Cmax). No further testing for phototoxicity was performed which is consistent with ICH guidance.<sup>28</sup>

## Nonclinical summary and conclusions

### Summary

- The nonclinical dossier was of high quality. All pivotal safety studies were Good Laboratory Practice (GLP) compliant. The dossier addressed the requirements of the ICH guideline for anti-cancer pharmaceuticals (S9).<sup>29</sup>
- Lenvatinib inhibited the tyrosine kinase activity of VEGF receptors -1 (Flt-1), -2 (KDR) and -3 (Flt-4) and the proto oncogene RET at clinically relevant concentrations. Lenvatinib is also likely to inhibit PDGF receptor  $\alpha$  and  $\beta$ , FGF receptors FGFR1-4 and KIT clinically. In vitro studies demonstrated inhibition of VEGF signalling and associated angiogenesis by lenvatinib at clinically relevant concentrations. In vivo, lenvatinib inhibited the growth of papillary, follicular, medullary and anaplastic thyroid cancer cell line xenografts in nude mice at estimated exposures at or below that anticipated clinically. Tumour angiogenesis was also inhibited.
- No clinically relevant off target binding was identified in secondary pharmacodynamics studies. Safety pharmacology studies found no adverse effects on the CNS or respiratory systems in rats at high exposure levels. Increased blood pressure was observed in dogs at moderate exposures (9x unbound Cmax at the MRHD). In vitro studies found inhibition of hERG channels, but the IC50 was  $>500$ x the anticipated unbound Cmax, and no QTc prolongation was observed in dogs at exposures 33x unbound Cmax or in monkeys in repeat dose toxicity studies at exposures  $\sim 7$ x unbound Cmax.
- The pharmacokinetics of lenvatinib was similar between monkeys, rats, dogs and humans, making these animals suitable for assessing lenvatinib toxicity. Lenvatinib

<sup>28</sup> International Conference on Harmonisation, "S10: Photosafety evaluation of pharmaceuticals", 13 November 2013.

<sup>29</sup> International Conference on Harmonisation, "S9: Nonclinical evaluation for anticancer pharmaceuticals", 29 October 2009.

had good oral bioavailability in animals and a moderate plasma half-life in animals and humans. Plasma protein binding was high in all species. Lenvatinib was widely distributed with highest levels in the liver and kidneys as well as ocular tissues which showed retention of lenvatinib. Over 70 metabolites of lenvatinib were observed in urine and/or faeces, which were the major routes of excretion. There were no major plasma metabolites identified in humans or animals, except for one in monkeys. The in vitro metabolite profile was similar between human and animal hepatocytes. CYP3A4 was responsible for the majority of metabolism, with aldehyde oxidase also involved.

- Based on in vitro studies, lenvatinib was a substrate for, and weak inhibitor of, P-glycoprotein and BCRP. There was no clinically relevant inhibition or induction of CYP or UGT enzymes in vitro.
- Lenvatinib had a low order of acute toxicity in SD rats, with the acute toxicity in dogs and monkeys also appearing to be low.
- Repeat dose studies by the oral route were conducted in SD rats (up to 6 months), beagle dogs (up to 4 weeks) and cynomolgus monkeys (up to 9 months). Maximum exposures (as unbound AUC) were high in the pivotal studies in rats (15x), low in dogs (0.6x) and moderate in monkeys (4x). Mortality secondary to GI and/or renal toxicity was observed in all species at relative exposures of 4 (in monkeys) or greater.
- The target organs for toxicity were consistent with class effects of receptor tyrosine kinase inhibitors and included the GI tract (in particular duodenum), kidneys, liver and gallbladder/bile ducts, pancreas, bone, teeth, ovaries, testes, epididymides, brain (choroid plexus), adrenals, pituitary, heart and lymphoid tissues. Vascular (arterial) lesions and associated pathology were commonly observed in a variety of anatomical sites, and are related to the pharmacology of lenvatinib. The observed toxicities were generally reversible. However, in some animals severe GI toxicity led to death even after cessation of dosing. There was also an apparent increase in susceptibility to bacterial infection in rats.
- Lenvatinib was not mutagenic in bacterial or mammalian cells in vitro, and was not clastogenic in vivo in a rat micronucleus assay. Carcinogenicity studies were not conducted which is acceptable.
- Reproductive toxicity studies were restricted to embryofetal development in rats and rabbits. Lenvatinib induced abortions (rabbits) and early resorptions (rats and rabbits) and was teratogenic at subclinical exposures. Lenvatinib crossed the placental barrier at low levels, and was excreted in the milk of lactating rats. Effects on male and female fertility were not directly assessed, but could be impaired clinically based on the toxicities observed in ovaries, testes and epididymides in repeat dose toxicity studies.
- The toxicity profile of lenvatinib was similar between juvenile and adult rats, but mortality occurred at lower doses in neonatal rats (PND7), and was accelerated in weanling rats (PND21).
- Lenvatinib was not phototoxic in a validated in vitro assay (3T3 Neutral Red uptake).
- The proposed limits for genotoxic and non-genotoxic impurities were not toxicologically qualified but are adequate based on the proposed indication (treatment of advanced cancer).<sup>30</sup>

---

<sup>30</sup> International Conference on Harmonisation, "S9: Nonclinical evaluation for anticancer pharmaceuticals", 29 October 2009.

## Conclusions

- The primary pharmacology studies support the proposed indication with efficacy against a variety of thyroid cancer cell line xenografts demonstrated in vivo at relevant doses.
- No clinically relevant hazards were identified in secondary and safety pharmacology studies except for hypertension in dogs.
- Repeat dose studies revealed the following findings which may be clinically relevant:
  - Arterial lesions and associated pathology (for example, haemorrhage)
  - Gastrointestinal toxicity (in particular duodenum, and including pancreas)
  - Renal toxicity (glomerulopathy)
  - Hepatotoxicity
  - Ovarian and testicular changes which may impair fertility
  - Endocrine system toxicity (pituitary and adrenals)
  - Increased bacterial infections.
- Lenvatinib does not pose a genotoxic hazard.
- Lenvatinib is a severe reproductive and developmental toxicant. The proposed Pregnancy Category D is appropriate.
- Lenvatinib is excreted in the milk of lactating rats. Juvenile animals are more sensitive to the effects of lenvatinib, even at lower systemic exposures. Therefore, lenvatinib may pose a significant risk to breastfed infants.
- There are no nonclinical objections to registration of Lenvima for the proposed indication.

## 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

#### Clinical rationale

DTC arises from follicular epithelial cells and are generally grouped into 2 cancer types, papillary thyroid cancers and follicular thyroid cancers. Differentiated thyroid cancer is usually asymptomatic for long period and commonly presented as a solitary thyroid nodule. The current treatment of choice for primary DTC is surgery, usually then followed by <sup>131</sup>I ablation and thyroxine therapy. Approximately 1/3 of metastatic thyroid cancers lose functional ability to concentrate iodine and radioiodine treatment may not be as effective. Once RR, DTC exhibits a more aggressive behaviour. The European Society of Medical Oncology and the National Comprehensive Cancer Network Oncology Guidelines 2013 recommend that patients with the RR-DTC move to treatment with anti angiogenic TKIs in clinical trials.

Elevated levels of VEGF have been noted in thyroid tumours. The intensity of VEGF expression has been correlated with a higher risk of metastasis and shorter disease free survival in patients with papillary thyroid cancer; however, its precise role in the

pathophysiology is not clear. The preclinical summary notes that the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone. Therefore, lenvatinib is also being developed as an anticancer therapy for use as in combination with other anticancer agents for the treatment of malignancies including thyroid cancer.

Lenvatinib is an oral, multiple TKIs that inhibits the kinase activities of VEGF receptors in addition to other pro angiogenic and oncogenic pathway related TKIs.

*Comment: The rationale is reasonable. However although the intensity of VEGF expression has been correlated with survival, whether inhibiting a kinase that is involved in this pathway improves survival, or is a correlation is unclear.*

## Guidance

There is a single pivotal trial. The relevant TGA adopted EU guideline<sup>31</sup> was used as a reference in this evaluation.

The EMA CHMP Guidelines on the evaluation of anticancer medicinal products in man<sup>32</sup> was also used as a reference for discussion on appropriateness of the choice of PFS in the pivotal Study 303 in this submission.

The PI was used to examine safety issues for the VEGF inhibitor class, specifically for those that are kinase inhibitors. The following have been in clinical practice for a period of time in a number of population groups: sunitinib, sorafenib, axitinib, regorafenib, etcetera, and also the monoclonal antibodies (mAbs), for example, aflibercept, ramucirumab, or VEGF mAb (for example, bevacizumab).

The PI for the FDA submission for lenvatinib is available on the FDA site.

*Comment: The sponsor has followed the relevant TGA guidance.*

## Contents of the clinical dossier

The clinical dossier documented a full clinical development program of pharmacology, efficacy and safety studies. The submission contained the following clinical information:

- Literature references
- A single pivotal efficacy study, E7080 G000-303. This was a placebo controlled, Phase III study in subjects with RR-DTC.
- Phase II studies. There were 2 open label studies submitted: E7080-J081-208 (A Phase II study in thyroid cancer) and E7080-G000-201 (A Phase II, Multicentre, Open label, Single Arm Trial to Evaluate the Safety and Efficacy of Oral E7080 in Medullary and Iodine-131 Refractory, Unresectable Differentiated Thyroid Cancers, Stratified by Histology). Thus, these included subjects with RR-DTC as well as other forms of advanced thyroid cancer (that is, anaplastic or medullary thyroid cancer).
- Studies in other indications, used for the safety analysis only:
  - Study 701 An Open-Label, Multicentre, Randomised, Phase Ib/II Study of E7080 in Combination With Carboplatin + Gemcitabine Versus Carboplatin + Gemcitabine Alone as Second Line Therapy in Patients With Platinum-Sensitive Recurrent Ovarian Cancer by CA125.

<sup>31</sup> European Medicines Agency, "Points to Consider on Applications with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99)", 31 May 2001.

<sup>32</sup> European Medicines Agency, "Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man: Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials (EMA/CHMP/27994/2008)", 5 December 2011.



- Study 702 An Open Label, Multicentre, Randomized, Phase Ib/II Study of E7080 (Lenvatinib) in Combination with Dacarbazine versus Dacarbazine Alone as First Line Therapy in Patients with Stage IV Melanoma
  - Study 703: Safety Report for A Phase II, Randomised, Double Blind, Placebo Controlled Study of Oral E7080 in Addition to Best Supportive Care (BSC) versus BSC Alone in Patients with Locally Advanced or Metastatic Non Squamous Non-Small Cell Lung Cancer Who Have Failed at Least Two Systemic Anticancer Regimens.
  - Study G000-203: An Open Label, Three Cohort, Phase II Study of E7080 in Subjects With Recurrent Malignant Glioma
  - Study G000-204: An Open Label, Single-Arm, Multicentre Phase II Study of E7080 [Lenvatinib] in Subjects with Advanced Endometrial Cancer and Disease Progression Following First Line Chemotherapy
  - Study G000-205: Safety report only. An Open Label, Multicentre Phase Ib/II Study of E7080 Alone, and in Combination With Everolimus in Subjects With Unresectable Advanced or Metastatic Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment
  - Study G000-206: Safety Report only. An Open Label, 2 Cohort, Multicentre, Phase II Study of E7080 (Lenvatinib) in Previously Treated Subjects With Unresectable Stage III or Stage IV Melanoma
  - Study G000-209: Safety Report only. A Multicentre, Open Label Phase II Study of the Safety and Activity of Lenvatinib (E7080) in Subjects With KIF5B-RET Positive Adenocarcinoma of the Lung
  - Study G000-304. A Multicentre, Randomised, Open Label, Phase III Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma.
  - E7080-J081-110. A Phase I Dose Escalation Study of E7080 in Combination with Carboplatin and Paclitaxel in Patients with Stage IIIB or IV Non-Small Cell Lung Cancer
  - E7080-J081-202: Safety Progress Report. Phase I/II Study of E7080 in Patients With Advanced Hepatocellular Carcinoma (HCC).
- Integrated Safety summary
  - Integrated Efficacy (pivotal study 303)

### Paediatric data

The submission did not submit data to support use in a paediatric population however a Paediatric Investigation Plan (PIP) is agreed in Europe. The date a study is requested to be reported as part of the PIP is June 2018. The sponsor has a waiver from having to submit a Paediatric Assessment in the US. As lenvatinib has been granted orphan drug designation in the US for treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer, the sponsor states it is exempt from the Paediatric Research Equity Act requirements.

*Comment: the sponsor did not specify if there was an unmet need for a treatment in this group. As there is no current data, this drug should not be used in paediatric patients and stated in the PI and CMI until data on efficacy and safety in this group becomes available.*

## Good clinical practice

The clinical studies in the submission complied with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice (as annotated with TGA comments), including appropriate ethical standards.<sup>33</sup>

Specifically, the pivotal study (303) was conducted in accordance with standard operating procedures (SOPs) of the sponsor or designee to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki, 2008;
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use;<sup>34</sup>
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312;
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All suspected unexpected serious adverse reactions (SUSARs) were reported, as required, to the Competent Authorities of all involved EU member states;
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP.

## Pharmacokinetics

### Studies providing pharmacokinetic data

Table 6 shows the studies relating to each pharmacokinetic topic.

**Table 6. Submitted pharmacokinetic studies.**

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK		
	Single dose		
	Bioequivalence †	E7080-A001-008 Open label, randomised, 2 period, 2 sequence crossover study to evaluate BE of 2 oral capsule formulations: both were bioequivalent to the reference formulation.	*
		E7080-A001-001 Comparative bioavailability study of a 10 mg new formulation (capsule) and a 10 mg old formulation	*

<sup>33</sup> "Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)", July 2000.

<sup>34</sup> International Conference on Harmonisation, "E6(R1): Guideline for good clinical practice", 10 June 1996.

PK topic	Subtopic	Study ID	*
		<p>(tablet) of lenvatinib in healthy subjects.</p> <p>Mean total exposure from capsule was approximately 10% less than that of the tablet. Mean Cmax was approximately 14% lower and mean t1/2 and median Tmax values were comparable between the capsule and tablet.</p>	
	Multi dose		
	Food effect	<p>E7080-A001-003</p> <p>Open-label, randomised, 2 way crossover bioavailability study to evaluate the effect of food on the PK of lenvatinib. Total lenvatinib exposure (AUC<sub>0-∞</sub>) for the fed group was ~ 6% greater than that of the fasted group. Cmax for the fed group was variable and 4.5% lower than that of the fasted group. The study was unpowered, the 90% CIs for AUC<sub>0-∞</sub> and AUC<sub>0-t</sub> were within the 80-125% CI BE range.</p>	*
	Drug interaction, healthy volunteers	<p>E7080-A001-004</p> <p>A single centre, randomised, crossover PK study in healthy volunteers to assess the influence of simultaneous CYP3A4 and P-gp inhibition on lenvatinib PK following single dose oral 5 mg ketoconazole increases AUC (15-19%) but no change in t1/2, Tmax</p>	*
		<p>E7080-A001-007</p> <p>A single centre, sequential design, PK study to assess the influence of CYP3A4 induction with multiple doses of rifampin, unbound lenvatinib exposure was reduced about 9% and about 18% for total lenvatinib.</p>	*

PK topic	Subtopic	Study ID	*
PK in special population	Target population (cancer)		
	Multi dose	E7080-E044-101	*
		E7080-A001-102	*
		E7080-J081-103	
		E7080-J081-105	*
		E7080-E044-104 Mass balance study of 14C Lenvatinib	*
	Lung cancer	E7080-J081-110 Phase I dose escalation study of lenvatinib with carboplatin and paclitaxel in Stage IIIB or IV non small cell lung cancer after multiple doses of lenvatinib; PK was not significantly affected by the coadministration	
	Hepatic Impairment	E7080-A001-006	*
	Renal Impairment	E7080-A001-005	*
	Food effect	E7080-A001-003	
		E7080-E044-101 Open label Phase I dose escalation study in subject with resistant and refractory solid tumours or lymphomas; a pilot food effect investigation was initiated once the MTD had been established and at least 12 subjects across both study sites were asked to participate	*
Genetic/ gender related PK	Males versus females	Not undertaken (gender modelled in population model)	
PK interactions		Under drug interactions above	
	Target population		

\* Indicates the primary aim of the study.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration. However, some of the studies included subjects with a variety of tumours including brain, skin, endometrial and haematological malignancies where the clinical pharmacokinetics may to be different.

### Evaluator's conclusions on pharmacokinetics

Levatinib is orally absorbed and does not have a significant extent of absorption interaction with drugs that modify gastric pH nor with a standard food intake. Food affects the rate of absorption however. Levatinib has relatively linear PK between doses of 3.2 to 32 mg QD (once daily), the range that includes the dose in the indication. It has elimination mediated predominantly by cytochrome P450 (CYP) 3A, aldehyde oxidase (AO) and nonenzymatic processes in humans. Urinary and fecal elimination of levatinib are minor pathways in humans,

Both ketoconazole (P-gp and CYP3A inhibitor) and rifampicin (a P-gp and CYP3A inducer) had a small impact on levatinib PK. There are no major circulating metabolites. In human plasma, levatinib accounted for approximately 97% of extracted radioactivity on average across all time points.

Severe renal impairment increases exposure by nearly two fold and severe hepatic impairment increases exposure by 2.7 fold (unbound). No significant ethnic differences were found in levatinib PK, although most patients were Caucasian. There were minimal pharmacokinetic differences between sexes and across the age range in levatinib exposure.

Subjects with body weight <60 kg had 36% higher exposure compared with subjects >60 kg.

Apparent total clearance following oral administration was 15% higher in healthy subjects and was comparable among DTC, medullary thyroid cancer (MTC) and other tumor types.

Overall, the significant pharmacokinetic issues are around the likely CYP3A4 and Pgp interactions, the increased exposure in renal and hepatic disease and the limitations of extrapolating data from the healthy volunteers to the DTC patients.

### Pharmacodynamics

#### Studies providing pharmacodynamic data

Table 7 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

**Table 7. Submitted pharmacodynamic studies.**

PD Topic	Subtopic	Study ID	Summary page
Primary Pharmacology	Effect on tumour size, relationship of exposure to outcome	E7080-G000-201	Clinical studies
	Effect on size on MRI	E7080-J081-103	NFE

PD Topic	Subtopic	Study ID	Summary page
	This study was predominantly a bioavailability study, a PD endpoint length or tumour on DCE-MRI was also measured.	E7080-A001-102	
Secondary Pharmacology	Effect on QTc	E7080-A001-002	
	Cancer biomarkers	E7080-J081-105	NFE - Mean changes in VEGF from baseline at Day 8 and Day 15 of Cycle 1 were 253.43% and 365.39%.
	Cancer biomarkers	E7080-E044-101	6 and added to Summary of the Phase II study E7080-G000-201 to enrich it.
Population PD and PK-PD analyses	Healthy subjects		
	Target population – relationship of exposure to response	E7080-E044-101	8 (clear relationship between exposure and hypertension and proteinuria)

PD endpoints in the Phase I E7080-J081-103 were surrogates in a different indication, the PK data from this study was added to the thyroid cancer population PK study.

E7080-a001-002 was a double blind study in healthy volunteers to assess the effect of E7080 on the QTc interval.

Study E7080-E044-101 included both PK data and PD biomarkers. These were identified and the biological effects of E7080 explored.

In Study E7080-A001-102, which was predominantly a bioavailability study, a PD endpoint DCE-MRI was also measured. Decreases in median Ktrans of tumour lesion (L/min) from baseline to 48 h post baseline were observed for all treatment cohorts.

Study E7080-J081-105 undertook exploratory PD studies and noted the plasma VEGF level tended to increase in subjects at Days 8 and 15 of Cycle 1. Mean changes in VEGF from baseline at Day 8 and Day 15 of Cycle 1 were 253.43% and 365.39%, respectively. In other PD biomarkers, there were no relevant differences.

E7050-G000-901: An Open Label, Multicentre Phase Ib/II Study of E7050 in Combination With E7080 in Subjects With Advanced Solid Tumors (Dose Escalation) and in Subjects With Recurrent Glioblastoma or Unresectable Stage III or Stage IV Melanoma After Prior Systemic Therapy (Expansion Cohort and Phase II). This was excluded from the PD analysis as it was a study in a different disease; however, it did have a safety data, but this was not evaluable in the submission.

Table 8 lists pharmacodynamic results that were excluded from consideration due to study deficiencies.

**Table 8. Pharmacodynamic results excluded from consideration.**

Study ID	PD results excluded
Study e7080-J081-103	Effect on VEGF, SDF1 $\alpha$ and thrombopoietin (increased at doses of 13 mg BID).
Study e7080-E044-101	Effect on PD biomarkers (exploratory)
Study e7080-J081-105	Effect on VEGF and other cancer biomarkers (exploratory PD)

#### Evaluator's conclusions on pharmacodynamics

There are a number of reports with PD endpoint. Most of these were exploratory.

Exposure is likely to be related to both a reduction in tumour size (although there are a number of confounders, and exposure is also related to the risk of hypertension. The relationship of exposure to outcomes appears to be mediated via a reduction in tumour size.

#### Dosage selection for the pivotal studies

The maximum tolerated dose (MTD) was determined to be 25 mg once daily as doses higher than this had a higher rate of associated higher adverse events (AEs) (hypertension and proteinuria). However, it was also noted that an increasing reduction in tumour growth was seen up to 32 mg dose.

Three Phase I studies (E7080-E044-101; E7080-J081-103; and E7080-A001-102) were conducted to determine the MTD of lenvatinib and the optimal frequency of administration. These studies examined escalating doses of lenvatinib administered QD or BID using continuous and interrupted dosing schedules. In Study E7080-E044-101, escalating doses of lenvatinib from 0.2 to 32 mg were given QD in continuous 28 day cycles to 82 subjects with advanced solid tumours. In Study E7080-E044-101, the MTD was determined to be 25 mg QD. Study E7080-A001-102 (monotherapy portion) was a dose escalation study (0.1 to 3.2 mg BID 7 days on/7 days off followed by 3.2 to 12 mg BID continuously) conducted in 77 subjects with solid tumours or resistant/refractory lymphomas. Study E7080-J081-103 was a dose escalation study (0.5 to 20 mg BID) in which 27 subjects with advanced solid tumours who were treated with lenvatinib BID in a 2 week on/1 week off schedule. In Study E7080-J081-103, the MTD was determined to be 13 mg BID.

In Study E7080-E044-101, although there was a trend towards a dose-response relationship with respect to partial response and progressive disease, there was also a clear relationship between dose and the probability of developing hypertension and

proteinuria. Proteinuria was the dose limiting toxicity, and the MTD of lenvatinib was determined to be 25 mg QD because as the dose of lenvatinib increased, the number of subjects requiring a dose reduction did.

The relationship of hypertension to efficacy is discussed in the submission and the sponsor provided an abstract reference which suggests there is a correlation between diastolic hypertension and response for another angiogenesis inhibitor, axitinib.<sup>35</sup>

Although 25 mg once daily was subsequently chosen for the pivotal study, it was acknowledged that maintaining that dosage for long term administration of lenvatinib could be challenging, as dose reductions were required in 54% of subjects. Dose reductions were required for 11% of the subjects with hypertension and for 17% of the subjects with proteinuria.

The starting dose of 25 mg QD was supported however by the population PK/PD analysis of the results from the combined 3 Phase I studies which included E7080-E044-101 (and also E7080-J081-103; and E7080-A001-102). The PK/PD analyses indicated that PFS was better with higher lenvatinib exposure and that other factors including ECOG PS, schedule effect, and development of hypertension or proteinuria were not significant factors. Analyses of response (Partial Response [PR] or durable Stable Disease [SD]) also showed that the probability of achieving a PR or durable SD significantly increased with an increase in C<sub>max</sub>, AUC<sub>0-24h</sub>, and C<sub>min</sub> at steady state and that the dosing schedule (BID versus QD) was not correlated with response. Therefore, it was recommended that the daily dose in future clinical trials be administered QD rather than BID to allow for higher lenvatinib C<sub>max</sub> at steady state. To simplify drug administration, a dosage of 24 mg once daily (two 10 mg capsules + one 4 mg capsule) was selected for continued lenvatinib development.

Following completion of the Phase I trials, the Phase II study E7080-G000-201 was conducted in 117 subjects, 58 subjects with RR-DTC. Lenvatinib dosage was 24 mg QD (2 subjects received 10 mg BID prior to a protocol amendment). The ORR was 50% for RR-DTC subjects, and median PFS was 12.6 months (follow up time of 14 months). There was no comparison group. No direct relationship between lenvatinib exposure (AUC at steady state) and response was detected. Reduction in tumour size was indeed found to be correlated to lenvatinib exposure in this Phase II study.

Based on these results, the current study was conducted using a lenvatinib dosage of 24 mg QD given continuously in 28 day cycles using an algorithm of dose interruptions/reductions and concomitant medications to manage lenvatinib toxicity.

During the conduct of the study, the data monitoring committee (DMC) recommended in February 2013 that the dosage of lenvatinib be reduced to 20 mg QD for subjects entering the OOL Lenvatinib Treatment Period due to frequent dose reductions observed with the 24 mg QD regimen. This change was made in Protocol Amendment 4 (dose reduction was implemented on 16 February 2013). Pursuant to Protocol Amendment 5, the starting dosage of lenvatinib returned to 24 mg QD.

*Comment: The dose chosen for the single pivotal study is appropriate. The ability to reduce the dose as needed for toxicity is noted*

---

<sup>35</sup> Kelly RJ, Rixe O. Axitinib-a selective inhibitor of the vascular endothelial growth factor (VEGF) receptor. *Target Oncol.* 4: 297-305 (2009).



## **Efficacy**

### **Studies providing efficacy data**

Efficacy in the proposed indication is supported by a single pivotal, placebo controlled, Phase III study in subjects with RR-DTC (E7080 G000-303) and 2 open label Phase II studies (E7080-G000-201 and E7080-J081-208) including subjects with RR-DTC as well as other forms of advanced thyroid cancer.

### **Evaluator's conclusions on efficacy**

The submission complies with TGA guidance. The single pivotal trial is noted. The primary endpoint of the pivotal study was achieved. There was a significant difference in lenvatinib versus placebo in PFS. Overall, survival was not significantly different however.

Study design was appropriate.

PFS is a relevant clinical endpoint. The EMA CHMP guidelines<sup>36</sup> were also used as a reference for discussion on appropriateness of the choice of PFS in the pivotal study.

The lack of apparent relationship between PFS and OS is noted.

In the first of the two Phase II studies, the pooled data showed there was very wide variability in AUC. Statistical effects of weight were seen, no differences were noted in age and gender however numbers were small for each stratum.

In the second Phase II study, at the time of data cutoff all evaluable subjects experienced tumour shrinkage after the initiation of lenvatinib treatment. The median PFS in DTC subjects had not yet been reached. The median PFS was 6.5 months (95% CI: 5.6, 7.3) in MTC subjects and 5.5 months (95% CI: 1.4, -) in Anatomical Therapeutic Chemical (ATC) subjects. In all histologic subtypes, the median OS had not yet been reached.

The dose range chosen is reasonable, with the algorithm used in the clinical trial to reduce dose to toxicity.

The clinical studies are reasonably applicable to the predominantly Caucasian, middle age and lack of comorbidity patients; however, the data does not support generalisability to the elderly and children. The findings of the simulated model data and population PK analysis are noted.

Long term efficacy data, especially in the context of a short term drug in a potentially chronic condition is unknown.

## **Safety**

### **Studies providing safety data**

The safety profile is provided by the 3 clinical studies: 452 subjects with RR-DTC and MTC. A total of 7 additional studies provided safety data: 656 subjects in total received lenvatinib.

All subjects had at least one treatment emergent adverse event (TEAE), with profiles seen with other VEGF inhibitors.

---

<sup>36</sup> European Medicines Agency, "Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man: Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials (EMA/CHMP/27994/2008)", 5 December 2011.

### ***Pivotal efficacy study***

In the pivotal efficacy study (303), the following safety data were collected: TEAEs, clinical laboratory test results, vital signs, 12 lead electrocardiogram (ECG) results, and left ventricular ejection fraction (LVEF). The AE verbatim descriptions were classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 16.0). AEs were coded to the MedDRA primary system organ class (SOC) and preferred term (PT). Progression of malignant disease was not recorded as an AE in this study.

AEs of particular interest, based on safety data from lenvatinib clinical and pharmacovigilance databases were closely monitored during the study. These were hypertension, proteinuria, GI events, fatigue, decreased weight, haemorrhagic events, GI perforation and fistula formation events, arterial, venous, and mixed vessel thromboembolic events, pancreatic events, renal events.

After database lock, the following events were identified as clinically significant: hypertension proteinuria, atrial and venous thromboembolic events, renal failure/impairment, liver injury/failure, and posterior reversible encephalopathy syndrome (PRES). These events are referred to as clinically significant AEs in this clinical study report.

Laboratory tests were summarised by visit for all visits with data for at least 10% of subjects in lenvatinib arm and by worst post baseline visit.

*Descriptive statistics for vital sign parameters (sitting systolic and diastolic BP, sitting heart rate, RR, temperature, weight) and changes from baseline were presented by visit for all visits with data for at least 10% of subjects in lenvatinib arm.*

There was no pivotal study that assessed safety as a primary outcome

### **Patient exposure**

The lenvatinib clinical development program (which includes a variety of other cancers) consists of 2 Phase III studies, 18 Phase I/Ib/2 studies in subjects with various cancers, 6 Phase I studies in healthy volunteers, and 1 study each in subjects with renal or hepatic impairment. The safety pooled analyses were based on data from subjects in studies that:

- included subjects with cancer who received lenvatinib continuously as monotherapy
- had a completed primary analysis, and
- had a completed Clinical Study Report: 101, 102 (monotherapy cohort/continuous dosing), 104, 105, 201, 203 (lenvatinib treated/monotherapy cohort), 204, 206, 208, and 303.

Selected safety data have been included for the following studies in healthy subjects, including those that also enrolled subjects with renal or hepatic impairment: E7080-A001-001, E7080-A001-002, E7080-A001-003, E7080-A001-004, E7080-A001-005, E7080-A001-006, E7080-A001-007, and E7080-A001-008.

Patient exposure data includes all studies up to 15 September 2013 for all studies for which study participation was ongoing except the pivotal Study 303 which was 15 Mar 2014.

The main analyses of safety are based on the following 4 analysis sets for the pooled studies, with emphasis on the studies in subjects with DTC.

- DTC Randomised Safety Set which includes placebo treated (n = 131) and lenvatinib treated (n = 261) subjects from the randomised portion only of Study 303.

- DTC Non randomised Safety Set (n = 191), which includes subjects with the proposed indication of DTC from Studies 201 and 208, as well as subjects from the optional open label (OOL) portion of Study 303. All subjects included in this Safety Set received lenvatinib treatment only.
- All DTC Lenvatinib Safety Set (n = 452), which includes all lenvatinib treated subjects from Studies 201, 208, and 303 (both the randomised and the OOL portions of the study).
- Non DTC Monotherapy Safety Set (n = 656), which includes all subjects who received single agent lenvatinib in studies conducted in subjects with cancer, excluding DTC: Studies 101, 102 (monotherapy cohort only/continuous dosing), 104, 105, 201 (MTC subjects only), 203, 204, 206, and 208 (MTC and ATC subjects only).

Individual Studies: Selected safety data (that is, exposure to study drug and TEAEs) were provided for the studies in healthy subjects (Studies 001, 002, 003, 004, 007, and 008) as well as for those that also enrolled subjects with renal impairment (Study 005) or hepatic impairment (Study 006). For the ongoing studies that had not yet reached the protocol specified primary analysis as of 15 September 2013, safety progress reports only are provided. These include the following studies: 202, 205, 304, and 703.

**Table 9. Number of lenvatinib treated subjects by development phase and indication – All Safety Sets.**

Phase Indication	Safety Sets			
	DTC Randomized <sup>a</sup>	DTC Non- randomized <sup>b</sup>	All DTC Lenvatinib <sup>c</sup>	Non-DTC Monotherapy <sup>d</sup>
<b>Phase 1 Studies</b>				
Advanced Solid Tumor	0	0	0	156
<i>Phase 1 Subtotal</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>156</i>
<b>Phase 2 and 3 Studies</b>				
Thyroid Cancer	261	191	452	72
ATC	0	0	0	9
DTC	261	191	452	0
MTC	0	0	0	63

At the time of data cut off, the median duration of treatment with lenvatinib was 11.1 months in the 'All DTC Lenvatinib Safety Set' and 3.5 months in the Non DTC Monotherapy Safety Set. In the DTC Randomised Safety Set, the median duration of treatment was 16.1 months in the lenvatinib arm and 3.9 months in the placebo arm.

**Table 10. Summary of study drug exposure – All Safety Sets.**

Parameter Statistic	Safety Sets				
	DTC Randomized		DTC Nonrandomized	All DTC Lenvatinib	Non-DTC Monotherapy
	Placebo (N=131)	Lenvatinib (N=261)	Lenvatinib (N=191)	Lenvatinib (N=452)	Lenvatinib (N=656)
<b>Duration of Treatment<sup>a</sup>, months</b>					
Mean (SD)	6.1 (5.47)	13.7 (8.24)	10.8 (9.35)	12.5 (8.84)	6.1 (8.25)
Median	3.9	16.1	8.2	11.1	3.5
Q1, Q3	2.1, 8.1	5.9, 19.6	3.9, 15.4	4.7, 18.8	1.6, 7.4
Min, Max	0, 28	0, 31	0.1, 45.9	0.1, 45.9	0.0, 89.6
<b>SY of Treatment<sup>b</sup></b>	67.1	298.8	171.2	470.0	331.1
<b>SY of Exposure<sup>c</sup></b>	65.38	269.45	153.95	423.40	304.91
<b>Cumulative Dose, mg</b>					
Mean (SD)	4311.9 (3669.98)	6573.7 (4289.54)	5555.4 (5157.58)	6143.4 (4697.63)	3143.7 (4005.04)
Median	2856.0	6070.0	4148.0	5252.0	1784.0
Q1, Q3	1536.0, 5904.0	3000.0, 9522.0	1732.0, 7568.0	2162.0, 8871.0	816.0, 3932.0
Min, Max	192, 18336	168, 17232	60.0, 28224.0	60.0, 28224.0	1.6, 32245.5
<b>Average Daily Dose<sup>d</sup>, mg/day</b>					
Mean (SD)	23.3 (1.74)	16.9 (5.13)	17.5 (4.81)	17.2 (5.00)	18.8 (6.00)
Median	24.0	16.2	18.0	16.8	20.5
Q1, Q3	23.8, 24.0	13.4, 21.5	14.1, 21.2	13.7, 21.5	15.2, 24.0
Min, Max	14, 24	6, 25	6.9, 24.0	5.8, 25.5	0.2, 32.0
<b>Relative Dose Intensity<sup>e</sup>, %</b>					
Mean (SD)	97.3 (7.25)	70.4 (21.38)	75.1 (20.73)	72.4 (21.21)	84.5 (18.82)
Median	100.0	67.5	77.6	70.8	92.3
Q1, Q3	99.3, 100.0	55.7, 89.6	59.5, 97.4	57.5, 92.9	73.7, 100.0
Min, Max	57, 100	24, 106	28.8, 100.0	24.3, 106.2	2.8, 100.0
<b>Dose Most Frequently Received<sup>f</sup>, mg</b>					
Mean (SD)	23.8 (1.32)	17.9(6.08)	18.9 (5.35)	18.4 (5.80)	20.0 (6.12)
Median	24.0	20.0	20.0	20.0	24.0
Q1, Q3	24.0, 24.0	14.0, 24.0	14.0, 24.0	14.0, 24.0	16.0, 24.0
Min, Max	14, 24	4, 24	4.0, 24.0	4.0, 24.0	0.2, 32.0
>24	NA	NA	NA	NA	17 (2.6)
24	127 (96.9)	111 (42.5)	78 (40.8)	189 (41.8)	376 (57.3)
20	2 (1.5)	30 (11.5)	47 (24.6)	77 (17.0)	85 (13.0)
>14 - <20	NA	NA	NA	NA	22 (3.4)
14	2 (1.5)	66 (25.3)	41 (21.5)	107 (23.7)	46 (7.0)
>10 - <14	NA	NA	NA	NA	34 (5.2)
10	0	40 (15.3)	18 (9.4)	58 (12.8)	38 (5.8)
8	0	9 (3.4)	6 (3.1)	15 (3.3)	11 (1.7)
>4 - <8	NA	NA	NA	NA	8 (1.2)
4	0	5 (1.9)	1 (0.5)	6 (1.3)	0
<4	NA	NA	NA	NA	19 (2.9)

**Post marketing data**

Not applicable.

**Evaluator's conclusions on safety**

Lenvatinib was associated with significant rates of hypertension, proteinuria, arterial thromboembolic events, renal events, liver events, GI perforation and fistula formation, QTc prolongation, decreased ejection fraction, hypocalcaemia, haemorrhage, and presumed perihematoma edema (PPE). The majority of these events were mild to moderate and did not result in discontinuation of treatment. These AEs are consistent with published data for other TKIs and VEGF/VEGFR targeted therapies.

There were no unexpected AEs.

## First round benefit-risk assessment

### First round assessment of benefits

The benefits of lenvatinib in the proposed usage are:

- Significantly improved PFS.
- Trend towards improved OS.

### First round assessment of risks

The risks of lenvatinib in the proposed usage are:

- Unknown clinical need (does asymptomatic disease need treatment).
- Large incidence of serious AEs.
- Survival benefit unclear.
- Significant interpatient variability in  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ ;
- Likely significant CYP3A4 and Pgp interactions,
- The increased exposure in hepatic disease and patients of small body size
- The  $AUC_{0-\infty}$  of the unbound lenvatinib for subjects with mild, moderate, and severe renal impairment were significantly elevated compared to that for normal subjects.

### First round assessment of benefit-risk balance

The benefit-risk balance of lenvatinib, given the proposed usage, could be favourable for a population with no other treatments: PFS is statistically significantly lengthened. However, the clinical need for this treatment in an asymptomatic group is not clear, notwithstanding the high incidence of potentially life threatening toxicities.

### First round recommendation regarding authorisation

Approval was recommended in the targeted population of RR-DTC.

## Clinical questions

### Additional expert input

- In the pivotal trial the choice of the rank preserving structural failure time (RPSFT) models to re-estimate the survival curves was unclear; and the upper limit of the CI was bordering on 1. The sponsor was requested to consider instead using a marginal structural model based on inverse probability of censoring weighting analysis as this may display CI that cross 1.

### Clinical questions

Responses to questions in some areas needed to be considered to understand the significance of the achievement of primary outcome significance noted in the clinical trial:

1. Firstly, whether placebo was an appropriate comparator in this single pivotal study an understanding of the current comparative treatments in Australia for this group is required and if known, the comparative efficacy (to placebo) of those treatments;

2. Why was placebo chosen as the comparator;
3. The clinical significance of the PFS;
4. The plasma concentrations of a number of blood parameters measured in the exploratory marker are interesting but several appear inconsistent in their magnitude or direction of change of concentration. The sponsor was requested to provide evidence of the clinical relevance of those parameters in PFS, OS or Quality of Life (QoL);
5. The inclusion criteria for the pivotal clinical trial did not include patients who were symptomatic. It is important to clarify if these patients (who clearly have imaging progression) need treatment, specifically as these drugs have significant side effects. The sponsor was requested to advise on the clinical need for this group; and
6. Was there any QoL data collected in this study and, if so, the sponsor be requested to provide it.

### **Second round evaluation**

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

### **Second round benefit-risk assessment**

#### **Second round assessment of benefits**

After consideration of the responses to clinical questions, the benefits of Lenvima in the proposed usage have been reassessed. Although not the requested indication, the potential PFS benefits of a therapy available for RR-DTC with symptomatic progressive disease unresponsive to other therapies could be clinically relevant.

#### **Second round assessment of risks**

No new clinical information was submitted in response to questions. Accordingly, the risks of Lenvima are unchanged from those identified in the first round.

#### **Second round assessment of benefit-risk balance**

The benefit-risk balance of Lenvima, given the proposed usage, is favourable.

The evaluator continues to believe benefit-risk balance of lenvatanib, given the proposed usage, could be favourable for a population with no other treatments: PFS is statistically significantly lengthened. However the clinical need for this treatment in an asymptomatic group is not clear, notwithstanding the high incidence of potentially life threatening toxicities and the lack of clinical evidence to assess the relative risk-benefit of this therapy in terms of QoL.

### **Second round recommendation regarding authorisation**

As the evidence for early versus late use is not made, and the medicine has significant toxicities, it is recommended to change the indication to:

*Lenvima is indicated for the treatment of patients with progressive, symptomatic radioactive iodine refractory differentiated thyroid cancer in whom other treatment options have failed.*

The PI and Consumer Medicines Information (CMI) need to be clear that the treatment improved PFS, although QoL may not be improved, and that the OS was no better than placebo.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted an EU-Risk Management Plan (RMP) version 6.0 dated 26 March 2015 (data lock point: 15 September 2013, 15 March 2014 for Study 303), Australian Specific Annex (ASA) dated February 2015 (align with EU-RMP version 1), and updated ASA version 2 dated August 2015

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 11.

**Table 11: Ongoing safety concerns.**

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> <li>• Hypertension</li> <li>• Proteinuria</li> <li>• Renal failure or impairment</li> <li>• Hypokalaemia</li> <li>• Cardiac failure</li> <li>• Posterior reversible encephalopathy syndrome (PRES)</li> <li>• Hepatotoxicity</li> <li>• Haemorrhagic events</li> <li>• Arterial thromboembolic events (ATEs)</li> <li>• QTc prolongation</li> <li>• Hypocalcemia</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Gastrointestinal perforation and fistula formation</li> <li>• Venous thromboembolic events (VTEs)</li> <li>• Abnormal pregnancy outcome, excretion of lenvatinib in milk</li> <li>• Male and female fertility</li> <li>• Pancreatitis</li> <li>• Bone and teeth abnormalities in the paediatric population</li> <li>• Impaired wound healing</li> </ul>

Summary of safety concerns	
	<ul style="list-style-type: none"> <li>• Interstitial Lung Disease (ILD) like conditions</li> <li>• Potential of lenvatinib for induction/inhibition of CYP-3A4 mediated drug metabolism</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Use in the paediatric population</li> <li>• Use in severe hepatic impairment</li> <li>• Use in severe renal impairment</li> <li>• Use in patients from ethnic origins other than Caucasian or Asian</li> <li>• Use in patients aged <math>\geq 75</math> years</li> </ul>

**RMP evaluator**

The evaluator has noted that haemorrhagic events are listed as an important identified risk. The sponsor states in the EU-RMP that this risk could be due to the inhibition of VEGF.

The sponsor has included all the class effects listed in the EU-RMP on the list of safety concerns. In addition, the sponsor has provided the following comments regarding the issue of impaired wound healing:

*Patients who were about to undergo major surgery up to 1 month or less before starting treatment in clinical studies were not treated with lenvatinib, and all the patients in the lenvatinib studies with impaired wound healing recovered without any serious complications. On this basis, impaired wound healing is not an identified risk but is classified as a potential risk.*

This is acceptable.

Subject to the evaluation outcomes of the nonclinical and clinical aspects of the Safety Specification, it is noted that the following adverse events have occurred in patients in the clinical trials:

- Thrombocytopenia (very common);
- Blood thyroid stimulating hormone (TSH) increase (common).

It is noted that the sponsor has stated in the EU-RMP that thrombocytopenia is:

*reversible and manageable using the dose reduction algorithm in the SmPC.*

Nonetheless, the sponsor should still provide justification as to why they are not considered safety concerns of lenvatinib or add them to the list of safety concerns in the ASA.

The pharmacovigilance and risk minimisation sections should be updated accordingly to provide plans for managing these safety issues.

**Pharmacovigilance plan**

Routine pharmacovigilance has been proposed for all the safety concerns. In addition, Study 201, 208, 211 and 303 have been proposed to monitor the following safety concerns:



- Important identified risk: hypertension, proteinuria, renal failure or impairment, hypokalaemia, cardiac failure, hepatotoxicity, haemorrhage events, arterial thromboembolic events, QTc prolongation, hypocalcaemia;
- Important potential risk: GI perforation and fistula formation, venous thromboembolic events, impaired wound healing, ILD like conditions.

A paediatric investigation plan (Study 207) has been agreed in the EU to monitor 'bone and teeth abnormalities in the paediatric population' (potential risk) and 'use in the paediatric population' (missing information). A drug-drug interaction study has also been proposed to monitor 'potential of lenvatinib for induction/inhibition of CYP-3A4 mediated drug metabolism' (potential risk).

### **RMP evaluator**

Protocols of ongoing and completed studies are not reviewed as part of this evaluation. There are two planned studies listed as additional pharmacovigilance activity:

- Study 211: the sponsor has advised that the primary objective of this study is to determine whether a starting dose of 20 mg or 14 mg QD will provide comparable efficacy with an improved safety profile to 24 mg QD dose. The secondary objective of the study is to evaluate progress free survival period in patients treated with doses of 24 mg, 20 mg and 14 mg QD; to evaluate safety and tolerability of doses of 24 mg, 20 mg, and 14 mg QD of lenvatinib; and to evaluate PK/PD relationship between exposure and efficacy/safety. The expected date for submission of the interim/final report is 31 August 2020.
- The drug-drug interaction study: the sponsor has advised that the aim of the study is to investigate the potential of lenvatinib for CYP3A4 inhibition/induction. The expected date for submission of the interim/final report is March 2018.

The sponsor has advised in the ASA that ongoing and planned studies referenced in the EU-RMP will not be conducted in Australia. The sponsor should clarify whether the study results are applicable to the Australian context.

It is noted that the sponsor stated in the ASA that 'In addition to routine pharmacovigilance measures, the following additional pharmacovigilance activities will occur'. No additional pharmacovigilance activities are listed in the section following the statement. The sponsor should provide clarification to this.

### **Risk minimisation activities**

The sponsor considers no additional risk minimisation is necessary. In addition, the sponsor states in the ASA:

*All of the concerns identified in the EU-RMP are relevant for patients in Australia. The risk minimisation activities proposed in the EU-RMP will be implemented in Australia.*

- Potential for overdose

The sponsor states:

*The highest tested doses of lenvatinib in clinical studies were 32 mg once daily and 20 mg twice daily. Accidental medication errors resulting in single doses of 40 to 48 mg have also occurred in clinical trials. The AEs observed at these doses were primarily hypertension, nausea, diarrhoea, fatigue, stomatitis, proteinuria, headache, and aggravation of PPE. Cases of accidental overdose at higher than tested doses of lenvatinib have been reported. These were either associated with adverse reactions consistent with the known safety profile of lenvatinib, or were without adverse reactions.*

*One subject in the randomisation phase of Study 303 (who had been admitted to Intensive Care Unit with severe hypoxia and respiratory failure secondary to lung metastases and possible opportunistic infection) was accidentally administered a single 144 mg dose of lenvatinib (6 times the recommended dose of 24 mg/day). No TEAEs were reported in association with this overdose. However, as the patient refused intubation and respiratory support and opted for hospice care only, she was withdrawn from the study and discharged to hospice. The subject died of respiratory failure and sepsis 2 days later.*

*One subject participating in Study 304 was accidentally administered a single dose of 120 mg of lenvatinib (10 times the clinical trial dose of 12 mg/day for a subject with hepatocellular carcinoma). The subject was admitted to intensive care in a specialist centre for nephrology with acute renal insufficiency, tumour lysis syndrome, cardiac insufficiency, and pneumopathy. The subject was subsequently transferred back to the study site, withdrew from the study and elected to receive palliative care.*

*There is no specific antidote for overdose with lenvatinib. In case of suspected overdose, lenvatinib should be withheld and supportive care initiated.*

- Potential for transmission of infectious disease

The sponsor states:

*No excipients or materials of animal origin are used in the manufacture of lenvatinib hard capsules; hence, there is no potential for transmission of infectious agents.*

- Potential for misuse for illegal purposes

The sponsor states:

*There have been no psychoactive effects reported with the use of lenvatinib. Therefore, there is no perceived potential for lenvatinib to be used for illegal purposes.*

- Potential for off-label use

The sponsor states:

*Lenvatinib has been developed only for the subset of patients with DTC who are refractory to radioiodine treatment. Patients whose tumour cells retain the ability to uptake radioiodine tend to be cured by standard surgery, radioiodine ablation, and thyroid hormone replacement.<sup>37</sup> Therefore, off-label use of lenvatinib in the broader DTC population seems unlikely in the face of its well-recognized clinical toxicities.*

*A broader indication of thyroid cancer is proposed for registration in Japan, including MTC and ATC. Other TKIs are registered for MTC (Cometriq [cabozantinib] and Caprelsa [vandetanib]) in the EU but none are registered for ATC. Hence, it seems possible that off-label use could occur in this indication.*

*Data from several Phase Ib/II studies have been published on the use of lenvatinib for the treatment of RCC,<sup>38</sup> HCC,<sup>39</sup> endometrial cancer,<sup>40</sup> and melanoma.<sup>41</sup> However,*

<sup>37</sup> Durante C, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab.* 91: 2892-9 (2006).

<sup>38</sup> Molina AM, et al. A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of metastatic renal cell carcinoma (RCC). *Cancer Chemother Pharmacol.* 73: 181-189 (2014).

<sup>39</sup> Ikeda M, et al. Current status of hepatocellular carcinoma in Japan. *Chin Clin Oncol.* 2: 40 (2013).

<sup>40</sup> Vergote I, et al. A phase II trial of lenvatinib in patients with advanced or recurrent endometrial cancer: angiopoietin-2 as a predictive marker for clinical outcomes. 2013 ASCO Annual Meeting poster.

<sup>41</sup> O'Day S, et al. A phase II study of the multitargeted kinase inhibitor lenvatinib in patients with advanced BRAF wild-type melanoma. 2013 ASCO Annual Meeting poster.

*given the early-phase nature of these studies and the multitude of other agents approved for treatment of these conditions, off-label use of lenvatinib in these indications seems unlikely.*

- Potential for paediatric off-label use

The sponsor states:

*DTC is rare in children or adolescents: fewer than 2% of DTC cases occur in individuals below the age of 20 years.<sup>42</sup> Clinical studies in the paediatric RR-DTC indication are scheduled to start at sites in Europe by December 2014, which will be prior to commercial launch of lenvatinib in the adult DTC indication; therefore, off label use for DTC in the paediatric population is expected to be negligible.*

### **RMP evaluator**

The sponsor's justification on routine risk minimisation is acceptable.

### **Reconciliation of issues outlined in the RMP report**

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

#### **Recommendation #1 in RMP evaluation report**

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

#### **Sponsor response**

No safety concerns have been raised by the nonclinical or clinical evaluators that require amendments to the RMP at this time. Should any safety considerations be raised later in the evaluation, where applicable, the sponsor will provide information that is relevant and necessary to address the issue in the RMP.

#### **Evaluator's comment**

The evaluator has noted the sponsor's response. The nonclinical evaluation report has recommended correction to the RMP document. The sponsor should update the RMP document as required by the nonclinical evaluator.

#### **Recommendation #2 in RMP evaluation report**

Subject to the evaluation outcomes of the nonclinical and clinical aspects of the Safety Specification, it is noted that the following AEs have occurred in patients in the clinical trials:

- Thrombocytopenia (very common);
- Blood thyroid stimulating hormone (TSH) increase (common).

It is noted that the sponsor has stated in the EU-RMP that thrombocytopenia is 'reversible and manageable using the dose reduction algorithm in section 4.2 of the SmPC'. Nonetheless, the sponsor should still provide justification as to why they are not

---

<sup>42</sup> Agate L, et al. New and old knowledge on differentiated thyroid cancer epidemiology and risk factors. *J Endocrinol Invest.* 35 (6 Suppl): 3-9 (2012).

considered safety concerns of lenvatinib or add them to the list of safety concerns in the ASA.

### ***Sponsor response***

Referencing the “All DTC Lenvatinib Safety Set” (n = 452), TEAEs of thrombocytopenia and platelet count decreased were reported in 7.7% and 5.5% of subjects, respectively. The overall combined frequency was 12.4% (56 subjects). The majority of events were CTCAE Grade 1 or 2. There was 1 SAE (0.2%) each of thrombocytopenia and platelet count decreased and while the TEAEs did result in dose interruption or dose reduction, there were none that resulted in treatment discontinuation.

Thrombocytopenia (and the related event, platelet count decreased) is considered an AE related to lenvatinib and is listed in the “Adverse Effects” section of the Australian PI as “Very Common.” The information presented above (specifically pertaining to the severity of events) shows that the majority of events were Grade 1 or 2, very few were serious, and there was a lack of treatment discontinuations as a result). Therefore, using the regulatory definitions per the EU “Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 1)” adopted by the TGA, the sponsor does not consider this event as “Important.” For this reason, the AE term “thrombocytopenia” does not warrant inclusion as an identified risk in the RMP. The statement in the EU-RMP that thrombocytopenia is ‘reversible and manageable using the dose reduction algorithm in Section 4.2 of the SmPC’ is supported.

### ***Blood thyroid stimulating hormone (TSH) increased***

Blood TSH increased and hypothyroidism has been reported with the VEGF targeted agents and are included as “Common” in the “Adverse Effects” section of the Australian PI.<sup>43</sup> An overview of the frequency and severity of these terms in the “All DTC Lenvatinib Safety Set” (n = 452) is presented. The TEAEs were of mild/moderate severity and did not result in dose reduction or interruption or treatment discontinuation. This may have been due to regular monitoring of thyroid function in the clinical trial setting and hence adjustment of thyroid replacement therapy. The current EU SmPC contains the following text in Section 4.4, Special warnings and precautions for use:

*Lenvatinib impairs exogenous thyroid suppression. TSH levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient’s therapeutic target*

to reflect the potential for the drug to affect thyroid function. The sponsor proposes to include this statement in the “Precautions” section of the Australian PI but to not include this as an important identified risk in the RMP. Similar wording is included in the US PI however the EU SmPC wording will be included in the Australian PI.

### ***Evaluator’s comment***

The sponsor’s response is acceptable. It is recommended to the Delegate that the following statement proposed by the sponsor be included under ‘Precaution’ in the PI:

*Lenvatinib impairs exogenous thyroid suppression. Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient’s therapeutic target.*

### ***Recommendation #3 in RMP evaluation report***

The pharmacovigilance and risk minimisation sections should be updated accordingly to provide plans for managing these safety issues.

<sup>43</sup> Haraldsdottir S, Shah MH. New era for treatment in differentiated thyroid cancer. *Lancet* 384: 286-8 (2014).

**Sponsor response**

See response at #2.

**Evaluator's comment**

The sponsor has provided acceptable response.

**Recommendation #4 in RMP evaluation report**

The sponsor has advised in the ASA that ongoing and planned studies referenced in the EU-RMP will not be conducted in Australia. The sponsor should clarify whether the study results are applicable to the Australian context.

**Sponsor response**

The ASA has been updated with this information.

**Evaluator's comment**

The evaluator has noted the addition of table 3.4 'Studies referenced in the pharmacovigilance plan of the RMP', which includes justification to the relevance of studies to Australia. The sponsor's response is satisfactory.

**Recommendation #5 in RMP evaluation report**

It is noted that the sponsor stated in section 2.3 of the ASA that 'In addition to routine pharmacovigilance measures, the following additional pharmacovigilance activities will occur'. No additional pharmacovigilance activities are listed in the section following the statement. The sponsor should provide clarification to this.

**Sponsor response**

Details of additional pharmacovigilance activities have been added the ASA.

**Evaluator's comment**

The sponsor states in the ASA:

*There will be no additional pharmacovigilance measures conducted in Australia.*

The sponsor should note: all the planned and ongoing studies involving Australian patients that have been considered as pharmacovigilance measures are 'additional pharmacovigilance activities' conducted in Australia. The sponsor should revise this in its next ASA update.

**Summary of recommendations**

It is considered that the sponsor's response to the TGA Section 31 Request has adequately addressed most issues identified in the RMP evaluation report. Outstanding issues are below.

**Outstanding issues***Issues in relation to the RMP*

**Recommendation 1:** The evaluator has noted the sponsor's response. The nonclinical evaluation report has recommended correction to the RMP document. The sponsor should update the RMP document as required by the nonclinical evaluator.

**Recommendation 2:** The sponsor's response is acceptable. It is recommended to the Delegate that the following statement proposed by the sponsor be included under 'Precaution' in the PI:

*Lenvatinib impairs exogenous thyroid suppression. Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone*

*administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.*

**Recommendation 5:** The sponsor states in the ASA: 'There will be no additional pharmacovigilance measures conducted in Australia.'

The sponsor should note: all the planned and ongoing studies involving Australian patients that have been considered as pharmacovigilance measures are 'additional pharmacovigilance activities' conducted in Australia. The sponsor should revise this in its next ASA update.

**Recommendation 9:** The evaluator has noted that the sponsor has agreed to the recommended PI changes. The recommendations remain for Delegate's consideration.

### ***Comments on the safety specification of the RMP***

#### *Clinical evaluation report*

The Prescription Medicines Authorisation Branch of the TGA has provided the following comments in the clinical evaluation report:

*The Safety Specification in the draft RMP is satisfactory.*

#### *Nonclinical evaluation report*

The Scientific Evaluation Branch of the TGA has provided the following comments in the nonclinical evaluation report:

*Results and conclusions drawn from the nonclinical program for lenvatinib detailed in the sponsor's draft RMP (Part II Module SII) are in general concordance with those of the Nonclinical Evaluator. However, the statement on page 18 regarding no effect of lenvatinib on blood pressure in dogs that received up to 0.5 mg/kg lenvatinib omits the observed increase in blood pressure at higher doses in dogs (6, 30 mg/kg). This should be added, with hypertension included as an "Important nonclinical safety findings (confirmed by clinical data)" on page 23.*

#### *RMP evaluator comment*

Hypertension is listed as an important identified risk in the RMP. Nonetheless, the evaluator supports the recommendation made by the nonclinical evaluator. The sponsor should revise the RMP documents as required.

### ***Suggested wording for conditions of registration***

#### *RMP*

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

*Implement EU-RMP version 6.0 dated 26 March 2015 (data lock point: 15 September 2013, 15 March 2014 for Study 303) with ASA version 2 dated August 2015 and any future updates as agreed by the TGA as a condition of registration.*

## **VI. Overall conclusion and risk/benefit assessment**

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

## Quality

The clearance document was considered. The absence of bioequivalence studies of 4 mg and 10 mg capsules was accepted. The lack of absolute bioequivalence data was drawn to the Delegate's attention. The GMP status of the site of drug substance manufacture was discussed.

There were no objections to registration on chemistry/biopharmaceutic grounds.

## Nonclinical

There were no objections to registration for the proposed use. The nonclinical evaluator considered the proposed Pregnancy Category D to be appropriate.

## Clinical

The clinical evaluator supported a narrower indication:

*Lenvima is indicated for the treatment of patients with progressive, symptomatic radioactive iodine refractory differentiated thyroid cancer in whom other treatment options have failed*

The evaluator emphasised that the PI should make clear that quality of life may not be improved and that OS was not formally shown to be better than in the placebo arm.

## Overview of data

There was one pivotal study, E7080 G000-303. This was a Phase III, placebo controlled study in subjects with RR-DTC.

In addition, there were two Phase II, single arm, open label studies that included RR-DTC patients as well as patients with other advanced thyroid cancers: E7080-J081-208 and E7080-G000-201.

Studies in other indication were also provided in the submission to inform safety. Many of these are too removed from the proposed usage to be informative (for example, use in a different cancer type and in combination with other agents).

## Pharmacokinetics

Some PK considerations are:

- A pronounced food effect is **not** apparent (Study E7080-E044-101), though C<sub>max</sub> was reduced somewhat with a high fat breakfast, and T<sub>max</sub> prolonged from 2 to 4-5 h
- Half-life is 28 h. Steady state is achieved in 5 days, with little accumulation.
- Lenvatinib is a substrate for P-gp and BCRP. The clinical evaluator noted that BCRP inhibition may result in altered lenvatinib exposure. Lenvatinib is a weak inhibitor of P-gp transport.
- In vitro data suggested lenvatinib inhibits CYP2C8 and CYP3A4, but modelling suggested a low risk of interaction with midazolam (CYP3A4 substrate) and repaglinide (CYP2C8 substrate). Modelling may not be predictive of a clinical effect.
- In vitro, **CYP3A4** was the predominant isoform for P450 mediated metabolism. There was a modest change in exposure to lenvatinib in subjects given rifampin or ketoconazole, but the clinical evaluator considered that even changes in AUC of the order of 9-19% might be relevant, based on the toxicity profile seen in the dose-ranging studies.

- Mass balance study (E7080-E044-104) identified multiple metabolic pathways, demethylation via CYP3A4 to “M2” being one, and metabolism by aldehyde oxidase being another. Non-enzymatic processes were also invoked. Each of these pathways of lenvatinib clearance (CYP3A4; AO; non-enzymatic) has a similar contribution to overall clearance.
- Metabolism occurs in both liver and kidney; excretion is primarily of metabolites and primarily in bile (~64% of radioactivity was recovered in the faeces; ~25% in urine; in total, only a small fraction was unchanged lenvatinib).
- Exposure to unbound lenvatinib as measured by  $AUC_{0-\infty}$  was lower in mild renal impairment, 29% higher in moderate renal impairment, and 84% higher in severe renal impairment, relative to healthy subjects. Patients with ESRD were not studied. There was no pronounced increase in total (bound and unbound) exposure, even with severe renal impairment (a 22% increase).
- Severe hepatic impairment increased exposure to unbound lenvatinib, so that  $AUC_{0-\infty}$  was 2.7 fold higher than in patients with normal hepatic function (and exposure to total lenvatinib was also substantially higher). Little difference was noted for moderate hepatic impairment.
- There was no clear cut interaction with gastric pH modifying agents.
- In population PK analysis E7080-002R-v1, an effect of body weight on PK was noted. This was also noted in population PK analysis E7080-007R-v1. Subjects weighing <60 kg had 36% higher exposure than subjects >60 kg.
- In Study E7080-G000-201, there was a correlation between lenvatinib exposure and reduction in tumour growth, but AUC did not predict PFS in DTC patients. There was a correlation between exposure and increasing blood pressure and also between exposure and proteinuria.

### Pharmacodynamics

In the pivotal study, no clear correlation was seen between lenvatinib exposure and PFS. In the same study, there was a correlation between lenvatinib exposure and grade 2+ hypertension. The clinical evaluation report states that treatment emergent hypertension was associated with greater tumour shrinkage, higher response rates and longer median PFS and OS.

### Efficacy

Dosage selection for the pivotal study is considered and is relevant given the post approval requirements in the US / EU for studies of lower starting doses. It is noted that during conduct of the pivotal study, the Data Monitoring Committee recommended that the starting dose be dropped from 24 mg to 20 mg (since there were frequent dose reductions with 24 mg QD); later the 24 mg starting dose was re-instated. This appears to have applied to patients enrolled in the optional open label treatment period (that is, patients crossing over from placebo post progression).

#### **Study E7080 G000-303 (“303”)**

This was a randomised, double blind, placebo controlled, Phase III study of lenvatinib in 131-Iodine refractory DTC. The primary endpoint was PFS. The study was conducted at 117 sites globally from 2011 to 2013 (the data cut off for the primary analysis was 15 November 2013). Patients needed 131-Iodine refractory or resistant disease, but also evidence of disease progression within 12 months. Patients could have no prior VEGF or VEGFR targeted therapy or 1 prior such therapy (but not 2+ such therapies).

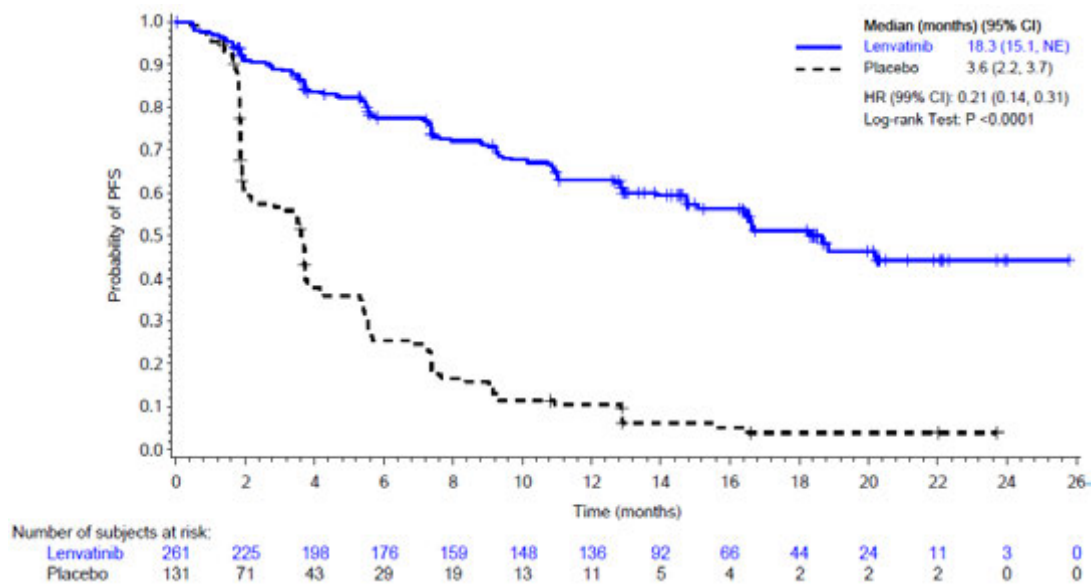


Randomisation was 2:1 (lenvatinib; placebo). The starting dose was 24 mg once daily, continuously. Subjects in the placebo arm could opt into open label lenvatinib treatment on progression.

A total of 261 subjects were randomised to receive lenvatinib, and 131 to receive placebo. Baseline characteristics were broadly balanced, except for gender (48% of lenvatinib subjects were male; 57% of placebo subjects were male). A slightly higher proportion of subjects had TSH 2-5.5  $\mu$ U/mL in the lenvatinib arm (3.8% versus 0.8%) suggestive of incomplete suppression by thyroxine. In the lenvatinib arm, the proportion with ECOG PS = 0 was greater than in the placebo arm (55% versus 52%) but so was the proportion with ECOG PS >1 (5% versus 1.5%).

There was a distinct improvement in PFS in patients receiving lenvatinib; median PFS using independent imaging review was 18.3 months in the lenvatinib arm, 3.6 months in the placebo arm (the stratified HR was 0.21 [95% CI 0.14-0.31]) as shown in figure below.

**Figure 4. PFS.**



ORR was 65% for lenvatinib, 1.5% for placebo: a dramatic effect. ORRs favour lenvatinib in each case (often by a large margin).

OS was similar across arms; an explanation may be crossover post progression (83% of placebo subjects crossed after progression). No OS detriment was apparent in the lenvatinib arm. RPSFT modelling was also supportive of no detriment, but has significant in built limitations.

Quality of life was not addressed, which is unfortunate given the reliance on PFS as the primary endpoint, the potentially long duration of treatment, and the clear toxicity of the agent (while some toxicities such as hypertension and proteinuria can occur in the absence of symptoms, they may cause symptomatic complications; and other toxicities such as diarrhoea are clearly likely to influence QoL).

### **Other studies**

Studies E7080-G000-201 and E7080-J081-208 were considered.

The evaluation of these studies contributed little extra to the benefit-risk balance for the proposed use, although variability across subjects in lenvatinib exposure was noted to be significant, and without obvious explanation.

It was noted:

*With mutation data available from only a limited number of subjects, the influence of KRAS, NRAS, VHL and/or BRAF [tumour mutation status] for DTC subjects and RET, PIK3CA and/or VHL for MTC subjects on the effect of lenvatinib on tumour size could not be detected.*

## Safety

Since lenvatinib inhibits the VEGF pathway, class side effects of VEGF inhibitors were considered to be AEs of particular interest.

The most robust safety data for lenvatinib in the proposed use comes from Study 303, though other analysis sets were defined, for example, the all DTC lenvatinib safety set (n = 452; median duration of treatment 11.1 months). Drug exposure is tabulated. Of interest, in Study 303, the dose most frequently received was 20 mg, not 24 mg; but a sizeable number of subjects most frequently received 14 mg or 10 mg; overall, 90% of lenvatinib patients needed dose modifications.

In Study 303 (“DTC randomised set”), prominent AEs for lenvatinib were hypertension (69% lenvatinib versus 15% placebo), diarrhoea (67% versus 17%), decreased appetite (54% versus 18%), weight decreased (51% versus 15%), nausea (47% versus 25%), fatigue (43% versus 24%), headache (38% versus 12%), stomatitis (37% versus 7%), vomiting (36% versus 15%), proteinuria (34% versus 3%), palmar-plantar erythrodysesthesia (32% versus 1%) and dysphonia (31% versus 5%). These significant imbalances extended to grade 3-4 events (grade 3-4 hypocalcaemia was also imbalanced: 5% versus 0%) and treatment related AEs. Evidently length of exposure varied across arms. Incidence rates remained distinctly imbalanced (that is, >2 fold difference) for diarrhoea, hypertension, headache, stomatitis, proteinuria, PPE, dysphonia, myalgia, abdominal pain and rash.

The significant imbalance in serious AEs is worth noting in the table below.

**Table 12. Serious AEs.**

MedDRA Preferred Term	Safety Sets				
	DTC Randomized		DTC Non-randomized	All DTC Lenvatinib	Non-DTC Monotherapy
	Placebo (N=131) n (%)	Lenvatinib (N=261) n (%)	Lenvatinib (N=191) n (%)	Lenvatinib (N=452) n (%)	Lenvatinib (N=656) n (%)
Subjects with at least 1 SAE	31 (23.7)	139 (53.3)	98 (51.3)	237 (52.4)	314 (47.9)
Pneumonia	3 (2.3)	10 (3.8)	5 (2.6)	15 (3.3)	12 (1.8)
Dehydration	0	7 (2.7)	7 (3.7)	14 (3.1)	19 (2.9)
Hypertension	0	9 (3.4)	3 (1.6)	12 (2.7)	18 (2.7)
Hypotension	0	4 (1.5)	5 (2.6)	9 (2.0)	9 (1.4)
Pulmonary embolism	2 (1.5)	5 (1.9)	4 (2.1)	9 (2.0)	17 (2.6)
General physical health deterioration	0	7 (2.7)	1 (0.5)	8 (1.8)	12 (1.8)
Malignant pleural effusion	1 (0.8)	3 (1.1)	5 (2.6)	8 (1.8)	0
Asthenia	0	2 (0.8)	4 (2.1)	6 (1.3)	8 (1.2)
Atrial fibrillation	0	2 (0.8)	4 (2.1)	6 (1.3)	2 (0.3)
Decreased appetite	0	2 (0.8)	4 (2.1)	6 (1.3)	8 (1.2)
Abdominal pain	0	1 (0.4)	4 (2.1)	5 (1.1)	21 (3.2)
Dyspnoea	5 (3.8)	3 (1.1)	2 (1.0)	5 (1.1)	9 (1.4)
Vomiting	0	4 (1.5)	1 (0.5)	5 (1.1)	19 (2.9)
Dysphagia	3 (2.3)	3 (1.1)	1 (0.5)	4 (0.9)	2 (0.3)
Diarrhoea	0	2 (0.8)	1 (0.5)	3 (0.7)	14 (2.1)
Haemoptysis	3 (2.3)	0	2 (1.0)	2 (0.4)	2 (0.3)
Nausea	1 (0.8)	0	1 (0.5)	1 (0.2)	18 (2.7)

Accompanying the reports of hypertension were three cases of posterior reversible encephalopathy syndrome (PRES) in the lenvatinib safety set.

About 15% of lenvatinib subjects discontinued treatment prior to disease progression, because of AEs, and this is after attempts to titrate the dose downwards.

Review of laboratory abnormalities also detected a small proportion of subjects in the lenvatinib arm with LFT derangements, none meeting 'Hy's Law' criteria. There were a similar small proportion of subjects in the lenvatinib arm with elevated amylase and/or lipase, apparently in the absence of clinical acute pancreatitis.

Lenvatinib changed the proportion of subjects whose TSH remained suppressed. Thyroxine is often part of treatment of DTC, to suppress TSH and so prevent TSH induced tumour growth. It is also required after thyroidectomy. Given efficacy reported above, and the ease of monitoring thyroid function and dose adjustment, this is not a major concern, although 14 subjects in Study 303's lenvatinib arm reported hypothyroidism (versus no subjects in the placebo arm). In the RMP evaluation report, this topic is discussed:

*Blood thyroid stimulating hormone (TSH) increased and hypothyroidism have been reported with the VEGF-targeted agents and are included as "Common" in the "Adverse Effects" section of the Australian PI...*

It is noted that sorafenib's PI includes a Precaution on this topic:

*In the DTC clinical trials, increases in TSH levels above 0.5mU/L were observed in Nexavar treated patients. When using Nexavar in differentiated thyroid carcinoma patients, close monitoring of TSH level and appropriate adjustment of thyroxine dosing is recommended.*

There was a signal that lenvatinib may induce QTc prolongation, at least in patients with DTC. This signal is despite a 'negative' thorough QT study. There were no reports of ventricular tachycardias/TdP. Diarrhoea, hypokalaemia and QTc prolongation together were seen in multiple patients.<sup>44</sup>

Renal impairment was more common with lenvatinib than with placebo, and this extended to acute renal failure.

Gastrointestinal perforation/fistula formation was also seen, rarely, in lenvatinib arm subjects.

### **Risk management plan**

The RMP proposed by the sponsor was considered generally acceptable by the TGA's RMP Evaluation area. A recommended condition of registration is:

*Implement EU-RMP version 6.0 dated 26 March 2015 (data lock point: 15 September 2013, 15 March 2014 for Study 303) with ASA version 2 dated August 2015 and any future updates as agreed by the TGA as a condition of registration.*

<sup>44</sup> European Medicines Agency, "Lenvima: European Public Assessment Report (EPAR) (EMA/250082/2015)", 26 March 2015.

---

## Risk-benefit analysis

### Delegate's considerations

#### *Efficacy*

A single pivotal study was provided in support of the proposed use. In terms of efficacy, this is acceptable since there was a large magnitude of effect accompanied by strong statistical significance. Also, results were consistent across subsets.

The TGA clinical evaluator notes that the pivotal study did not provide strong evidence for use in the elderly and in children. While DTC can occur in children, lenvatinib has a mechanism of action that suggests specific toxicity in young children. The PI contains a suitable warning in the Dosage and Administration section:

*Lenvatinib must not be used in children younger than 2 years of age because of safety concerns identified in animal studies. The safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established (see CLINICAL TRIALS). No data are available.*

Similarly, for the elderly, the PI states, reasonably:

*No dose adjustment is required on the basis of age. Limited data are available on the use in patients aged  $\geq 75$  years.*

The TGA evaluator notes that long term efficacy is unknown, and that this is relevant given that the condition may be 'chronic' in some. While this is true, the follow-up in Study 303 was reasonable given that patients had progressive, 131-Iodine refractory DTC.

#### *Dose*

FDA and EMA have asked for studies of lower starting doses. In both jurisdictions, the 24 mg starting dose was thought to have a positive benefit-risk balance, but there was a view that a lower starting dose should be studied to determine if it might have an improved benefit-risk balance. Refer also to discussion in the FDA Cross Disciplinary Team Leader's report.

#### *Indication and overall benefit-risk balance*

The sponsor's proposed wording is:

*Lenvima is indicated for the treatment of patients with progressive, radioactive iodine refractory differentiated thyroid cancer.*

In Study 303, almost all patients had distant metastases at baseline; 4/261 patients (in the lenvatinib arm) had locally advanced disease.

The FDA approved indication is narrower than the one proposed in Australia, due to restriction to locally recurrent or metastatic disease. All patients will have had surgery, so progressive disease must be locally recurrent or metastatic.

The EMA's approach was to refer to locally advanced or metastatic disease. This would rule out use in patients with no metastases and with locally recurrent disease that was not advanced.

An alternative would be to specify use in metastatic disease, since almost all patients in Study 303 did have metastatic disease at baseline. However, it is reasonable to include patients with locally advanced disease, where surgery is less likely to be curative, given there is also a requirement for radioiodine-refractory disease.

The clinical evaluator proposed a 'last line' indication however there is a reasonable body of evidence from Study 303 in patients who were sorafenib-naïve. A 'last line' use would consign patients to receiving sorafenib and theoretically doxorubicin before use. While

lenvatinib was not studied head-to-head with sorafenib, there was no indication from gross cross study comparison that outcomes were worse with lenvatinib than with sorafenib; and while toxicities varied across agents, both carry significant safety risks so it cannot be said with any confidence that one is clearly safer than the other (see EPAR).

The Delegate supports the following indication:

*Lenvima is indicated for the treatment of patients with progressive, locally advanced or metastatic, radioactive iodine refractory differentiated thyroid cancer.*

### **GMP status**

The clearance note draws attention to the GMP status of the site of the drug substance manufacturer. On balance, the Delegate considers that manufacturing and quality control procedures are acceptable. This is because: there was previous clearance at that site; there is a current application for renewal; no issue with the site is known to the Chemistry stream leader at TGA, and it appears likely that this site is also used to supply lenvatinib to other countries<sup>45</sup> but there has been no major issue with manufacture/quality control of lenvatinib drug substance arising overseas, to the Delegate's knowledge.

### **Summary of issues**

Lenvatinib is a TKI with anti angiogenic properties, proposed for use in patients with progressive RR-DTC.

There was only one pivotal study (Study 303). This study was well designed and conducted. Its inclusion/exclusion criteria allowed for extrapolation of outcomes to most of the proposed target population. There was a valuable treatment benefit, with a dramatic extension in the time patients remain progression free (relative to placebo), from ~4 to ~18 months (accepting that PFS provides a relevant benefit to patients in this setting, and in the absence of a sign that overall survival is worsened). The estimated benefit relative to placebo was clearly statistically significant. A subgroup analysis of PFS showed similar efficacy across important subgroups.

Quality of life was not measured, and this was considered a deficiency.

In the same study, lenvatinib demonstrated substantial toxicity. This was in keeping with its known pharmacological effects. Severe or life threatening reactions were very common, and there was an imbalance in toxicity even after adjusting for the distinct imbalance in exposure across arms. In ~90% of subjects, dose modification was required. However, it is relevant that duration of treatment with lenvatinib was substantially longer than with placebo, suggesting dose modification is feasible in dealing with toxicity, for most patients.

The sponsor is committed to conducting a study of alternative starting doses, and this study's results should be provided to the TGA when available.

### **Proposed action**

If the sponsor provides a suitably modified PI document, the Delegate will approve the application to register lenvatinib for the following indication:

*Lenvima is indicated for the treatment of patients with progressive, locally advanced or metastatic, radioactive iodine refractory differentiated thyroid cancer.*

The Delegate proposes to request from the company a commitment to provide the TGA with results from the planned study of alternative, lower starting doses in DTC, when the

---

<sup>45</sup> For example, the FDA Chemistry review notes lenvatinib is manufactured under cGMP by Eisai Co Ltd at its Kashima Plant in Japan. Also, the EMA Rapporteur day 80 critical assessment report on quality aspects notes the same plant as the source of drug substance (Kashima Plant, 22 Sunayama, Kamisu-shi).

Clinical Study Report is available. The midazolam-lenvatinib interaction study results should also be provided when available.

### **Request for ACPM advice**

Lenvatinib has orphan designation in Australia, for DTC. In the US, lenvatinib also has orphan status for DTC. Lenvatinib is approved for use in DTC in the US. The TGA website states:

***If FDA has approved an orphan drug product for marketing in the USA***

*Evaluation of the application for registration on the ARTG may be expedited if you can assist us in obtaining copies of the complete FDA evaluation report(s).*

*In this case:*

- *provide a comprehensive summary of the similarities/differences between the data package submitted to TGA and the data packages submitted to the FDA*
- *Include this when submitting the registration dossier.*

*Note: This situation will not apply if FDA approval is not recent (more than 2 years) and/or you have become aware of any additional safety issues.*

In the spirit of this policy, and given access to US review documents at Drugs@FDA and the EMA European Public Assessment Report (EPAR)<sup>46</sup> (and other EMA review documents), the Delegate thinks it reasonable to use US FDA and EU EMA critiques of the lenvatinib DTC submission as sources of 'advice' about this application.

The Delegate elects not to consult the Advisory Committee on Prescription Medicines (ACPM) as after reviewing FDA and EMA documents and has no substantial questions.

### **Advisory committee considerations**

The ACPM was not consulted for this submission.

### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Lenvima (lenvatinib as lenvatinib mesilate) 4 mg and 10 mg hard capsules indicated for:

*Lenvima is indicated for the treatment of patients with progressive, locally advanced or metastatic, radioactive iodine refractory differentiated thyroid cancer.*

### **Specific conditions of registration applying to these goods**

- The lenvatinib (lenvatinib as mesilate) EU-RMP version 6.0 dated 26 March 2015 (data lock point: 15 September 2013, 15 March 2014 for Study 303) with ASA version 2 dated August 2015 and any future updates as agreed by the TGA will be implemented in Australia.

---

<sup>46</sup> European Medicines Agency, "Lenvima: European Public Assessment Report (EPAR) (EMA/250082/2015)", 26 March 2015.

## **Attachment 1. Product Information**

The PI approved for Lenvima at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia  
Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605  
<https://www.tga.gov.au>