Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sorafenib

Proprietary Product Name: Nexavar

Sponsor: Bayer Australia Ltd

August 2014

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 <http://www.tga.gov.au>.

About AusPARs

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

Contents

List of common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the curve
Cmax	Maximum concentration
CR	Complete Response
CT	X-Ray Computed Tomography
CV	Coefficient of Variation
DCR	Disease Control Rate
DoR	Duration of Response
DTC	Differentiated Thyroid Cancer
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FACT-G	Functional Assessment of Cancer Therapy: General
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRQoL	Health Related Quality of Life
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
LDH	Lactate Dehydrogenase
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
OS	Overall Survival

Abbreviation	Meaning
PD	Pharmacodynamics
PET	Positron Emission Tomography
PFS	Progression free survival
PI	Product Information
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response
PRO	Patient Reported Outcome
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RAI	Radioactive Iodine
RECIST	Response evaluation criteria in solid tumours
RR	Response Rate
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Stable Disease
T3	Tri-iodothyronine
T4	Thyroxine
TGA	Therapeutic Goods Administration
Tmax	Time of maximum concentration
TSH	Thyroid Stimulating Hormone
TTP	Time to Progression

I. Introduction to product submission

Submission details

Type of submission:	Extension of Indications and changes to the PI
Decision:	Approved
Date of decision:	22 April 2014
Active ingredient(s):	Sorafenib
Product name(s):	Nexavar
Sponsor's name and address:	Bayer Australia Ltd 875 Pacific Highway Pymble NSW 2073
Dose form(s):	Tablet
Strength(s):	200 mg
Container(s):	Blister pack
Pack size(s):	60 tablets
Approved therapeutic use:	*Differentiated Thyroid carcinoma:* *Nexavar is indicated for the treatment of patients with locally advanced or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine.*
Route(s) of administration:	Oral (PO)
Dosage:	The recommended daily dose of Nexavar is 400 mg (2 x 200 mg tablets) taken twice a day, either without food or together with a moderate fat meal.
ARTG number (s):	123158

Product background

This AusPAR describes the application by the sponsor to register Nexavar for the following extension of indication:

> *The treatment of patients with locally advanced or metastatic, progressive, differentiated thyroid carcinoma refractive to radioactive iodine.*

The proposed dose in this new indication is 400 mg (2 times 200 mg tablets) taken twice a day.

Primary cancer of the thyroid gland is an uncommon malignancy affecting approximately 2420 persons in Australia in 2012 and causing an estimated 130 deaths. The five major types of thyroid carcinoma and their relative incidences are shown in Table 1.[1]

Table 1. The major types of thyroid carcinoma and their relative incidences.

Type of thyroid carcinoma	Relative incidence
Papillary carcinoma	80%
Follicular carcinoma	11%
Medullary carcinoma	4%
Hürthle cell carcinoma	3%
Undifferentiated/anaplastic carcinoma	2%

Papillary, follicular and Hürthle cell tumours arise from the follicular epithelium of the thyroid, which is responsible for the production of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Medullary carcinoma arises from the C cells of the thyroid that are responsible for the production of calcitonin. The term 'differentiated thyroid carcinoma' (DTC) encompasses papillary, follicular and Hürthle cell carcinomas. Current (NCCN) clinical practice guidelines for differentiated thyroid cancer recommend the use of thyroidectomy, with remnant ablation by radioactive iodine (RAI) therapy in selected patients. No separate Australian clinical practice guidelines exist currently.

Patients are additionally treated with thyroxine to suppress thyroid stimulating hormone (TSH) as TSH can stimulate growth of the thyroid cancer cells. Poor TSH control is associated with a worse outcome. Disease recurrence is common and is treated with repeated surgery and/or RAI. In patients with unresectable disease that is refractory to RAI, there are limited treatment options. Poorly differentiated and anaplastic thyroid cancers are the major common causes of death due to a lack of currently effective treatments. Cytotoxic chemotherapy (such as doxorubicin) is considered to have poor efficacy. RAI refractory disease, which is the indication proposed by the sponsor is rare, with an estimated incidence of 4 cases per million of population.

The rationale for examining the efficacy and safety of sorafenib in differentiated thyroid cancer, as explained by the sponsor, is as follows. In thyroid carcinoma tissues, vascular endothelial growth factors (VEGFs) and VEGF receptors are often overexpressed, both in tumour cells and supporting vascular endothelium. Also in these tumours, activating mutations are often found in genes encoding signalling molecules of the MAP kinase[2] pathway. Sorafenib has been shown to inhibit multiple serine/threonine and receptor tyrosine kinases involved in cell proliferation and angiogenesis.

Numerous agents exist targeting the signalling pathways coupled to the receptor tyrosine kinase pathways. However, vandetanib is the only product registered in Australia for the treatment of patients with symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

[1] Hundahl SA, Fleming ID, Fremgen AM and Menck HR. A National Cancer Data Base Report on 53,856 Cases of Thyroid Carcinoma Treated in the U.S., 1985–1995. *Cancer* 1998 Dec 15; 83 (12): 2638-48.
[2] Mitogen-activated protein kinases also known as MAP kinases are serine/threonine/tyrosine-specific protein kinases. Also known as the **Ras-Raf-MEK-ERK pathway**.

The sponsor has confirmed in their response to the TGA's request for further information that the formulation of sorafenib used in the pivotal clinical study was identical to that currently registered in Australia.

Regulatory status

Sorafenib was approved by the TGA for the indications:

- *Advanced renal cell carcinoma* on 25 September 2006
- *Advanced hepatocellular carcinoma* on 25 February 2008

The TGA designated sorafenib as an orphan drug on 6 March 2013for the indication

- *The treatment of patients with radioactive iodine treatment (RAI) refractory, locally advanced or metastatic differentiated thyroid cancer (DTC).*

Overseas status

USA. The US FDA approved sorafenib for the indication

> *Locally recurrent, or metastatic, progressive differentiated thyroid carcinoma refractory to radioactive iodine treatment* on 22 November 2013.

The dose approved for this indication is identical to that proposed in the submission to the TGA.

European Union (EU). Nexavar was approved on 23 May 2014 for the following indication:

> *Treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine*

For this submission, the sponsor obtained a product specific paediatric waiver '*on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments*'.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

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

Cancer of the thyroid is an uncommon malignancy. The Australian Institute of Health and Welfare estimated that in 2012 the incidence of thyroid cancer in Australia would be 2420 persons and that it would cause 130 deaths.[3] The major types of thyroid carcinoma and their relative incidences are summarised under *Product Background* above.

Papillary, follicular and Hürthle cell tumours arise from the follicular epithelium of the thyroid which is responsible for the production of the thyroid hormones T4 and T3. Medullary carcinoma arises from the C cells of the thyroid that are responsible for the production of calcitonin. The term 'differentiated thyroid carcinoma' encompasses papillary, follicular and Hürthle cell carcinomas.

Current clinical practice guidelines for differentiated thyroid cancer[4,5] recommend the use of surgery (thyroidectomy), followed remnant ablation by RAI therapy in selected patients. Patients are also treated with thyroxine to suppress TSH levels, as TSH can stimulate growth of thyroid cancer cells. Disease recurrence is common and is treated with repeated surgery and/or RAI. In patients with unresectable disease that is refractory to RAI there are limited treatment options. Cytotoxic chemotherapy (such as doxorubicin) is considered to have poor efficacy. RAI-refractory disease, which is the indication proposed by the sponsor is rare with an estimated incidence of 4 cases per million of population.[6]

The rationale for examining the efficacy and safety of sorafenib in differentiated thyroid cancer is explained by the sponsor as follows. In thyroid carcinoma tissues, VEGFs and VEGF receptors are often overexpressed, both in tumour cells and supporting vascular endothelium. Also in these tumours, activating mutations are often found in genes encoding signalling molecules of the MAP kinase pathway (RAS, Raf, MEK and ERK). Sorafenib has been shown to inhibit multiple kinases involved in cell proliferation and angiogenesis, for example Raf kinase and VEGF receptors.

Guidance

The following European Medicines Agency (EMA) guidelines, which have been adopted by the TGA, are considered relevant to the current submission:

- Guideline on the evaluation of anticancer medicinal products.[7]
- Appendix 1 to the guideline on the evaluation of anticancer medicinal products relating to the use of progression-free survival as a primary endpoint.[8]

[3] Australian Institute of Health and Welfare & Australasian Association of Cancer Registries 2012. Cancer in Australia: an overview, 2012. Cancer series no. 74. Cat. no. CAN 70. Canberra: AIHW.
[4] Cooper DS, David S, Doherty GM et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*; 2009; 19 (11): 1164-1214.
[5] National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology, Thyroid Carcinoma, Version 1.2013. Available from: <http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf>
[6] Xing M, Haugen BR, Schlumberger M. Progress in molecular-based management of differentiated thyroid cancer. *Lancet* 2013; 381:1058-1069
[7] European Medicines Agency. Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr.); 2005. Available from: <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#chmp205>
[8] European Medicines Agency. Appendix 1 To The Guideline On The Evaluation of Anticancer Medicinal Products In Man: Methodological Considerations For Using Progression-Free Survival (PFS) As Primary Endpoint In Confirmatory Trials For Registration (EMEA/CHMP/EWP/27994/2008); 2008. Available from: <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#chmp27994>

- Points to consider document on applications based on one pivotal study.[9]

Compliance with these guidelines is considered in the relevant sections of this report.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- A full study report for one pivotal Phase III, randomised, double blind and placebo controlled trial (Study 14295);
- Two pharmacokinetic (PK) reports based on sparse PK sampling performed in Study 14295;
- Some limited postmarketing data based on adverse event reports received by the sponsor regarding patients who had received 'off-label' sorafenib for the treatment of thyroid cancer.
- Literature references. These included publications relating to five investigator initiated Phase II studies, which the sponsor cited as supportive evidence for the application.

Paediatric data

The submission did not include paediatric data. According to the sponsor's application, both the EMA and the FDA have waived any requirement for paediatric data. The EMA granted a waiver on the grounds that the drug does not represent a significant therapeutic benefit over existing treatments. The FDA granted a waiver on the grounds that the drug had received an orphan designation for thyroid cancer.

> Comment: Thyroid cancer is rare in children. The sponsor's arguments that led to the EMA waiver were not presented in the TGA application. For completeness, the sponsor should provide these.

Good clinical practice

The study report for the pivotal clinical trial in this submission included an assurance that the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP).

The protocol and all protocol amendments were reviewed and approved by each study site's institutional ethics committee before the start of the study and before implementation of any amendments.

Pharmacokinetics

Studies providing pharmacokinetic data

There were no new PK studies in the submission. Some sparse PK sampling was included in the pivotal efficacy study and the resulting PK data are summarised Attachment 2.

[9] European Medicines Agency. Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99); 2001. Available from: <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#ewp2330>

Pharmacodynamics

Studies providing pharmacodynamic data

No new pharmacodynamic studies were included in the submission. The pivotal study (14295) included exploratory analyses of the relationship between tumour mutations and sorafenib efficacy. These data are reviewed in Attachment *2 Results for other efficacy outcomes*.

Dosage selection for the pivotal studies

The starting dose chosen for the pivotal study was 400 mg twice a day (BD), which is the same starting dose approved for current indications of hepatocellular carcinoma and renal cell carcinoma. The rationale for the 400 mg BD dose was not discussed in the current submission but it appears to have been the maximum tolerated dose (MTD) in early Phase I studies.[10]

Efficacy

Studies providing efficacy data

The pivotal efficacy study was study 14295, also known as the DECISION study (stu**D**y of soraf**E**nib in lo**C**ally advanced or metastat**I**c patient**S** with radioactive **I**odine refractory thyr**O**id ca**N**cer).

The sponsor identified five, single-arm, Phase II studies of the use of sorafenib in DTC from the literature.[11, 12, 13, 14, 15, 16, 17]Although the sponsor supported several of these, the studies were described as being 'investigator-sponsored' and only published papers (rather than detailed study reports) were included in the submission.

> Comment: The sponsor has included these studies as supportive evidence only. Neither a detailed literature search strategy, agreed beforehand with the TGA, nor a search output has been provided. It therefore cannot be assumed that the five studies presented reflect a complete or balanced view of the available literature.

The efficacy data from these five studies, including the results of the sorafenib arm in Study 14295 for comparison is presented in Attachment 2. Response rates in the Phase II studies varied from 15-38%. All responses were partial responses.

[10] Semrad TJ, Gandara DR and Lara PN. Enhancing the clinical activity of sorafenib through dose escalation: rationale and current experience. *Therapeutic Advances in Medical Oncology*; 2011 March; 3(2): 95-100.
[11] Ahmed M, Barbachano Y, Riddell A et al. Analysis of the efficacy and toxicity of sorafenib in thyroid cancer - a phase II study in a UK based population. *Eur J Endocrinol*. 2011; 165: 315-322.
[12] Schneider TC, Abdulrahman RM, Corssmit EP, et al. Long-term analysis of the efficacy and tolerability of sorafenib in advanced radio-iodine refractory differentiated thyroid carcinoma: final results of a phase II trial. *Eur J Endocrinology* 2012; 167: 643-650.
[13] Gupta-Abramson V, Troxel AB, Nellore A et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol* 2008; 26: 4714-4719.
[14] Brose MS, Troxel AB, Harlacker K et al. Completion of a phase II study of sorafenib for advanced thyroid cancer. *Eur J Cancer.* 2009;7(suppl):22. Abstract 51LBA. [ESMO 2009 Abstract].
[15] Keefe SM, Troxel ABH, Rhee S, Puttaswamy K et al. Phase II trial of sorafenib in patients with advanced thyroid cancer. *J Clin Oncol*. 2011;29 (suppl):375S. Abstract 5562. [ASCO 2011 Abstract]
[16] Kloos RT, Ringel MD, Knopp MV et al. Phase II trial of sorafenib in metastatic thyroid cancer. *J Clin Oncol* 2009; 27: 1675-1684.
[17] Chen l, Shen Y, Luo Q, et al. Response to sorafenib at a low dose in patients with radioiodine-refractory pulmonary metastases from papillary thyroid carcinoma. *Thyroid* 2011; 21 (2): 119-124.

Comment: Although cross-trial comparisons are not reliable, the efficacy results from these studies in terms of RR and PFS are generally comparable to, or more favourable than, those seen in Study 14295.

Evaluator's conclusions on efficacy

The pivotal study was well designed and conducted. The design complied with the relevant EMA guidelines adopted by the TGA.[7, 8] The study demonstrated that sorafenib is clearly an active agent in RAI-refractory DTC, with a statistically significant ($p<0.0001$) improvement in Progression free survival (PFS) compared to placebo.

The magnitude of the efficacy benefit is considered clinically significant. The risk of experiencing a PFS event (that is, disease progression or death) was reduced by approximately 40% (hazard ratio (HR): 0.587; 95% Confidence Interval (CI): 0.454-0.758) and median PFS was increased by approximately 5 months (10.8 versus 5.8 months). The study did not demonstrate a benefit in terms of overall survival and this is most likely due to the trial design which permitted crossover from placebo to sorafenib after disease progression. The EMA guidelines indicate that PFS is acceptable as a primary endpoint in Phase III studies and the TGA has previously approved new anticancer therapies on the basis of a PFS benefit in the absence of a demonstrated Overall Survival (OS) benefit.

The efficacy benefit is considered valuable given the serious nature of the disease being treated and the lack of alternative treatments.

The exploratory Health Related Quality of Life (HRQoL) data suggested that patients treated with placebo had a better quality of life however the differences were of doubtful clinical significance.

Only one pivotal study has been submitted to support use of sorafenib in DTC and the TGA has adopted an EMA guideline that addresses this situation. It requires that the study should be 'exceptionally compelling'. In the opinion of this evaluator, the pivotal study meets the criteria laid down in this guideline; the study design minimised the potential for bias, the population included in the study was representative of the population likely to receive the drug in clinical practice, the efficacy benefit was clinically significant, was highly statistically significant, and was consistent across subgroups. The clinical rationale for using sorafenib in DTC is also plausible.

The published Phase II studies submitted by the sponsor also provide some supportive evidence of efficacy.

Overall it is considered that the efficacy of sorafenib in the treatment of RAI refractory DTC has been adequately established.

Safety

Studies providing safety data

One pivotal efficacy study (Study 14295) provided evaluable safety data. For further details of design and safety data collected in this study please see Attachment 2.

The published Phase II studies reported adverse events and laboratory abnormalities.

Patient exposure

Safety data were available for a total of 517 subjects in the submitted studies. Two of the Phase II studies pooled safety data from patients with DTC and subjects with other types of thyroid cancer.

Table 2. Exposure to sorafenib and placebo in clinical studies.

Study type/ Indication	Pivotal study		Uncontrolled Studies
	Sorafenib	**Placebo**	**Sorafenib**
Pivotal			
Double-blind phase Open label phase From placebo group From sorafenib group	**207** **150** 55	209 -	- -
Phase II			
Ahmed 2009	-	-	34 (1)
Schneider 2012	-	-	31
Gupta-Abramson 2008	-	-	30 (2)
Kloos 2009	-	-	56 (1)
Chen 2011	-	-	9
TOTAL for sorafenib	**357**		**160**

(1) Ahmed 2009 and Kloos 2009 included subjects with other thyroid cancer types in the safety database presented.
(2) For Gupta-Abramson 2008, detailed safety data were only presented for the first 30 subjects.

Safety issues with the potential for major regulatory impact

Liver toxicity

Liver Function test (LFT) abnormalities are common with sorafenib treatment. However, in the pivotal study no evidence of severe drug induced liver injury was observed. The PI for sorafenib already lists drug induced hepatitis (with a life threatening or fatal outcome) as a rare adverse event.

Haematological toxicity

Cytopaenias are a common adverse event with sorafenib treatment. There were no reports of pancytopaenia or aplastic anaemia in the pivotal study.

Serious skin reactions

Serious skin toxicities, principally hand-foot syndrome and rash/desquamation are common with sorafenib and this was confirmed in the pivotal study. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported in postmarketing experience and are listed in the current PI.

Cardiovascular safety

Sorafenib is known to be associated with cardiovascular toxicity. Hypertension, myocardial infarction/ischaemia, QT prolongation[18] and congestive heart failure are all listed in the currently approved PI. The new safety data provided with the current submission did not indicate any novel cardiovascular toxicity.

Unwanted immunological events

Anaphylactic and hypersensitivity reactions are listed in the draft PI as uncommon adverse reactions. In the pivotal study, one subject experienced a Grade 4 anaphylactic reaction (considered related) and one had a Grade 4 allergic reaction (considered unrelated). Both subjects were receiving sorafenib.

Postmarketing data

As sorafenib had been used 'off-label' for the treatment of thyroid cancer for some time prior to the current application, the sponsor had received reports of adverse events (AEs) occurring in this population. The sponsor's *Summary of clinical safety* included an analysis of AE reports from patients receiving sorafenib for thyroid cancer.

A total of 1354 cases had been received up to 31 March 2013. Of these, 582 were classed as serious. The sponsor's analysis focused on those that were considered serious, related to sorafenib (either by the reporter or the sponsor) and unexpected. There were 88 of these cases. Individual AEs with more than one report included the following:

- Atrial fibrillation (2 reports). Both subjects had 'hypertensive decompensation' and one had hypokalaemia, both known AEs associated with sorafenib;
- Dyspnoea (6 reports). Most reports had insufficient information. Some were most likely related to disease progression (lung metastases, pneumonia). Interstitial lung disease like events are known to be uncommonly associated with sorafenib treatment;
- Cerebrovascular accident (2 reports). Both reports had insufficient information to clearly understand the event. Hypertension and haemorrhage are both known AEs with sorafenib.

Many of the 'unexpected' AEs were simply different terms used to describe known AEs (such as 'inability to walk' and 'gait disturbance' in subjects with hand-foot syndrome; 'pharyngeal oedema' in subjects with mucositis).

Overall, the review of the postmarketing reports did not suggest any novel toxicity for the drug.

Evaluator's conclusions on safety

The pattern of toxicity seen with sorafenib in the submitted studies was generally consistent with that previously documented for sorafenib. The most common AEs were dermatological (hand-foot syndrome, alopecia, rash/desquamation), gastrointestinal (diarrhoea, anorexia, mucositis), constitutional (fatigue, weight loss), hypertension and hepatic (elevated transaminases).

Novel toxicities identified in the new population were hypocalcaemia and elevated TSH levels.

[18] QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval, a ***QTc,*** is often calculated.

The data suggested that some toxicities were more common in the thyroid cancer population than in the renal cell carcinoma and hepatic carcinoma populations. This would be consistent with the observation that systemic exposure to sorafenib is greater in the thyroid cancer population.

The toxicity of sorafenib is significant. Compared to placebo treatment, sorafenib treatment was associated with an excess incidence of Grade 3/4 AEs of 34% (64.3% versus 30.1%) and an 11% excess incidence of serious AEs (37.2% versus 26.3%). However, in most patients, sorafenib toxicity was manageable with dose interruptions and reductions, as the incidence of discontinuations due to AEs was increased by only 15% (18.8% versus 3.8%). Sorafenib was not associated with an increase in treatment related deaths.

Overall, the toxicity of sorafenib in the treatment of patients with advanced DTC has been adequately documented.

First round benefit-risk assessment

First round assessment of benefits

The benefits of sorafenib in the proposed usage are:

- A significant reduction of approximately 40% in the risk of disease progression (or death) events. Median progression free survival was increased by approximately 5 months.

First round assessment of risks

The risks of sorafenib in the proposed usage are:

- An increased risk of several adverse events which have previously been documented with the drug.
- An increased risk of two novel adverse events; hypocalcaemia and elevated TSH.

In a significant proportion of patients these events may be severe or life threatening (Grade 3 or 4). However, there does not appear to be an increased risk of fatal adverse drug reactions. In most patients the toxicities can be managed and only 15% of subjects have to discontinue the drug due to adverse events caused by the drug.

First round assessment of benefit-risk balance

The benefit-risk balance of sorafenib, given the proposed usage, is considered favourable. This assessment takes into account the nature of the population (subjects with a life threatening illness) and the very limited alternative treatments available.

First round recommendation regarding authorisation

It was recommended that the application be approved.

Clinical questions

General

Please provide an assurance that the formulation of sorafenib used in the pivotal study (14295) was identical to that currently registered in Australia.

Please outline the arguments that were put to the EMA to obtain the paediatric waiver.

Pharmacokinetics

Please provide an update on the progress of the investigations being undertaken to determine the mechanism responsible for the increased sorafenib exposure observed in thyroid cancer patients.

Efficacy

Please provide the results of the follow-up analysis of overall survival that was due to be conducted nine months after the primary completion date of 31 August 2012. Please advise whether any further analyses of overall survival are planned.

Second round evaluation of clinical data submitted in response to questions

The sponsor's responses have been taken into account in the Delegate's overview below and a second round clinical evaluation was not generated.

V. Pharmacovigilance findings

Risk management plan

The sponsor initially submitted a Risk Management Plan EU RMP Version 12.0 dated 12 June 2013 with Australian Specific Annex (ASA) Version 1.0 dated July 2013 which was reviewed by the TGA's Office of Product Review (OPR).

The sponsor provided a summary of ongoing safety concerns which are shown in Table 3.

Contents of the submission

The sponsor proposes routine pharmacovigilance activities to monitor the specified ongoing safety concerns. This includes a number of specific follow-up questionaries. In regards to additional pharmacovigilance, the sponsor has listed one ongoing study however there are some inconsistencies in the pharmacovigilance plan presented.

The sponsor concludes that routine risk minimisation activities are sufficient for all ongoing safety concerns.

Table 3. Ongoing safety concerns

Summary of safety concerns	
Important identified risks	Severe skin adverse events Hand-foot skin reaction (HFSR) Hypertension Reversible posterior leukoencephalopathy syndrome (RPLS) Hemorrhage including lung hemorrhage, gastrointestinal (GI) hemorrhage and cerebral hemorrhage Arterial thrombosis (myocardial infarction) Congestive heart failure (CHF) Squamous cell cancer of the skin Gastrointestinal perforations Symptomatic pancreatitis and increases in lipase and amylase Hypophosphatemia Safety and efficacy in patients with non-small cell cancer of the lung with squamous histology Renal dysfunction Interstitial lung disease-like events Drug-induced hepatitis
Important potential risks	Arterial thrombosis (cerebral ischemia) Wound healing complications Microangiopathy Pregnancy
Important missing information	Safety in children Safety and efficacy in patients with hepatocellular carcinoma (HCC) and Child-Pugh B liver dysfunction

Reconciliation of issues outlined in the RMP report

The following section summarises the OPR's first round evaluation of the RMP and the evaluator's comments on the sponsor's response to the first round recommendations.

1. Recommendation in RMP first round evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA's consolidated request for further information 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 Risk Management Plan, 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.

Bayer was requested to note the clinical evaluator's first round comments regarding the safety specification of the RMP: '*The Safety Specification in the draft Risk Management Plan does not appear to have been updated to include the novel AEs of hypocalcaemia and elevated TSH in thyroid cancer subjects.*'

Evaluator's comment to the Delegate regarding the sponsor's response: This recommendation remains.

2. Recommendation in RMP first round evaluation report

In light of the context that the submitted RMP is the first reviewed by the TGA, together with the absence of a summary of changes to the RMP versions over time, it is requested that the sponsor submit the most recent RMP evaluation report from the European Union.

The sponsor's response was considered acceptable.

3. Recommendation in RMP first round evaluation report

Pending the evaluation of the nonclinical and clinical aspects of the Safety Specifications (SS), it is recommended the following be added to the list of ongoing safety concerns, unless the sponsor can provide compelling justification for their exclusion:

Elevated TSH levels in differentiated thyroid carcinoma should be added as an important identified risk for this indication. This risk should be given specific follow up within the Periodic Safety Update Report (PSUR) process.

Evaluator comment to the Delegate regarding the sponsor's response: This recommendation remains.

4. Recommendation in RMP first round evaluation report

In light of the recent published case reports of pancreatic atrophy, it is reasonable that pancreatic exocrine insufficiency/pancreatic atrophy be added to the list of ongoing safety concerns.[19]

Evaluator comment to the Delegate regarding the sponsor's response: This recommendation remains.

5. Recommendation in RMP first round evaluation report

The following adverse drug reactions have been identified by the sponsor in a recent safety review and on the 21 February 2013 the EU updated the Summary of Product Characteristics (SmPC) accordingly. Due to the serious nature of these adverse reactions, the following should be given specific follow-up within the PSUR process:

i. Hypokalaemia

ii. Proteinuria

iii. Nephrotic syndrome

Could the sponsor also confirm that these risks will be added to the list of ongoing safety concerns in the RMP?

Please note that the clinical evaluator also recommended that hypocalcaemia should be added to the safety specification of the RMP.

6. Recommendation in RMP first round evaluation report

For completeness, the following should also be added to the list of important missing information:

i. Use in lactation

ii. Off-label use

Evaluator comment to the Delegate regarding the sponsor's response: The recommendation regarding the addition of lactation to the ongoing safety concerns remains.

7. Recommendation in RMP first round evaluation report

There appears to be internal inconsistency regarding the pharmacovigilance plan presented within the ASA and EU RMP. The sponsor is requested to clarify or amended the following:

Section 1 of EU RMP Part III lists studies that are complete in the Pharmacovigilance plan. This includes Study ADVL-0413 and GIDEON. Section 1 of the EU RMP titled '*Safety concerns and overview of planned pharmacovigilance actions*' should be amended accordingly.

[19] Hescot et al. Pancreatic atrophy – a new late toxic effect of sorafenib. *NEJM* 2013; 369:1475-1476

Evaluator comment to the Delegate regarding the sponsor's response: This recommendation remains.

Unfortunately the pharmacovigilance plan in the ASA has not been updated. Completed studies remain listed within the pharmacovigilance plan.

8. Recommendation in RMP first round evaluation report

A number of studies listed in Section 4.4 Table 4.2 are not listed within Section 1 and do not have specific safety concerns assigned. This includes Study 14792, 15039, 15246, 16399, 15038. Furthermore, these studies are not listed in the summary of the pharmacovigilance plan, in Table 5.1 listing on-going and planned studies or within the ASA.

The Post Authorisation Safety Studies (PASS) will either generate safety data that will simply support the known safety profile of the medicine, or will generate data that will provoke applications to amend the Australian registration details. To this end, the sponsor must provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.

9. Recommendation in RMP first round evaluation report

Study 100561 is listed in Section 1 of EU RMP Part III. It is assigned as a planned pharmacovigilance action for the ongoing safety concern of Congestive heart failure (CHF). However, this study is not listed elsewhere in the pharmacovigilance plan or within the ASA. Furthermore, no current milestones for this study are provided within Part III of the RMP.

The pharmacovigilance plan should therefore be updated accordingly.

10. Recommendation in RMP first round evaluation report

The ASA does not list any other studies as listed in the EU RMP version 12.0. The ASA should be updated with all ongoing studies and appropriate milestones.

The sponsor's response was considered acceptable.

11. Recommendation in RMP first round evaluation report

Annex 6 of the EU RMP is titled '*Protocols for proposed and on-going studies in part III'*. However, only Study E2805 is listed. The status of Studies 14792, 15039, 15246, 16399 and 15038 appears to be ongoing however they are not listed in Annex 6.

This issue was clarified by the sponsor in their response, however the PASS will either generate safety data that will simply support the known safety profile of the medicine or will generate data that will provoke applications to amend the Australian registration details. To this end, the sponsor must provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.

12. Recommendation in RMP first round evaluation report

The following statement made by the sponsor in Annex 6 (of the RMP) appears inconsistent with the pharmacovigilance plan presented in the EU-RMP: *'No studies are proposed for additional pharmacovigilance activities in RMP Part III*.'

The sponsor's response was considered acceptable.

13. Recommendation in RMP first round evaluation report

The questionnaires do not appear to collect data on the dose and duration of treatment with sorafenib. It is recommended that the forms be amended accordingly.

The sponsor's response was considered acceptable.

14. Recommendation in RMP first round evaluation report

The distribution method and current status of these questionaries in Australia remains unclear. The sponsor should clarify if these questionaries are currently in use within Australia. If not, will these be implemented and please provide milestones for this additional activity. It is important that the ASA accurately captures this information.

The sponsor's response was considered acceptable.

15. Recommendation in RMP first round evaluation report

The following questionnaires are listed within the pharmacovigilance plan but have not been provided in Annex 6 (of the RMP). It is requested that the sponsor provide these additional questionnaires:

i. Stevens-Johnson Syndrome

ii. Interstitial lung disease (ILD)-like events

The sponsor's response was considered acceptable.

16. Recommendation in RMP first round evaluation report

In regard to the proposed routine risk minimisation activities, the Delegate may wish to revise the draft product information document as follows:

Under '*Precautions'* the wording regarding TSH Suppression in Differentiated Thyroid Carcinoma (DTC) should be strengthened to accurately capture the nature of this precaution. The evaluator is concerned that the current statement may not adequately communicate the numbers observed. For example, the US FDR approved product leaflet states the following '*Nexavar impairs exogenous thyroid suppression. In the DTC study, 99% of patients had a baseline thyroid stimulating hormone (TSH) level less than 0.5 mU/L. Elevation of TSH level above 0.5 mU/L was observed in 41% of Nexavar-treated patients as compared with 16% of placebo-treated patients. For patients with impaired TSH suppression while receiving Nexavar, the median maximal TSH was 1.6 mU/L and 25% had TSH levels greater than 4.4 mU/L. Monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC*.'

The sponsor responded that they would await advice from the Delegate in relation to this OPR recommendation.

17. Recommendation in RMP First Round evaluation report

Under '*Post-market experience'*, a statement should be added regarding the post market reports of pancreatic atrophy/pancreatic exocrine insufficiency.[20]

The sponsor responded that they would await advice from the Delegate in relation to this OPR recommendation.

18. Recommendation in RMP first round evaluation report

In regard to the proposed routine risk minimisation activities, the Delegate may wish to revise the draft consumer medicine information document to reflect the approved changes to the Product Information.

The sponsor responded that they would await advice from the Delegate in relation to this OPR recommendation.

[20] Reference: Segolene Hescot, Olivier Vignaux, et al. Pancreatic Atrophy- A New Late Toxic Effect of Sorafenib - The New England journal of Medicine 2013; 369:1475-1476

Summary of OPR recommendations

It is considered that the sponsor's response to the TGA request for further information has not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

- The sponsor has not added a number of ongoing safety concerns in the updated RMP or ASA, including hypocalcaemia, elevated TSH in thyroid cancer subjects, pancreatic atrophy, hypokalaemia, proteinuria, nephrotic syndrome or use in lactation (see recommendations below, including recommendations from the clinical evaluator).
- The OPR evaluator would like to draw the clinical evaluator and Delegate's attention to the sponsor's inclusion of '*increased exposure in differentiated thyroid carcinoma (DTC) patients*' as a potential interaction in the safety specification of the updated EU RMP (dated 31 October 2013). However, the sponsor has chosen to exclude this risk from the summary of the safety specification (table of ongoing safety concerns). The implications of excluding this risk from the ongoing safety concerns include no pharmacovigilance activities, risk minimisation or PSUR reporting for this risk.
- The ASA requires amendment. The pharmacovigilance plan continues to refer to studies that are complete. This is misleading, when in fact only one study is currently ongoing (E2805 (ASSURE) ECOG Study). There are no planned pharmacovigilance studies as shown the ASA. The PASS and studies referenced in the pharmacovigilance plan will generate safety data that will simply support the known safety profile of the medicine, while others will generate data that will provoke applications to amend the Australian registration details. To this end, it is suggested that the sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia. The ASA must not be accepted until these issues are amended. Furthermore, these tables are directly used within the AUSPAR summary and must accurately describe the actual pharmacovigilance plan.
- In regards to routine risk minimisation, suggested changes to the Australian product Information document were recommended to the Delegate.

Comments on the safety specification of the RMP

Clinical evaluation report

The clinical evaluator made the following comment regarding the safety specification of the RMP in the first round clinical evaluation report: '*The Safety Specification in the draft Risk Management Plan does not appear to have been updated to include the novel AEs of hypocalcaemia and elevated TSH in thyroid cancer subjects. Otherwise the Safety Specification appears acceptable.'*

Key changes to the updated RMP

The sponsor provided an updated RMP (Version 12 dated 31 October 2013) with Australian Specific Annex Version 1.1 dated January 2014. The sponsor has provided the following table summarising the changes to the RMP v12.0 dated 12 June 2013 to v12.0 dated 31 October 2013.

Table 4. Summary of changes to the RMP v12.0 dated 12 June 2013 to v12.0 dated 31 October 2013.

Section	Changes made	Rationale for change
Part I	Version number (12.0), sign-off date (31Oct 2013).	Update document version and sign-off date.
SVII Identified and potential risks	Torsade de pointes is included as an important potential risk page 194 of the EU RMP	Torsade de pointes is added as a potential risk based on EMEA request considering the modest QT prolongation effect of sorafenib and higher frequency of severe hypocalcaemia in DTC patients which is a risk factor for torsade de pointes.
	Increased exposure in patients with differentiated thyroid cancer (DTC) is included as a potential interaction page 207 of the EU RMP	Increased exposure in DTC patients is added as a potential interaction (no substance identified) based on EMEA request in the view of the higher concentration of sorafenib in DTC patients.

Suggested wording for conditions of registration

RMP

The European Risk Management Plan (Version 12 dated 31 October 2013) with Australian Specific Annex Version 1.1 dated January 2014), revised to the satisfaction of the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator recommended approval of the application. The sponsor's responses to the evaluator's request for further information (*Clinical questions* above) have been taken into account in this overview and a second round clinical evaluation was not generated.

Pharmacokinetics

Study 14295 pivotal efficacy study

This study included a sparse population PK evaluation as a secondary outcome. This evaluated the exposure of sorafenib in subjects with DTC using the area under the time-

concentration curve from time 0 to 12 hours at steady-state ($AUC_{(0\text{-}12h).ss}$). Sparse PK data was obtained from 113 of 207 subjects randomised to sorafenib in the pivotal trial. The mean sorafenib ($AUC_{(0\text{-}12h).ss}$) was similar between Caucasian and Asian subjects in the PK population with DTC.

In comparison to the systemic exposure observed in patients with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC) and non-thyroid/RCC/HCC, the $AUC_{(0\text{-}12).ss}$ seen in patients with DTC was approximately 70% higher. Similarly, the plasma concentration of the sorafenib metabolite M-2 at steady state was higher than that seen in non-DTC cancer patients (Table 5).

Table 5. Steady-state plasma M-2 mean (%CV) [range] concentration from thyroid cancer, hepatocellular carcinoma and renal cell carcinoma subjects.

	Thyroid Cancer Pool	RCC Pool	HCC Pool
Steady State Concentration (mg/L)	1.41 (93%) [0.21 – 10.66] N = 115	0.50 (118%) [0.02 – 6.66] N = 265	0.51 (110%) [0.05 – 5.38] N = 234

Sorafenib is predominately metabolised by CYP3A4 and UGT1A9. A population pharmacokinetic assessment of Study 14295 subjects did not reveal an individual factor responsible for this difference in exposure, but did confirm that neither inhibition of CYP3A4 nor inhibition of UGT1A9 (by T4 or T3) were responsible for the increase in exposure observed. No positive relationship between total T3 concentration or free T4 concentration and either sorafenib AUC or the AUC for the metabolite M-2 was seen.

Efficacy

Dosage selection

The starting dose of 400 mg twice daily is the same as that for the two currently approved indications.

Dose delays and dose reductions were permitted if adverse events occurred; the minimum dose permitted was 200 mg once daily. This advice is contained in the updated product information.

Extension of indication-pivotal Study 14295

This was a Phase III, randomised, double blind, placebo-controlled trial in adult patients with locally advanced or metastatic DTC which was RAI refractory and not amenable to curative surgery or radiotherapy, with Eastern Cooperative Oncology Group (ECOG) performance status 0-2. Patients had to have met the RECIST criteria for disease progression within 14 months prior to enrolment. The first patient was enrolled on 15 October 2009 and data cut-off was 31 August 2012.

Of 556 patients enrolled, 419 were randomised 1:1 to either sorafenib 400 mg twice daily (n=207) or placebo (n=210); two patients were erroneously randomised into the sorafenib arm. Sorafenib was administered as a daily ongoing therapy, but for the purposes of the trial, follow-up was divided into 28 day episodes of treatment. Randomisation was according to age (dichotomised to <60 years or ≥61 years), and geographical region. Subjects continued on their assigned treatment until either: disease progression, unacceptable toxicity, non-compliance or withdrawal of consent. If disease progression was confirmed while on treatment, un-blinding could occur so that sorafenib assigned patients could continue with the treatment and placebo assigned patients could cross-over to sorafenib treatment.

Twenty patients were excluded from the per-protocol analysis but the reasons for exclusion were not given in the dossier.

Progression-free survival

At the time of data cut-off, 250 PFS events had occurred, 17 (6%) less than that specified in the sample size calculation. At this time, 66 subjects remained on their assigned treatment in the double blind phase and 65 subjects were receiving ongoing sorafenib treatment in the open-label phase (12 originally assigned and 53 cross-over from placebo).

There was a statistically significant reduction in the risk of a PFS event in the sorafenib group (hazard ratio 0.587 (95% CI: 0.454, 0.758), p<0.0001). The estimates of median PFS were 10.8 months in the sorafenib group versus 5.8 months in the placebo group.

The proportion of subjects with PFS was higher with sorafenib at 3, 6, 9, 12 18 and 24 months of follow-up.

Analysis of PFS according to exposure quartile was performed for the PK analysis set, demonstrating that the range of median PFS was similar across all groups (Table 6).

Table 6. Study 14295 – Progression-free survival by sorafenib PK exposure group

	Units	Low exposure group (Q1) N = 28	Medium exposure group (Q2+Q3) N = 57	High exposure group (Q4) N = 28
$AUC_{(0\text{-}12h),ss}$ (geometric mean)	mg*h/L	43.7	75.5	129.3
$AUC_{(0\text{-}12h),ss}$ (range)	mg*h/L	29.0-58.1	59.2-101.8	101.9-186.2
Number (%) of subjects with event		18 (64.3 %)	35 (61.4 %)	13 (46.4 %)
Number (%) of subjects censored		10 (35.7 %)	22 (38.6 %)	15 (53.6 %)
25th percentile [95% CI]	days	162 [59; 206]	166 [103; 250]	269 [62; 329]
Median [95% CI]	days	278 [162; 686]	294 [231; 393]	509 [271; 561]
75th percentile [95% CI]	days	728 [332; A]	556 [393; A]	561 [509; 561]
Range (incl. censored values)	days	(1 - 814)**	(1 - 834)**	(1 - 561)**
Range (without censored values)	days	(56 - 728)	(20 - 556)	(52 - 561)

Central assessment incl. clinical progression due to bone irradiation
PK analysis set - subjects randomized to sorafenib
Source: Module 5.3.3.5, Report PH-37331, Table 14.4 / 5a
** censored observation
Q: Quartile
A: Value cannot be estimated due to censored data
Median, percentile and 95 % CIs computed using Kaplan-Meier estimates

Overall survival

At the data cut-off of 31 August 2012 only 99/417 (24%) patients had died, thus precluding an estimate of median survival duration. At that time point, there was no overall survival (OS) difference between the two treatment arms (hazard ratio 0.8 (95% CI 0.54, 1.90) p=0.138). An update of OS analysis with 9 months additional follow-up using the cut-off date of 31 May 2013 again demonstrated no difference in OS between the treatment arms; hazard ratio 0.88 (95% CI 0.63, 1.24) p=0.236. The evaluation of OS, at both time-points, is confounded (as documented by the sponsor) due to the inclusion of patients that crossed over from placebo to open-label sorafenib following disease progression while on-study and cannot therefore be meaningfully assessed beyond this point. The sponsor has not reported the number of patients that had crossed-over at the later analysis point as the analysis was based on the as-randomised population.

The Delegate notes that a further analysis of OS is planned when 240 survival events have occurred.

Time to progression

The median time to disease progression was longer in the sorafenib arm (337 days) as compared the placebo arm (175 days). The hazard ratio for time to progression was 0.56 (95% CI 0.43, 0.72) p<0.0001.

Disease control rate and response rate

The proportion of patients achieving disease control was significantly different between the two study arms: 169/196 (86.2%) in the sorafenib arm and 150/201 (74.6%) in the placebo arm had disease control (p=0.015.).

No patients in either treatment arm achieved a complete response. The proportion of patients with stable disease was equal in both treatment arms; 74%. Partial response was seen in 24/196 (12.2%) of the sorafenib arm versus 1/201 (0.5%) of the placebo arm. The low responsiveness to sorafenib is comparable to the experience seen in the treatment of renal cell carcinoma.

Duration of response

The median duration of response in the 24 subjects in the sorafenib arm that achieved a partial response was 10.2 months (range 7.4 to 16.6).

Cross-over

At the point of first progression of disease, 46 subjects continued sorafenib and 137 subjects initially randomised to placebo continued on open-label sorafenib. The 95% confidence intervals for median PFS were similar for both open-label groups, with a point estimate of median PFS 204 days (95% CI 118, 260) in the sorafenib-continuing group and 292 days (95% CI 239, 355) in the placebo cross-over group.

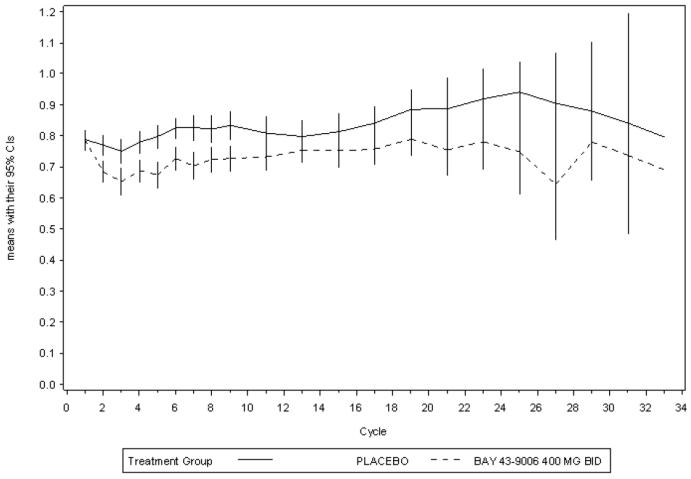
Health-related quality of life

High compliance with the EQ-5D questionnaire[21] was maintained throughout follow-up, with 89.5% to 99.2% of all evaluable patients completing the questionnaire until Cycle 33. End of treatment assessments were obtained in 70% of the sorafenib arm and 34.8% of the placebo arm. The 95% confidence interval for the mean EQ-5D score was higher for the sorafenib arm between Cycles 2 and 9 but this difference was not sustained thereafter.

A similarly high proportion of response was seen for the FACT-G questionnaire, with 89.5% to 100% of evaluable patients completing the assessment until cycle 33. As for the EQ-5D, the 95% confidence interval for the mean Functional Assessment of Cancer Therapy - General (FACT-G) score was higher for the sorafenib arm between Cycles 2 and 11 but this difference was not sustained thereafter.

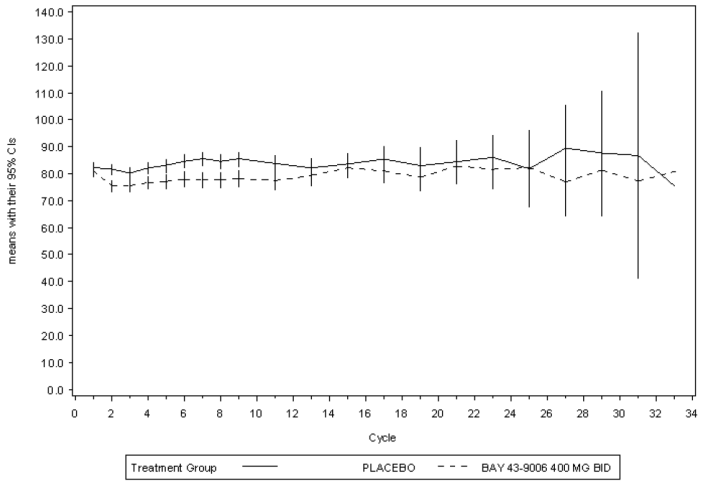
Collectively, the crude quality of life assessment measurements demonstrated a transient benefit of sorafenib early in the treatment course and did not demonstrate a worsening of quality of life as compared to placebo (Figures 1 and 2).

Figure 1. EQ-5D index questionnaire by treatment cycle.



[21]EQ-5D™ is a standardised instrument for use as a measure of health outcome.

Figure 2. FACT-G questionnaire total score by treatment cycle.



Biomarker analysis

A total of 256 subjects had testing for tumour mutations of which 47.3% did not have a mutation detected. Of those with a mutation detected, the most commonly occurring were BRAF[22] (47.3%) and RAS (N, H or K) (19.5%). No difference in efficacy outcomes was observed between those with or without a mutation and therefore cannot be used as a prognostic tool.

Safety

Exposure, dose interruptions and discontinuations

The median overall time under treatment during the double-blind phase of the study was 46.1 weeks for the sorafenib arm and 28.3 weeks for the placebo arm. Dose interruptions were more common in the sorafenib arm (76.8% versus 54.5% with placebo), with 87% requiring between 1 and 3 interruptions, predominately due to toxicity. Dose reductions occurred more commonly in the sorafenib arm 68.1% versus 11.5% with placebo), predominately due to toxicity. Discontinuation due to adverse events was more common in the sorafenib arm 18.8% versus 3.8% in the placebo arm; the adverse events leading to discontinuation were comparable with the general adverse event profile.

Overview of adverse events

The safety analysis set during the double-blind phase comprised 207 subjects in the sorafenib arm and 209 subjects in the placebo arm. The overall incidence of treatment emergent adverse events (TEAE) was higher in with sorafenib (98.6%) as compared the placebo arm (87.6%). Grade 3 and 4 TEAEs combined and deaths were more common in the sorafenib arm; 63.3% versus 30.1% and 6.8% versus 2.9% respectively.

In the open label phase, patients continuing sorafenib (n=55) had a lower incidence of TEAEs (85.5%) as compared with those subjects who were initially randomised to placebo and subsequently crossed-over (99.3%).

Analysis of the safety profile according to exposure quartile in the PK population did not demonstrate an exposure-AE relationship.

[22] BRAF is a human gene that makes a protein called B-Raf. The gene is also referred to as proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, while the protein is more formally known as serine/threonine-protein kinase B-Raf. The B-Raf protein is involved in sending signals inside cells, which are involved in directing cell growth.

Deaths and other serious AEs

During the double-blind treatment period or within 30 days of discontinuation, there were 18 deaths, 12 of which were in the sorafenib arm and 6 in the placebo arm. The majority of deaths were due to disease progression. One death in the sorafenib arm was attributed to being related to the study drug (consistent with the known risk of myocardial infarction) and one subject in the placebo arm receiving concomitant enoxaparin died as a result of a subdural haemorrhage.

In the open label phase, all deaths (n=49) occurring in patients receiving sorafenib were attributed to disease progression.

Serious adverse events were more common in the sorafenib arm 37.2% versus 26.3% with placebo, the commonest events being constitutional symptoms, rash/desquamation and secondary malignancy.

AEs of special interest

No new AEs of special interest with sorafenib exposure were identified from the pivotal study. In particular, no increase in the incidence of second malignancies other than the known risk of squamous cell carcinoma of the skin is reported.

Specific toxicities

Hypocalcaemia and hypophosphataemia

Hypocalcaemia was a newly reported common adverse event in the double blind phase of treatment occurring more frequently in the sorafenib arm during the double-blind phase; 18.8% versus 4.8% with placebo. The majority of hypocalcaemia events were Grade 3 or less (14.4% of the sorafenib arm versus 12.7% of the placebo arm). Grade 4 events were reported in 6 subjects (2.9% total) treated with sorafenib and 2 subjects (1.3% total) treated with placebo. No Grade 5 hypocalcaemia events were reported. A dose-response effect for hypocalcaemia was demonstrated, with 4, 9 and 36 events reported for subjects on an average daily sorafenib dose of <400mg/day, ≥400 and <600 mg/day and ≥600 mg/day respectively. Similarly, the incidence of hypophosphataemia was higher in the sorafenib arm 19.3% versus 11.0% in the placebo arm. In the absence of any evidence to the contrary, such as the proportion of subjects with post-thyroidectomy hypoparathyroidism, the very common incidence of hypocalcaemia is assumed to be directly related to sorafenib exposure.

Hypophosphataemia occurred more commonly in the sorafenib arm, with 6 (2.9% all subjects) Grade 1 to 3 events and 7 (4.7% all subjects) in the placebo arm. No Grade 4 or 5 events were reported.

Hepatotoxicity

Hypoalbuminaemia, hyperbilirubinaemia and elevation of liver enzymes were more commonly observed in the sorafenib arm, consistent with the known side-effect profile. No subjects fulfilled the criteria for Hy's law.

Cardiotoxicity

Hypertension was reported in 43.0% of the sorafenib arm and 13.4% of the placebo arm. The known risk of cardiac ischaemia/infarction was reported for two patients in the sorafenib arm but not in any patients in the placebo arm.

Thyroid function

DTC is responsive to TSH and is associated with a worse outcome if TSH is not suppressed. Exogenous thyroxine is administered to DTC patients to suppress TSH by negative feedback to a level below 0.1 mU/L for high and intermediate-risk patients with the aim of improving the outcome of the cancer. For low risk patients the target range of for TSH

suppression is 0.1 to 0.5 mU/L. Despite treatment with exogenous thyroxine to suppress the effect of TSH on tumour associated TSH receptors, elevations of TSH were more commonly reported in the sorafenib arm 33.3% versus 13.4% with placebo. Consequently, elevation of TSH seen in DTC patients reflects inadequate or ineffective dosing with thyroxine. Elevations in T4 and T3 were more common in the sorafenib arm. A potential explanation for this finding is the increased incidence of hypoalbuminaemia in this arm.

Renal impairment

Grade 1 and 2 elevations of creatinine were reported in 6.8% of the sorafenib arm and 5.3% of the placebo arm. No Grade 3 or 4 elevations reported.

Relative safety profile of sorafenib in other cancers

A comparison of the adverse events rates in differentiated thyroid carcinoma, renal cell carcinoma and hepatocellular carcinoma was performed. Notable events with a higher rate of occurrence in DTC were diarrhoea, weight loss, hypocalcaemia, alopecia and palmar-plantar erythrodyaesthesia. The increased incidence of diarrhoea and weight loss may be a result of thyroid dysfunction rather than sorafenib per se. Pyrexia, nausea and vomiting had a lower rate of occurrence in DTC.

Supportive Phase II studies and postmarketing experience

No new toxicities have been described from five published Phase II studies of sorafenib use in DTC or from 1354 cases of 'off-label' use.

Clinical evaluator's recommendation

The clinical evaluator recommended that the application be approved

Risk management plan

The RMP evaluator identified the following issues for the Delegate to consider:

Hypocalcaemia

Hypocalcaemia was reported as an adverse event with higher frequency in Study 14295 (DTC) compared to the rates of hypocalcaemia reported in other studies. The Delegate notes that the sponsor has conservatively updated the EU RMP (version 12.1) and ASA for hypocalcaemia as a risk factor for QT prolongation and torsade de pointes.

Elevated TSH levels

The RMP evaluator recommended that "elevated TSH levels" should be added as an ongoing safety concern.

Exogenous thyroxine is administered to DTC patients to suppress TSH by negative feedback to a level below 0.1 mU/L for high and intermediate-risk patients with the aim of improving the outcome of the cancer. For low risk patients the target range of for TSH suppression is 0.1 to 0.5 mU/L. Consequently, elevation of TSH seen in DTC patients may reflect inadequate or ineffective dosing with thyroxine or deterioration in disease status rather than a direct effect of sorafenib itself.

The sponsor states, in regard to thyroxine dosing: '*Increased TSH levels could easily be managed by increasing the dose of thyroid hormone replacement therapy. Hence TSH elevation above 0.5mU/L is not considered a safety finding but rather an important clinical consideration for the overall management of patients with advanced DTC. The importance of*

monitoring TSH is highlighted in the proposed label in the Precaution section of the Australian Product Information.'

The Delegate is in agreement with the position of the sponsor that 'elevated TSH levels' do not need to be added as an "ongoing safety concern", given that monitoring of TSH levels and thyroxine dose-adjustment is the standard medical practice for this condition.

Pancreatic atrophy

The RMP evaluator recommended '*In the light of the recent published case reports of pancreatic atrophy, it is reasonable that pancreatic exocrine insufficiency/pancreatic atrophy be added to the list of ongoing safety concerns*'.

There are two published case reports of pancreatic atrophy and exocrine dysfunction in association with sorafenib exposure, resulting in steatorrhoea. From the two case reports it is not known whether the symptoms represented an irreversible change in pancreatic function but the authors state "*clinical symptoms, steatorrhoea and their biologic correlates resolved within 2 weeks of interruption of treatment*". The case reports do not demonstrate complete pancreatic exocrine dysfunction since the faecal elastase of one subject was elevated (2 times upper limit of normal (ULN)) instead of the decrease one would expect. Symptoms for the two individuals occurred after 18 months and 3 years, respectively, after sorafenib was commenced.

Given that diarrhoea is a symptom and not a diagnosis, the common occurrence of diarrhoea seen in sorafenib expose patients may include patients with exocrine pancreatic dysfunction. This diagnosis of exocrine pancreatic dysfunction requires specific investigation of exocrine function and not solely an assessment of pancreatic volume.

The sponsor has identified three further case reports of steatorrhoea from their global integrated clinical database of 3357 subjects. None of these subjects had decreases in amylase (3 subjects tested) or lipase (2 subjects tested) in association with steatorrhoea; therefore a certain diagnosis of exocrine pancreatic insufficiency cannot be made in these three individuals. No cases of pancreatic atrophy were identified from the sponsor's database.

Given the information available and the relatively small total denominator of patients exposed to sorafenib the Delegate considers it not possible to categorically refute a connection between either pancreatic atrophy, or pancreatic exocrine insufficiency and sorafenib exposure and should therefore be included in the list of ongoing safety concerns. Since 3357 subjects are identifiable in the company database, it remains plausible that either condition occurs with the descriptive frequency of 'rarely' or 'very rarely'.

References

Hescot et al. Pancreatic atrophy–a new late toxic effect of sorafenib. *NEJM* 2013; 369:1475-1476

Sullivan. Pancreatic atrophy from sorafenib. *NEJM* 2014; 370:186

Hypokalaemia, proteinuria and nephrotic syndrome

The Delegate notes that hypokalaemia is identified as a common adverse drug reaction (ADR) in the PI and therefore does not need to be additionally added to the list of ongoing safety concerns.

The Delegate notes that proteinuria is listed as a common ADR and nephrotic syndrome as a rare ADR therefore neither need to be additionally added to the list of ongoing safety concerns.

Increased sorafenib exposure in DTC

The increased exposure seen in patients with DTC is documented in the PI. The Delegate concurs with the sponsors' position that a potential pharmacological interaction does not fulfil the criteria of a 'safety concern'.

Reconciliation of issues outlined in the RMP report

Matters raised in the RMP were resolved to the satisfaction of the OPR prior to a final decision on this application.

Risk-benefit analysis

Delegate's considerations

There are currently limited treatment options for patients who have local recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine and consequently the disease has a poor outcome.

In the pivotal study, no patients achieved a complete response but a statistically significant proportion of subjects achieved a partial response or disease-control as a result of sorafenib exposure. Progression free survival was significantly longer, approximately five months for patients treated with sorafenib as compared to placebo. The assessment of overall survival is impaired by patients who crossed over from placebo to sorafenib. Health related quality of life assessments were obtained from a substantial number of trial entrants which demonstrated an early, temporary, improvement in quality of life score. Quality of life assessments were not worse than placebo in the later course of the illness, which together with the improvement in progression-free survival represents a benefit from treatment. No improvement in overall survival was demonstrated following sorafenib treatment.

The safety profile of sorafenib in differentiated thyroid carcinoma was generally comparable with the known adverse event profile of sorafenib, with hypocalcaemia and elevated TSH being newly reported toxicities. Impairment of TSH suppression is of concern given that this is an intended therapeutic intervention in patients with thyroid carcinoma. Elevation of TSH can be managed by titration of exogenous thyroxine routinely administered to patients and will require ongoing monthly TSH level assessment. Similarly, hypocalcaemia can be treated using oral supplementation. However, the comparative adverse event profile between cancers for which the drug is indicated demonstrates the absolute risk of adverse events is not the same for each disease type and may be associated with the increased exposure of sorafenib reported in patients with differentiated thyroid carcinoma. The sponsor has been unable to determine the cause of the increased exposure observed. A dose-response effect of sorafenib on occurrence of hypocalcaemia was demonstrated.

Conclusion

Efficacy of sorafenib in the proposed indication has been satisfactorily established. Given the limited treatment options for patients with disseminated thyroid cancer, the safety profile of sorafenib is acceptable for the proposed indication.

Proposed action

The Delegate proposed to approve the application.

The TGA's Office of Medicines Authorisation has a policy that where the US FDA has granted orphan designation for a drug and gone on to approve that use, evaluation for that use may be expedited here.

The clinical evaluation was supportive of the application.

Taking the clinical and RMP evaluations and the FDA position into account, the Delegate provisionally decided not to ask for Advisory Committee on Prescription Medicines (ACPM) advice about this application.

Request for ACPM advice

No advice was requested (see above).

Request for sponsor response

The sponsors' comments on proposed changes to the RMP and PI were requested. The details of these PI deliberations are beyond the scope of this AusPAR.

Advisory committee considerations

This application was not submitted to ACPM for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Nexavar containing sorafenib as tosylate for the new indication:

Differentiated thyroid carcinoma[23]

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

Specific conditions of registration applying to these goods

1. The European Risk Management Plan (Version 12 dated 31 October 2013) with Australian Specific Annex Version 1.1 dated April 2014), revised to the satisfaction of the TGA, must be implemented.

   An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required.

[23] The full indications are now:
Hepatocellular carcinoma.
Nexavar is indicated for the treatment of patients with advanced hepatocellular carcinoma (HCC).
Renal cell carcinoma
Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).
Differentiated thyroid carcinoma
Nexavar is indicated for the treatment of patients with locally advanced or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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