



**Australian Government**

**Department of Health**

Therapeutic Goods Administration

# Australian Public Assessment Report for Regorafenib

Proprietary Product Name: Stivarga

Sponsor: Bayer Australia Ltd

**November 2015**

**TGA** Health Safety  
Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- 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.
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- 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.

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# Contents

<b>Most common abbreviations</b>	<b>5</b>
<b>I. Introduction to product submission</b>	<b>8</b>
Submission details	8
Product background	8
Regulatory status	9
Product Information	10
<b>II. Quality findings</b>	<b>10</b>
<b>III. Nonclinical findings</b>	<b>10</b>
Introduction	10
Pharmacology	11
Pharmacokinetics	11
Toxicology	12
Nonclinical summary and conclusions	12
<b>IV. Clinical findings</b>	<b>13</b>
Introduction	13
Pharmacokinetics	17
Pharmacodynamics	19
Dosage selection for the pivotal studies	19
Efficacy	20
Safety	22
First round benefit-risk assessment	33
Clinical questions	34
Pharmacodynamics	34
Efficacy	35
Safety	35
Second round evaluation of clinical data submitted in response to questions	36
Second round benefit-risk assessment	36
<b>V. Pharmacovigilance findings</b>	<b>36</b>
Risk management plan	36
<b>VI. Overall conclusion and risk/benefit assessment</b>	<b>48</b>
Quality	48
Nonclinical	49
Clinical	49
Risk management plan	52
Risk-benefit analysis	52

Outcome	60
<b>Attachment 1. Product Information</b>	<b>60</b>
<b>Attachment 2. Extract from the Clinical Evaluation Report</b>	<b>60</b>

## Most common abbreviations

Abbreviation	Meaning
ACPM	Advisory committee on prescription medicines
ALT	Alanine aminotransferase
ARTG	Australian register of therapeutic goods
AST	Aspartate aminotransferase
AusPAR	Australian Public Assessment Report
BCRR	Blinded central radiology review
BMI	Body mass index
BSC	Best supportive care
$C_{av_{md}}$	Average concentration in plasma after multiple dosing
CBR	Clinical benefit rate
CCDS	Company core data sheet
CHMP, EU	Committee for Medicinal Products for Human use
CL	Clearance
CR	Complete response
CRC	Colorectal cancer
CT	Computed tomography
DCR	Disease control rate
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
FAS	Full analysis set
FDA	US Food and Drug Administration
GIST	Gastrointestinal stromal tumours
HCC	Hepatocellular carcinoma
HFSR	Hand-foot-skin reaction

Abbreviation	Meaning
HRQoL	Health-related quality of life
IGFBP	Insulin-like growth factor binding protein
IIV	Inter-individual variability
KIT	Mast/stem cell growth factor receptor (tyrosine kinase)
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
mCRC	Metastatic colorectal cancer
MedDRA PT	Medical Dictionary for Regulatory Activities Preferred Term
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition scan
NCE	New chemical entity
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NPC	Numerical predictive check
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptor
PFS	Progression free survival
PI	Product information
PPES	Palmar-plantar erythrodysesthesia syndrome
PR	Partial response

Abbreviation	Meaning
PRO	Patient reported outcomes
PSUR	Periodic Safety Update Report
QoL	Quality of Life
RECIST	Response evaluation criteria in solid tumours
SAF	Safety analysis set
SAP	Statistical analysis plan
SOC	System organ class
TKI	Tyrosine Kinase inhibitor
TTP	Time to progression
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VPC	Visual predictive check
WT	Wild type

## I. Introduction to product submission

### Submission details

<i>Type of submission:</i>	Extension of Indication
<i>Decision:</i>	Approved
<i>Date of decision:</i>	18 March 2015
<i>Date of ARTG entry:</i>	20 March 2015
<i>Active ingredient(s):</i>	Regorafenib
<i>Product name(s):</i>	Stivarga
<i>Sponsor's name and address:</i>	Bayer Australia Ltd 875 Pacific Highway, Pymble, New South Wales 2073
<i>Dose form(s):</i>	Tablet
<i>Strength(s):</i>	40 mg
<i>Container(s):</i>	Bottle
<i>Pack size(s):</i>	28 and 3 x 28
<i>Approved therapeutic use:</i>	<i>Stivarga is indicated for the treatment of patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.</i>
<i>Route(s) of administration:</i>	Oral (PO)
<i>Dosage:</i>	4 × 40 mg tablets daily at the same time each day for 3 weeks on therapy (21 days) followed by 1 week off therapy (7 days) to comprise a cycle of 4 weeks (28 days)
<i>ARTG number (s):</i>	200553

### Product background

This AusPAR describes the application by Bayer Australia Ltd to extend the indications of Stivarga® to include the treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with two tyrosine kinase inhibitors. The proposed dose and dosage regimen for the new indication is the same as that for the currently approved antineoplastic indication.

Regorafenib inhibits multiple protein kinases including those involved in normal cell functions and in oncogenesis, tumour angiogenesis and maintenance of the tumour microenvironment. Other drugs registered for the treatment of GIST are imatinib and sunitinib.



Currently, Stivarga is registered for the treatment of treatment of metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

The proposed dose and dosage regimen for the new indication is the same as that for the currently-approved antineoplastic indication (4 × 40 mg tablets daily at the same time each day for 3 weeks on therapy (21 days) followed by 1 week off therapy (7 days) to comprise a cycle of 4 weeks (28 days)).

Relevant TGA adopted European guidelines for this application include:

- EMA/CHMP/205/95/Rev.4: Guideline on the evaluation of anticancer medicinal products in man.
- EMA/CHMP/27994/2008/Rev.1 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/CPMP/EWP/1776/99 Rev. 1 Guideline on Missing Data in Confirmatory Clinical Trials.
- CPMP/EWP/2330/99: Points to consider on application with I. Meta-analyses; 2. One pivotal study

### Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 29 November 2013.

At the time the TGA considered this application, similar applications had been approved in the European Union (EU), the USA, Switzerland and Canada and had been submitted in New Zealand (see Table 1 for details).

**Table 1: International regulatory status**

Country	Regulatory status	Date of approval	Approved indications
European Union Rapporteur: The Netherlands. Co-rapporteur: Italy	Approved	28 July 2014	Stivarga is indicated for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib
United States of America (priority review)	Approved	25 January 2013	Stivarga is indicated for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.
Canada	Approved	4 October 2013	Treatment of adult patients with metastatic and/or unresectable gastrointestinal stromal

Country	Regulatory status	Date of approval	Approved indications
			tumors (GIST) who have had disease progression on or intolerance to imatinib mesylate and sunitinib malate treatment. Approval of STIVARGA is based on Progression Free Survival (PFS) (see Clinical Trials)
Switzerland	Approved	13 November 2014	Stivarga is indicated for the therapy of patients with metastatic or inoperable gastrointestinal stromal tumors (GIST) previously treated with two tyrosine kinase inhibitors (imatinib and sunitinib).
New Zealand	Submitted		

### 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 <<https://www.tga.gov.au/product-information-pi>>.

## II. Quality findings

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

## III. Nonclinical findings

### Introduction

The nonclinical submission consisted of one primary pharmacology study to support the new indication, two studies (a safety pharmacology and a pharmacokinetic study) that were submitted previously but were not evaluated, studies to assess the disposition of and possible pharmacokinetic drug interactions with the two main pharmacologically active metabolites of regorafenib (M-2 and M-5) and a toxicity study in juvenile animals.

The results from these studies are discussed below only with their relevance to the new indication or for possible changes to the Product Information document.

## Pharmacology

### Rationale and mechanism of action

Approximately 85% of GISTs harbour a gain-of-function mutation of KIT<sup>1</sup>. Regorafenib is an inhibitor of KIT kinase as well as Platelet-derived growth factor receptor (PDGFR)- $\alpha$ . (activating mutations of this enzyme have been observed in some GISTs). Therefore, regorafenib is expected to have anti-tumour activity against most GIST types.

### Primary pharmacology

In mice bearing xenografts of human GIST, oral regorafenib treatment inhibited tumour growth. Tumour regression was observed in two different models. The efficacious dose (50 mg/kg; 150 mg/m<sup>2</sup>) was similar to the clinical dose (160 mg; 106 mg/m<sup>2</sup>) on a body surface area basis. Tumour re-growth was observed with the cessation of treatment but anti-tumour activity was seen with re-treatment. The submitted pharmacology study supports the proposed indication.

## Pharmacokinetics

### Pharmacokinetic drug interactions

M-2 and M-5 are significant human metabolites (exposures similar to or greater than regorafenib) that are pharmacologically-active. Therefore, these metabolites could potentially alter the pharmacokinetic profile of co-administered drugs that are substrates for enzymes or transporters. Likewise, co-administered drugs that alter the pharmacokinetics of M-2 or M-5 could alter the safety/efficacy profile of regorafenib.

Studies examining the metabolism of M-2 suggested a prominent role of cytochrome P450 (CYP) isozyme 3A4 in the degradation of M-2. Therefore, inducers or inhibitors of CYP3A4 may alter the plasma kinetics of M-2. As the Stivarga PI document already contains sufficient warnings regarding the co-administration of regorafenib with CYP3A4 inducers/inhibitors no further additions are recommended.

Neither M-2 nor M-5 induced CYP1A2, 2B6 or 3A4 expression in human hepatocytes. A similar profile was observed with regorafenib.

Unlike regorafenib, M-2 and M-5 are substrates for P-glycoprotein. Given M-2 and M-5 are excreted into bile and undergo enterohepatic recirculation inhibitors/inducers of P-glycoprotein may alter the plasma exposures to M-2 and M-5 (by affecting re-absorption). However, these compounds are highly permeable, so the extent of the effect is unknown. Nonetheless, a statement should be included in the PI document.

Both M-2 and M-5 were weak substrates for breast cancer resistance protein (BCRP). Inhibitors/inducers of BCRP may alter the disposition of M-2 and M-5. A statement to this effect should be included in the PI document.

At concentrations far exceeding those expected clinically, M-2 and M-5 had no significant inhibitory activity on Multidrug resistance-associated protein 2 (MRP2) or organic cation transporter (OCT) activity in *in vitro* assays. Regorafenib was also not an inhibitor of MRP2 transport. Therefore, drug interactions involving MRP2 and OCT transporters are not anticipated.

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<sup>1</sup> Overton, L.C. and M.C. Heinrich. (2014) Regorafenib for treatment of advanced gastrointestinal stromal tumours. *Expert Opin. Pharmacother.* **15(4)**: 549-558.

Both M-2 and M-5 had significant inhibitory activity on BCRP transport. While the 50% inhibitory concentration ( $IC_{50}$ ) values (0.39  $\mu$ M and 0.15  $\mu$ M for M-2 and M-5, respectively) were approximately 33 times higher than the clinical free plasma peak concentration ( $C_{max}$ ) for these metabolites<sup>2</sup>, the margin is not sufficient to eliminate the possibility that these metabolites may alter the disposition of BCRP substrates<sup>3</sup>. M-2 was also an inhibitor of P-glycoprotein ( $IC_{50}$  1.5  $\mu$ M; 125 times the clinical  $C_{max}$ ), but M-5 was not an inhibitor of this transporter. Both BCRP and P-glycoprotein are expressed in the GI tract and both M-2 and M-5 are excreted in bile. Therefore, M-2 and M-5 may alter the disposition of co-administered BCRP substrates and M-2 may alter the disposition of P-glycoprotein substrates. As regorafenib is also an inhibitor of BCRP and P-glycoprotein, only minor modification to the text in the PI document is recommended.

## Toxicology

### Paediatric use

Stivarga® is not intended to be used in a paediatric patient group. Nonetheless, the sponsor conducted a juvenile animal study to support a paediatric development program for the drug. Juvenile rats (aged 15 days at the commencement of treatment) received regorafenib ( $\leq 4$  mg/kg/day orally (PO)) for 20 days, followed by a 4 week recovery period to assess the reversibility of findings. There were no consistent differences in regorafenib exposure on Day 1 of dosing compare to Day 20 and exposures were generally similar to those seen in adults at equivalent doses.

In general, findings in juvenile animals were similar to those seen in adult animals (at similar doses/exposures) with target organs being the liver, skin, teeth, bone/cartilage, GI tract, reproductive organs, haematopoietic/lymphoreticular system and endocrine system. Many of the changes observed are indicators of growth retardation, emaciation and dehydration. Retarded development may be attributed to the anti-proliferative and anti-angiogenic action of regorafenib.

While growth retardation appeared to be reversible, there were some findings that were either not reversible or were not completely reversible: dilation and hyperplasia of the duodenum, gross discolouration/fracture of teeth, and increased width of epiphyseal growth zones, growth plate involution or osteochondrosis. The bone and teeth effects are particularly relevant to a paediatric patient group. While similar bone and teeth effects were observed in adult rats, they are not considered relevant to adult human subjects; unlike primates, rodent teeth grow continuously and rodent physes have significant postpubertal growth.

Therefore, effects on developing bones and teeth are an additional concern for paediatric patients. It is recommended that statements be included in the PI document.

### Nonclinical summary and conclusions

- No major deficiencies were identified in the submitted nonclinical dossier.
- Regorafenib suppressed tumour growth in mice bearing xenografts of human GIST. The efficacious dose was similar to the clinical dose, thus supporting the proposed indication.

<sup>2</sup> Free fractions were calculated as 12 nM and 4.4 nM for M-2 and M-5, respectively (see the report for PM-2012-02342-3-4; pp 9-10)

<sup>3</sup> EMA Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr.\*)

- No additional safety concerns are indicated by the submitted data.
- There are no nonclinical objections to the proposed extension of indications.
- A number of nonclinical studies were submitted that are relevant to statements in the PI document. Amendments to the PI were recommended to the Delegate.

## 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

The Sponsor's clinical rationale was outlined in the covering letter of the submission, the sponsor's Clinical overview and in the introduction to pivotal trial 14874 as follows:

*GIST is the most common form of mesenchymal tumour in the gastrointestinal tract. The estimated incidence of GIST in the total population is 11 – 20 patients per million/year.*

*These tumours can start anywhere in the gastrointestinal tract, but they occur most often in the stomach (50% to 70%) or the small intestine (20% to 30%)... Patients tend to be middle aged or older, with a slight male predominance... Aggressive GISTs metastasise to the liver and in the abdomen, rarely to the lymph nodes.*

*The most important criteria for the assessment of the malignant potential of GISTs are tumour size and mitotic rate. Approximately 90% of GISTs express CD117, the antigen based on the KIT receptor tyrosine kinase (RTK), which can be detected by immunohistochemical KIT staining. Primary KIT mutations are found in approximately 70 – 80 % of GIST and occur predominantly in exon 11, occasionally in exon 9, and only rarely in exons 13 and 17. In 4 to 7% of GISTs, mutations are found in platelet-derived growth factor receptor  $\alpha$  (PDGFR $\alpha$ ), most frequently in exon 18.*

*In patients with metastatic and/or unresectable GIST, molecular targeted therapy has been the focus of the therapeutic approach over the past decade. The role of radiation therapy is generally considered limited in the management of GIST patients. Similarly, attempts to treat GISTs with systemic chemotherapy have been unsuccessful, with responses typically less than 10% at the cost of significant toxicities.*

*Imatinib (Glivec), and upon imatinib failure, sunitinib (Sutent), both tyrosine kinase inhibitors (TKIs), are currently approved for the treatment of metastatic and/or unresectable GISTs in Australia. However despite the activity of sunitinib, the majority of patients with metastatic GIST will progress within 6-9 months and there is no third line therapy with any activity against this disease approved by regulatory authorities anywhere in the world apart from the United States and Canada where STIVARGA is registered for this indication.*

*Imatinib and sunitinib may fail due to the clonal emergence of secondary mutations in the tyrosine kinase receptors KIT or PDGFR $\alpha$ , or in signalling molecules such as BRAF which restores receptor signalling activity and leads to tumour relapse.*

*Treatment options are limited for patients progressing on imatinib and sunitinib. Second-generation TKIs, such as sorafenib, dasatinib, and nilotinib, have shown*

*activity in patients with imatinib- and sunitinib-resistant GIST. Although the current NCCN guidelines allow consideration of other commercially available small molecule kinase inhibitors such as nilotinib or sorafenib, they cannot be regarded as a 'standard' or 'approved' treatment for patients who have progressed.*

*Regorafenib, an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (vascular endothelial growth factor receptor [VEGFR]1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumour microenvironment (platelet derived growth factor receptor [PDGFR], fibroblast growth factor receptor [FGFR]), may potentially overcome the mutation induced resistance through binding to structurally different mutant kinases.*

Further, the sponsor's justification for the proposed label given in the sponsor's Clinical Overview of the submission states:

*The proposed label considers the currently available approved treatment options for patients with GIST. The only approved treatments for patients with GIST are the two TKIs imatinib and sunitinib. All patients in the pivotal trial (14874) had been treated with these TKIs. They had to present with disease progression on, or intolerance to, imatinib, and disease progression on sunitinib treatment. Patients with GIST have a high unmet medical need and further effective therapies are required. This application presents data demonstrating a positive benefit/risk assessment of regorafenib for this population.*

**Comment:** The clinical rationale for the submission as stated by the sponsor would seem valid and acceptable; for the treatment of aggressive GIST not responding to currently approved therapies and for which there is no currently approved standard treatment.

## Contents of the clinical dossier

### *Scope of the clinical dossier*

The clinical dossier documented a development program of pharmacological analyses, pivotal and other clinical trials relating to the proposed extension of indications. Updated safety data was also included.

The submission contained the following clinical information which has been evaluated:

- Pharmacokinetic (PK) studies
  - PH-36984 (11651) Open label, Phase I study to determine the safety, tolerability, maximum tolerated dose, PK, and biomarker status of BAY 73-4506 in patients with advanced malignancies
  - PH-37053 (14996) Uncontrolled, open-label, non-randomised, Phase I study to investigate the PK, safety, tolerability and efficacy of BAY 73-4506 in Chinese patients with advanced, refractory solid tumours

**Comment:** Interim reports of the above two studies (11651 and 14996) were previously evaluated by the TGA in the application for the indication of previously treated metastatic CRC. The updated clinical study reports (CSRs) submitted with this application have been evaluated only with respect to the new information provided.

- One pharmacodynamic (PD) study
  - PH-36866 (14814) An open-label, non-randomized Phase I study of regorafenib (BAY 73-4506) to evaluate cardiovascular safety parameters, tolerability,

pharmacokinetics, and anti-tumour activity in patients with advanced solid tumours

**Comment:** The interim report of the above study (14814) was previously evaluated by the TGA and this submitted final report has been evaluated with respect to changes from the interim report.

- Full population pharmacokinetic (Pop PK) analyses
  - R-8731 (14653) Population PK analysis of regorafenib and metabolites M2 and M5 in studies 11650 and 14387
  - R-8814 (16282) Population PK analysis of regorafenib and metabolites M2 and M5 in Phase III studies 14387 and 14874
- Other Pop PK analysis reports
  - PH-37027 (16392) Exploratory analysis of regorafenib PK using physiologically-based PK modelling – effect of hepatic and renal impairment
  - PH-37386 Regorafenib dose selection document
- One pivotal efficacy/safety study in the proposed indication, and supporting analyses.
  - A59137 (14874) A randomised, double-blind, placebo-controlled Phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC for subjects with metastatic and/or unresectable GIST whose disease has progressed despite prior treatments with at least imatinib and sunitinib (GRID)
    - § PH-37123 (14874) Genetic biomarker analysis of study 14874 (GRID)
    - § PH-37168 (14874) Non-genetic biomarker analysis of study 14874 (GRID)
- Supportive study in the proposed indication, and supporting document
  - 14935 Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GIST after failure of imatinib and sunitinib: a multicentre Phase II trial (published journal paper)
- One other safety study (not related to proposed indication)
  - A62282 (14596) An uncontrolled open label multicentre Phase II safety study of BAY 73-4506 in patients with hepatocellular carcinoma
- One pooled safety analysis
  - Global integrated analysis of safety (included in the sponsor's Summary of Clinical Safety)
- One protocol document related to proposed indication
  - 16339 Protocol: An open-label expanded access program of regorafenib in patients with GIST after disease progression on or intolerance to imatinib and sunitinib

The submission also contained the following protocols and reports that have not been fully evaluated here. This is because they were either not directly relevant to the proposed indication in this submission or the safety of regorafenib as monotherapy or were an exploratory analysis (generally based on the population PK analysis):

- PH-37121 (11728) An uncontrolled, open-label Phase II study in subjects with metastatic adenocarcinoma of the colon or rectum who are receiving first line chemotherapy with mFOLFOX6 in combination with regorafenib.

- 15808 Protocol: A randomised, double-blind, placebo controlled Phase III study of regorafenib plus BSC versus placebo plus BSC in Asian subjects with mCRC who have progressed after standard therapy (CONCUR).
- 15967 Protocol: An open-label Phase IIIb study of regorafenib in patients with mCRC who have progressed after standard therapy
- Pop PK analysis exploratory reports
  - R-8737 (14653) Exposure-response analysis of regorafenib in Phase III study 14387.
  - PH-36914 (14387) –Exploratory analysis of relationship between the exposure to regorafenib parent compound and regorafenib aggregate (regorafenib compound and its two active metabolites M2 and M5) and relevant safety data in Phase III study 14387.
  - PH-37122 (14387) - Exploratory analysis of relationship between the exposure to total regorafenib (regorafenib aggregate, irrespective of plasma protein binding) and relevant safety data in Phase III study 14387.
  - R-8813 (16282) Exposure-response analysis of regorafenib in Phase III GRID study 14874.
  - PH-37281 (14874) Exploratory analysis of relationship between the exposure to regorafenib parent compound, regorafenib aggregate, and regorafenib total and relevant safety data for pooled data from GRID (Study 14874) study.
  - PH-37105 (14387+14874) Exploratory analysis of relationship between the exposure to regorafenib parent compound, regorafenib aggregate, and regorafenib total and relevant safety data for pooled data from CORRECT (Study 14387) and GRID (Study 14874) studies.
  - R-8715 (14935) A non-randomised open-label, multi-center Phase II study evaluating the efficacy and safety of regorafenib in patients with metastatic and/or unresectable GIST, resistant or tolerant to at least imatinib and sunitinib. This was an analytical report of bio-analytical samples, and has not been evaluated in this CER.

### ***Paediatric data***

The submission did not include paediatric data. A paediatric investigation plan is in effect in the EU, while a paediatric waiver has been granted in the US due to the impracticality of performing paediatric studies for CRC, and the drug being granted orphan drug status for GIST.

**Comment:** Due to the low incidence of GIST in the paediatric population, paediatric data is not necessary for this submission.

### ***Good clinical practice***

It was stated that the conduct of all clinical studies submitted in this application met all local legal and regulatory requirements. All studies were stated to have been conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP).

All population PK and exposure-response evaluations were stated to have been conducted in accordance with the recent FDA guidance on population pharmacokinetics (1999) and reported in accordance with the respective EMEA guideline (2007).



## Pharmacokinetics

### Studies providing pharmacokinetic data

Table 2 shows the studies relating to each pharmacokinetic topic. The main pharmacokinetic data submitted with this submission related to population pharmacokinetic analyses.

**Table 2. Submitted pharmacokinetic studies.**

PK topic	Subtopic	Study ID (report number)	*
<b>PK in special populations</b>	Target population § - Single dose		
	- Multi-dose	14996 (PH-37053, 2 <sup>nd</sup> Interim report)	
	Cancer patients		
	Hepatic impairment		
	Renal impairment		
	Neonates/infants/children/adolescents		
	Elderly		
<b>Genetic/gender-related PK</b>	Males versus females		
	Chinese patients	14996 (PH-37053, second Interim report)	*
<b>Population PK analyses</b>	Healthy subjects		
	Target population	14653 (R-8731) 16282 (R-8814)	* *
	Other		

\* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Table 3 lists pharmacokinetic results that were excluded from consideration due to study deficiencies.

**Table 3: Pharmacokinetic results excluded from consideration.**

Study ID	Subtopic(s)	PK results excluded
11651 (PH-36984)	Expansion cohort analysis of patients with HCC and NSCLC	Effect of hepatic impairment on regorafenib PK - not based on representative sample
14653 (R-8738)	Exposure-response analysis of regorafenib in Phase III study 14387	Exploratory analysis – not fully evaluated

Study ID	Subtopic(s)	PK results excluded
14387 (PH-36914)	Exploratory analysis of regorafenib exposure and safety data in study 14387	Exploratory analysis – not fully evaluated
14387 (PH-37122)	Exploratory analysis of regorafenib exposure and safety data in study 14387	Exploratory analysis – not fully evaluated
16282 (R-8813)	Exposure-response analysis of regorafenib in Study 14874	Exploratory analysis – not fully evaluated
14874 (PH-37281)	Exploratory analysis of regorafenib exposure and safety data from Study 14874	Exploratory analysis – not fully evaluated
14387+14874 (PH-37105)	Exploratory analysis of regorafenib exposure and pooled safety data from Studies 14387 and 14874	Exploratory analysis – not fully evaluated
16392 (PH-37027)	Exploratory analysis of regorafenib pharmacokinetics using physiologically-based pharmacokinetic (PBPK) modelling – effect of hepatic and renal impairment	Exploratory analysis, based on modelled parameters (no actual patients with hepatic or renal impairment) and in virtual populations, base model not submitted for evaluation.

### Evaluator's conclusions on pharmacokinetics

The main pharmacokinetic data submitted with this submission related to two population pharmacokinetic analyses, both based on a base population PK model derived from Study 11650. The first analysis also used sparse sampling data from Study 14387 (R-8731) and the second analysis was an update on the first which also used data from Study 14874 (R-8814). These population PK analyses modelled the PK of regorafenib and its two main active metabolites M2 and M5 after multiple dosing, and looked at the impact of various pre-specified covariates.

These population PK analyses were adequately performed, however a limitation is that there were limited subjects with hepatic and renal impairment in the datasets used to construct the model (31/461 patients with mild-moderate hepatic impairment). Therefore, the ability of the models to predict the PK of patients with hepatic or renal impairment (particularly moderate or severe hepatic impairment) is limited.

The main findings of the population PK analyses were that the covariates found to have a significant impact on the PK of parent regorafenib were bilirubin level at baseline (greater exposure with higher bilirubin levels), study (greater exposure in Study 14387 compared to Study 14874), and body mass index (BMI) (greater exposure with higher BMI). Both metabolites M2 and M5 were also influenced by these covariates via their effect on parent regorafenib, and in addition the metabolites were also influenced by, race (lower exposure in Asian populations) and body weight (lower exposure with increasing weight). Sex also had a significant effect on the PK of M5 (higher exposure in females).

As the contribution of these covariate effects to overall variability were small (for parent regorafenib a decrease in unexplained variability in clearance (CL) from co variance (CV)= 46 % to 44%), none of these covariate effects were assessed by the sponsor to be clinically

relevant. However, as discussed, it is the opinion of this evaluator that there is insufficient data from patients with hepatic impairment to be confident in this conclusion. Therefore it is recommended that the proposed wording in the PI be amended accordingly. The conclusions that effects of race, sex and BMI/weight on the PK of regorafenib and its metabolites are not clinically significant are considered probable however the differences with race may have significance in light of differences in the safety profile of regorafenib between races (see *Safety in special populations*, Attachment 2). Only an interim report was provided for Study 14996 (PH-37053) in Chinese patients and no additional conclusions have been drawn regarding the PK of regorafenib in this patient group.

The results of Study 11651 (PH-36984) were not considered in this evaluation as the assessment of the impact of hepatic impairment on PK in a cohort of patients with hepatocellular carcinoma were based on single dosing only, and not multiple dosing as is proposed for the clinical indication. The PK after multiple dosing has been found to be significantly different compared to single dosing and this difference could plausibly be greater with hepatic impairment given that regorafenib is metabolised primarily by the liver and has the adverse effect of severe hepatic toxicity.

The results of several exploratory analyses of the effect of regorafenib (and metabolite) exposure levels and response and safety parameters based on the population PK analyses have not been fully evaluated, as these were exploratory in nature and not primary outcomes of the studies. These are briefly described in the Efficacy (*Analyses performed across trials (pooled analyses and meta-analyses)* Attachment 2) and Safety (*Studies providing evaluable safety data*, Attachment 2) sections.

## **Pharmacodynamics**

### **Studies providing pharmacodynamic data**

One study (14814) was submitted providing pharmacodynamic data on the effect of regorafenib on cardiovascular safety parameters, specifically QT/QTc<sup>4</sup> intervals and left ventricular ejection fraction (LVEF) in subjects with solid tumours. An interim report of this study was previously evaluated by the TGA and the updated final CSR was submitted with this application. This PD study did not have any deficiencies that excluded its results from consideration.

### **Evaluator's conclusions on pharmacodynamics**

The final CSR for Study 14814 did not provide any evidence of an association between regorafenib use and QT prolongation after one cycle of maximum treatment or clinically significant worsening of LVEF after 2 cycles of maximum treatment.

### **Dosage selection for the pivotal studies**

With this submission, 'PH-37386 Regorafenib dose selection document' was included. This was a non-compartment PK evaluation dated 21 June 2013 and outlined the rationale for the selection of regorafenib dose for Phase II-III clinical development based on Phase I data from Studies 11650 and 11651. In Study 11650, regorafenib was administered at

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<sup>4</sup> In cardiology, the 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. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. The QT interval is dependent on the heart rate in an obvious way (the faster the heart rate the shorter the R-R Interval and QT interval) and may be adjusted to improve the detection of patients at increased risk of ventricular arrhythmia (QTc).

dosages from 10 mg to 220 mg orally daily with a 21 days on/7 days off schedule, and an maximum tolerated dose (MTD) was determined to be 160 mg once a day (QD) with intermittent dosing. In Study 11651, regorafenib was administered orally daily in a continuous treatment regimen with a dose range from 20 mg to 140 mg, and a MTD was determined to be 100 mg QD with a continuous dosing schedule.

Based on analysis of the two Phase I studies, the regorafenib dose selected for further clinical development was 160 mg once daily in the treatment schedule 21 days on/7 days off (over 100 mg once daily with continuous dosing), based on the following considerations:

- The safety/tolerability of the two MTD dosages were similar with the two dosage regimens, however for approximately the same extent of toxicity, a 20% higher total dose of regorafenib could be delivered at MTD in the intermittent schedule in a 28 day period.
- A break in dosing provided by the intermittent schedule may give patients a chance to at least partially recover from toxicities, and early clinical efficacy results did not suggest an increase in tumour flare during the treatment break period.
- The higher exposure during the dosing days in the intermittent schedule may prove advantageous with respect to anti-tumour activity in some tumours.
- An intermittent dosing schedule may offer an advantage in terms of 'combinability' with cytotoxic agents which are dosed intermittently and decrease the chances of any possible PK drug-drug interaction.

**Comment:** It is noted that this dose selection document was produced at a date much later than the initiation of the Phase II and III trials which it seeks to inform. The individual Phase I studies 11650 and 11651 were previously evaluated by the TGA and have not been evaluated again in this CER. Nevertheless, the dosage selection for further development would seem acceptable based on the rationale outlined above, and this has been the dose and formulation used in subsequent clinical trials for a range of indications. This is also the dosage currently registered for treatment of metastatic CRC in Australia.

In Pivotal Study 14874 in this submission, in line with the dose selection document, patients randomised to regorafenib received 160 mg orally once daily for 3 weeks of every 4 week (28 day) cycle (intermittent dosing: 3 weeks on/1 week off treatment). Each 160 mg dose consisted of four 40 mg immediate-release coated tablets, with rapid dissolution characteristics under in vitro test conditions. Regorafenib was to be taken in the morning with approximately 240 mL of water after a low-fat (< 30% fat) breakfast.

**Comment:** The dosage selection for the pivotal trial in this submission would seem acceptable and is in line with that determined in the dose selection document.

## Efficacy

### Studies providing efficacy data

One pivotal efficacy/safety study in the proposed indication, and supporting analyses were provided.

- A59137 (14874) A randomised, double-blind, placebo-controlled Phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC for subjects with metastatic and/or unresectable GIST whose disease has progressed despite prior treatments with at least imatinib and sunitinib (GRID)

- PH-37123 (14874) Genetic biomarker analysis of study 14874 (GRID)
- PH-37168 (14874) Non-genetic biomarker analysis of study 14874 (GRID)
- Supportive study in the proposed indication and supporting document
  - 14935 Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GIST after failure of imatinib and sunitinib: a multicentre Phase II trial (published journal paper)

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

*For treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with two tyrosine kinase inhibitors*

#### **Pivotal study 14874**

This was a generally well conducted study. The primary outcome of centrally assessed progression free survival (PFS) is acceptable, with overall survival (OS) assessed as a secondary outcome. Queries related to the handling of missing data have been posed as questions to the sponsor (see *Clinical questions*).

For the primary outcome of PFS after a pre-specified 144 events, there was a statistically and clinically significant beneficial effect of regorafenib treatment of 4.8 months (95% confidence interval (CI): 4.0-5.7) over placebo of 0.9 months (95% CI: 0.9, 1.1), with a Hazard Ratio (HR) of 0.268 (95%CI 0.185, 0.388,  $p < 0.000001$ ). This result was supported by secondary and subgroup analyses and the magnitude of this effect is sufficient that some differences in the baseline disease characteristics between the placebo and regorafenib patient groups are not likely to significantly impact on the results.

The immaturity of OS data means that no definitive conclusions can be drawn on the effect of regorafenib treatment on OS compared to placebo, although a beneficial effect of regorafenib was suggested with a HR of 0.772 (95% CI: 0.423, 1.408). Analysis of further OS data as it becomes available would be beneficial and is recommended. However, the ability of subjects randomised to the placebo group to cross over to regorafenib treatment on disease progression means that the true OS benefit attributable to regorafenib will be difficult to estimate.

Analysis of other secondary efficacy outcomes including Time to Progression (TTP), Overall Response Rate (ORR), Disease Control Rate (DCR) and duration of response supported the benefit shown in PFS in the primary analysis of regorafenib over placebo.

However, there was no demonstrated benefit of regorafenib in terms of Quality of Life compared to placebo but rather a clinically meaningful decrease in role functioning was observed.

Overall, the use of one pivotal study in this submission appears acceptable. The study was satisfactorily conducted to ensure internal validity (randomisation and use of centrally blinded assessments); external validity (subjects were representative of the target group); the results were clinically relevant and statistically significant (large gains in PFS compared to placebo); data quality was good and internally consistent across subgroups and endpoints; and there were multiple centres involved across many countries representing the likely target population.

#### **Supportive study 14935**

Study 14935 was a Phase II study assessing the clinical benefit of regorafenib in patients with unresectable or metastatic GIST who had previously been treated with imatinib and sunitinib. The results found a CBR of 79% (95% CI: 61%, 91%) and PFS 10.0 months (95% CI: 8.3 - 14.9) with regorafenib treatment. Due to different methodologies, these results

cannot be directly compared with those of the clinical trial, although it is noted that they are in a similar direction although of greater magnitude. Reasons for the different magnitude of the results may include the longer time between tumour assessments in this study, as well as the use of investigator rather than central assessments. Despite this, the results of this study are in agreement with and therefore support those of the pivotal Study 14874 in patients with metastatic or unresectable GIST.

### ***Biomarker analyses***

Only exploratory biomarker analyses have been performed and thus no definitive conclusions can be drawn regarding the efficacy of regorafenib according to biomarker status. Exploratory evidence suggests a beneficial effect of regorafenib over placebo with KIT mutations. However, in two patients with KRAS<sup>5</sup> and BRAF<sup>6</sup> mutations, clinical outcomes were poorer. Due to the importance of risk-benefit considerations in treatment decisions, further evidence regarding the efficacy of regorafenib in patients with KRAS and BRAF mutations would be beneficial, particularly in light of documented differences in the efficacy of imatinib and sunitinib according to biomarker status. Further comment has been sought from the sponsor as a clinical question (see *Clinical questions* below).

## **Safety**

### **Studies providing safety data**

#### ***The following studies provided evaluable safety data:***

##### *Pivotal efficacy studies*

In the pivotal Study 14874, all 198 randomised patients who had received at least one dose of study medication were included in the analysis of safety (SAF). Relevant for the analysis, this was separated into: the double-blind treatment period (regorafenib versus placebo) that included 132 patients randomised to receive regorafenib + BSC and 66 patients randomised to placebo + BSC (n=198 in total), and the combined double blind and/or open-label period (all regorafenib treated patients) which included those patients randomised to and who received regorafenib (n=132) and those randomised to placebo who crossed over to regorafenib in the open label phase (n=56), for an overall n=188. The Safety follow-up period included a 30 ( $\pm$  7) day window after last intake of study drug, after which patients entered the Survival Follow-up Period (at which time patients were followed for survival only at 3 month intervals and safety follow up was ceased).

##### *Dose-response and non-pivotal efficacy studies*

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study 14935 provided data based on a published journal paper only. Only commonly occurring toxicities (occurring in  $\geq$  25% of patients) were presented in this paper, which limits the interpretation and analysis of this study from a safety perspective.
- Study 14814 provided data on the effect of regorafenib on cardiovascular safety parameters, specifically QT/QTc intervals and left ventricular ejection fraction (LVEF).

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<sup>5</sup> Kirsten rat sarcoma viral oncogene homolog (KRAS) is a protein that in humans is encoded by the KRAS gene. The protein product of the normal KRAS gene performs an essential function in normal tissue signaling and the mutation of a KRAS gene is an essential step in the development of many cancers.

<sup>6</sup> 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. It is faulty (mutated) in some human cancers.

*Other studies evaluable for safety only*

*Study 14596* (A62282) was an uncontrolled open label multicentre Phase II safety study of regorafenib in patients with hepatocellular carcinoma (HCC). The primary objective was to assess the safety profile of regorafenib, with secondary endpoints to assess its efficacy in HCC patients with liver function status Child-Pugh Class A<sup>7</sup> who had failed prior systemic treatment with sorafenib.

**Comment:** Study 14596 was not included in the efficacy evaluation because it was an uncontrolled study for a different indication than that proposed in this application, and had a different underlying population. Furthermore, the primary endpoint was safety rather than efficacy. The report submitted was an updated addendum of an earlier report that was previously evaluated by the TGA and included a detailed PK analysis. Only the updated safety information provided in the Addendum with this application has been evaluated in this CER.

*Pooled safety data*

**Global integrated analysis:** Data cut-off 28 February 2013. The main analysis included only completed company sponsored studies for which a clean clinical database was available. Three data pools were produced from 10 clinical studies of regorafenib in cancer patients:

- Pool 1: All regorafenib monotherapy-treated patients in completed Phase I to III studies (n=1,073) including:
  - 2 Phase III studies (14387 and 14874)
  - 6 uncontrolled Phase I and II studies of regorafenib at the intended dosing regimen of 160mg daily for 3 weeks on/1 week off treatment cycles (Studies 11726, 14596, 12434, 13172, 14814 and 14996)
  - 2 Phase I dose escalation studies (11650 and 11651)
    - § Pool 2: Includes placebo-controlled safety data from the double-blind period of the pivotal Phase III study in patients with GIST (Study 14874, n=132)
    - § Pool 3: Includes placebo-controlled safety data from the double-blind phase of the Phase III studies 14387 and 14874 (n=632)

**Comment:** Throughout this CER, reference is primarily made to Pool 1 of the global integrated analysis, as the results of Pool 2 are presented separately as that of Pivotal Study 14874. The safety results of Study 14387 that make up the rest of Pool 3 were previously evaluated by the TGA.

**Bayer HealthCare safety database:** Includes all serious adverse events (SAEs) from completed and ongoing studies (including combination studies) (more than 3,500 patients) and early access programs (more than 500 patients), SAEs reported within an ongoing patient support program and spontaneous reports (data cut-off 28 February 2013).

- Non-pooled studies in cancer patients included: 15808, 15967, 11728, 11656, 14458, 14935, 15579, 15344 and 15968.

<sup>7</sup> Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis.

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%



- Non-pooled studies in healthy volunteers included: 12435, 12436, 12437, 14656 and 15524.

**Comment:** The above studies were not submitted for evaluation and have thus not been evaluated. The results from the summaries of SAEs and deaths are included in *Deaths and other serious adverse events, Attachment 2*).

### Patient exposure

A summary of exposure to regorafenib and comparators in clinical studies presented in this submission is provided in Table 4 and exposure to regorafenib according to dose and duration is provided in table 5.

*Pivotal Study 14874:* During the double-blind period, patients who were assigned to receive regorafenib + BSC underwent a median treatment duration of 22.94 weeks (mean 20.22 weeks) and patients who were assigned to receive placebo + BSC underwent a median of 6.98 weeks (mean 9.08 weeks). Among the placebo + BSC patients who crossed over to open-label treatment with regorafenib + BSC, the median treatment duration with regorafenib + BSC was 14.96 weeks (mean 15.26 weeks). The median treatment duration with regorafenib + BSC for all (n=188) regorafenib-treated patients across both study periods was 22.94 weeks (mean 21.12 weeks).

The median daily dose of regorafenib during the double-blind treatment period was 146.83 mg (mean 139.79 mg). Patients who crossed over from placebo received a median daily dose of 160.00 mg regorafenib (mean 146.19 mg) and the median daily dose to all regorafenib-treated patients for both study periods was 153.06 mg regorafenib (mean 140.31 mg).

Dose modifications were more common among patients who were assigned to receive regorafenib + BSC. During the double-blind period, dosing modifications were instituted for 72.0% of regorafenib-treated patients and 25.8% of placebo-treated patients. Among the placebo + BSC patients who crossed over to open-label treatment with regorafenib + BSC, dose modifications were instituted for 72.7% of patients. The overall frequency of modifications for patients who received any regorafenib during the two study periods was 73.8%.

*Supportive study 14935:* Data for this study was submitted as a published journal paper only. Therefore, the toxicity data presented was limited and only included commonly occurring events. As of the reporting date (28 July 2011), 33 patients had been exposed to 280 cycles of regorafenib, with a median of 8 cycles (range 2 to 17 cycles). A breakdown of duration of treatment was not available.

*Study 14596:* The median treatment duration was 19.5 weeks (mean 31.9 weeks, range 2 to 103 weeks) or 5.0 cycles. There were 9 subjects who were treated for 14 or more cycles in this study, taken to be equivalent to more than 12 months of treatment. The mean actual daily dose of regorafenib was 143.59 mg, with the median actual daily dose being 158.11 mg (range: 90.4 to 160.0 mg).

**Table 4: Exposure to Regorafenib and comparators in clinical studies.**

Study type/ Indication	Controlled studies		Uncontrolled studies	Total Regorafenib
	Regorafenib	Placebo	Regorafenib	
Clinical pharmacology				



Study type/ Indication	Controlled studies		Uncontrolled studies	Total Regorafenib
	Regorafenib	Placebo	Regorafenib	
<b>Indication 1:</b> metastatic or unresectable GIST				
· Pivotal	188 (132+56)	66		188
· Other			33*	33*
· <b>Subtotal Indication 1</b>				
<b>Indication 2:</b> HCC				
· Pivotal				
· Other			36	36
· <b>Subtotal Indication 2</b>				
<b>TOTAL</b>	<b>188</b>	<b>66</b>	<b>69</b>	<b>257</b>

\* Full safety data not provided in published paper

**Table 5: Exposure to Regorafenib in clinical studies according to dose and duration.**

Study type/ Indication	Proposed dose range = Proposed maximum dose			
	≥ 3 months	≥ 6 months	≥ 12 months	Any duration
<b>Clinical pharmacology</b>				
<b>Indication 1:</b> metastatic or unresectable GIST				
· Placebo-controlled	133	60	0	188
· Active-controlled				
· Uncontrolled				33
<b>Subtotal Indication 1</b>				
<b>Indication 2:</b> HCC				
· Placebo-controlled				
· Active-controlled				
· Uncontrolled	24	17	9	36
<b>Subtotal Indication 2</b>				

Study type/ Indication	Proposed dose range = Proposed maximum dose			
	≥ 3 months	≥ 6 months	≥ 12 months	Any duration
<b>TOTAL</b>	<b>157</b>	<b>77</b>	<b>9</b>	<b>257</b>

*Global integrated analysis:* As of the data cut-off 28 February 2013, in Pool 1 there were 1,073 patients who were exposed to regorafenib for a mean duration of 17.65 weeks and a median duration of 11.71 weeks (range 0.1 to 179.4). The mean number of cycles completed was 4.7 (median 3.0, range 1 to 46), and the mean daily dose of regorafenib was 138.88 mg (median 157.14, range 10.0 to 220.0).

### Safety issues with the potential for major regulatory impact

#### *Liver toxicity*

It is noted that liver dysfunction/failure events are known to be a class effect of Vascular Endothelial Growth Factor (VEGF) inhibitors.<sup>8</sup>

In pivotal *Study 14874*, one subject died as a result of treatment-related acute hepatic failure. This subject had advanced GIST and no history of liver disease and was assessed as having a severe drug induced hepatic injury and met Hy's law laboratory criteria. Severe drug induced hepatotoxicity is a known adverse effect of regorafenib and is included in the Precautions section of the PI.

It was noted that pivotal Study 14874 had as an inclusion criterion: '*Adequate liver function as assessed by the following laboratory requirements conducted within 7 days of starting study treatment: Total bilirubin  $\leq 1.5 \times$  the upper limit of normal (ULN), and Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)  $\leq 3.0 \times$  ULN ( $\leq 5 \times$  ULN for patients with liver involvement of their GIST)*'.

**Comment:** It is noted that the subject in Study 14874 who experienced treatment-related hepatic failure had no history of hepatic disease or hepatic metastases. This is in contrast to previously documented acute hepatic toxicity cases associated with regorafenib, which had occurred on a background of hepatic metastases as documented in the PI. Therefore, the wording of the PI should be amended to reflect this new finding.

Based on the fact that subjects were required to have adequate hepatic function for inclusion in Study 14874, no conclusions can be drawn from this study on the safety of regorafenib in subjects with hepatic impairment. This is an important consideration given the known potential for hepatotoxicity and has implications for the interpretation of population PK analyses based on this data.

Due to safety concerns associated with hepatic toxicities  $\geq$  Grade 3, the study protocol for Study 14874 was amended to require closer liver monitoring (from fortnightly to weekly in the first 2 months of treatment) and a revised dose modification scheme (specific to elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) or bilirubin) which were implemented via protocol Amendment 2 (26 July 2011).

**Comment:** Given the potential for severe drug-induced hepatic toxicity as an adverse effect of regorafenib, more frequent monitoring of hepatic function and for a longer duration may be warranted than is currently recommended in the PI,

<sup>8</sup> Chen, HX, Cleck, JN. Adverse effects of anticancer agents that target the VEGF pathway. *Nat Rev Clin Oncol* 2009; 6: 465-477

which recommends liver function tests (LFTs) be performed at least every 2 weeks for the first 2 months of treatment and then monthly thereafter. This has been posed as a question to the sponsor (See Clinical questions) and included as a comment on the PI.

In *Study 14596* in patients with HCC, it was noted that 2 out of 36 subjects developed Grade 5 liver dysfunction and one subject experienced Grade 3 liver dysfunction. In all subjects this was attributed to disease progression rather than to treatment with study drug.

**Comment:** On review of the case narratives of the subjects who died from or experienced liver dysfunction in *Study 14596*, the opinion of this evaluator is that it is inconclusive as to whether the cause of fatal liver dysfunction is solely due to disease progression, or whether there is a contributory component from regorafenib treatment. Regardless, the rate of death due to hepatic dysfunction is higher in this group of subjects with HCC (5.6%), and thus indicates that caution is required in the treatment of patients with hepatic impairment with regorafenib.

*Global integrated analysis.* In Pool 1 of the analysis, 13 out of 1073 (1.2%) subjects had a Grade 5 hepatic failure or abnormal hepatic function adverse event. Overall 16 patients met Hy's law laboratory criteria: 4 patients without malignant liver pathology in addition to 12 patients with underlying liver pathology.

*Cumulative review in all regorafenib trials.* The sponsor's review of over 3,500 patients identified 4 cases of severe drug-induced liver injury (DILI) all considered drug related and 9 cases of significant transaminase increases (6 considered possibly drug-related). It was assessed that these events predominantly occur in the first 2 months of treatment (although low numbers warrant caution in interpretation). It was reported that recovery was observed following drug interruption or discontinuation in most of the cases of significant transaminases elevations and in cases with mild to moderate liver dysfunction suspected to be regorafenib-related. However, remedial treatments in 3 out of 4 cases of severe DILI did not prevent further deterioration. The sponsor concluded that this suggests that early recognition and timely drug withdrawal are the single most important strategy to prevent regorafenib-induced liver dysfunction from progressing to severe DILI.

**Comment:** This evaluator agrees with the assessment of the sponsor that early recognition and management of liver function abnormalities with drug withdrawal will help to prevent episodes of acute hepatic toxicity. However, more frequent monitoring of LFTs than 2 weekly as suggested in the PI may be warranted due to the seriousness of the condition, and initial weekly LFT monitoring as was performed in the pivotal clinical trial may be a better alternative. This has been posed as a question to the sponsor (see Clinical questions).

### ***Haematological toxicity***

There was no evidence of haematological toxicity due to regorafenib in pivotal *Study 14874*.

### ***Serious skin reactions***

*Study 14874.* Hand-foot skin reaction (HFSR) is a known toxicity of VEGF inhibitors.<sup>8</sup> In *Study 14874*, HFSR (or PPE syndrome) was observed at a higher incidence in regorafenib-treated patients (56.8%) than the placebo-treated patients (13.6%). Grade 3 HFSR were reported in 27 (20.5%) patients in the regorafenib + BSC treatment arm and 1 (1.5%) patient in the placebo + BSC arm. Hand-foot skin reactions could usually be managed by dose reductions or interruptions, and was the most common cause for these modifications. Analysis of cycle-specific and cumulative event rates revealed that the majority of patients

who experienced events of HFSR were affected in their first 2 cycles of treatment. HFSR was also more common in Asian patients compared to non-Asian patients.

Rash is also a known toxicity of VEGF inhibitors.<sup>8</sup> During the double-blind period, maculopapular rash was reported in 18.2% of regorafenib patients compared to 3.0% of placebo patients. Most of these were Grade 1 in intensity and were adequately managed with dose interruptions.

*Global integrated analysis:* In Pool 1, although any adverse event (AE) in the System organ Class (SOC) Skin and subcutaneous tissues was high (73.3%, the most common being HFSR), the proportion of patients having a SAE in that SOC was low at 17 out of 1073 (1.6%) of subjects. Only 1 subject had Grade 4 Stevens-Johnson Syndrome and 1 subject had Grade 4 rash.

**Comment:** Skin reactions were common in patients treated with regorafenib. However they were generally mild and managed with dose interruptions or reductions without the need to cease treatment.

### ***Cardiovascular safety***

Cardiac ischaemia/infarction events are a known class effect of VEGF inhibitors.<sup>8</sup>

In pivotal *Study 14874*, one event each of acute coronary syndrome (Grade 3, unrelated) and cardiac arrest (Grade 5, possibly related) were reported for patients who received regorafenib + BSC during the double-blind treatment period.

Hypertension is also noted as a class effect of VEGF inhibitors<sup>8</sup> and was observed as a treatment emergent AE (TEAE) in 78 out of 132 (59.1%) of subjects in the regorafenib arm in the double blind section of the study compared to 18 out of 66 (27.3%) of the placebo arm. Grade 3 events were reported for 36 (27.3%) patients in the regorafenib arm and 3 (4.5%) patients in the placebo arm. One event of hypertension was categorised as an SAE associated with reversible posterior leukoencephalopathy syndrome. Analysis of cycle-specific and cumulative event rates revealed that the majority of TEAEs of hypertension occurred within the first two cycles of treatment with regorafenib.

Cardiac failure was noted in one patient in each treatment arm during the double blind period and thus was not increased in the regorafenib arm.

**Comment:** From the results of *Study 14874*, the episode of Grade 5 sudden cardiac arrest possibly related to study drug is noted as an important cardiac related adverse event. Hypertension is also an important cardiac adverse event which can be severe, and generally occurs within the first two cycles of treatment.

*Study 14814.* As discussed in Pharmacodynamics (Attachment 2), *Study 14814* did not provide any evidence of an association between regorafenib use and QT prolongation after 1 cycle of maximum treatment, or clinically significant worsening of LVEF after 2 cycles of maximum treatment.

*Global integrated analysis.* In Pool 1, 119 out of 1073 (11.1%) subjects had any AE in the SOC Cardiac disorders, the most common being tachycardia (2.2% of all subjects), palpitations (1.9%) and atrial fibrillation (1.6%). 34 out of 1073 (3.2%) subjects had a SAE in the SOC of cardiac disorders, the most common being cardiac ischaemic events (15 subjects or 1.5%) and atrial fibrillation (AF) and cardiac arrest (5 subjects or 0.5% each).

**Comment:** There are no new changes to the cardiac safety profile of regorafenib following evaluation of the submitted data.

### ***Gastrointestinal perforation and fistulae SAEs***

GI perforation and GI fistula are known class-effects of VEGF-antagonists. Based on previous assessments, GI perforation (including cases with reported fatal outcomes) and

GI fistula have been determined as adverse drug reactions (ADRs) for regorafenib. Intra-abdominal malignancy is the main risk factor.

*Cumulative review from regorafenib safety database.* From more than 3,500 patients treated with regorafenib until 23 February 2013, 20 perforation events were identified in regorafenib-treated patients (estimated frequency 0.57%), of which 9 cases were fatal. This compares with an estimated frequency of 0.31% in the placebo groups of the studies. From the safety database, 13 GI fistula events were identified in regorafenib treated patients of whom none were fatal.

**Comment:** This evaluator agrees with the sponsor that there is a possible increased risk of GI perforation/fistula in regorafenib treated patients. This is in keeping with the precautions already listed within the PI, although this could be reworded to reflect this possible increase in risk.

### Postmarketing data

The Periodic Safety Update Report (PSUR) No. 2 for regorafenib covered the period 27 Mar 2013 until 26 Sep 2013, for the indications of previously treated metastatic CRC and GIST (the latter indication being approved in the US since February 2013). The reporting period included 2,987 patients in ongoing company sponsored clinical trials and tablet sales representing an estimated exposure of 14,331 patients. Relevant findings from this PSUR included:

- 10 case reports of atrial fibrillation which were assessed as not having convincing evidence of a causal association. Sponsor action: no immediate action, AF to be further monitored.
- 34 cases of renal failure related events with regorafenib treatment, 16 of which were spontaneous reports and 18 were from interventional studies and early access programs. Of the latter, 5 cases were considered related to regorafenib treatment by the investigator, however sponsor assessments remained pending for some. Sponsor action: no immediate action, cases of renal failure to continue to be monitored.
- 256 cases of 'hepatic disorders', of which 137 were spontaneous reports and 128 were from studies. 75 cases were reported from interventional studies and early access programs, of which none were compatible with severe liver injury but 5 were assigned as cases with significant transaminases increase all possibly related to regorafenib. Of the remaining 190 postmarketing cases (53 from observational studies and 137 spontaneous reports), there were 2 cases compatible with regorafenib-induced severe liver injury (one case fatal) and 7 with significant transaminases increase, all of which assessed as possibly related to regorafenib use. It was noted that 10 of the above 14 reported cases of hepatic injury were in Japanese patients. This was explained by the sponsor as being due to recent marketing authorisation of regorafenib in Japan, the early postmarketing phase vigilance system in that country and the overall 75% of spontaneous reports newly received being from Japan, therefore indicating country-specific reporting differences most likely contributing to the increased number of cases. Sponsor action: cases in keeping with current description in CCDS – continue to monitor.

**Comment:** The large proportion of postmarketing cases of significant hepatic injury from Japan warrants further monitoring to exclude a race-specific susceptibility to hepatic impairment with regorafenib in Japanese patients. This has been posed as a question to the sponsor under *Clinical questions* below.

Considering that spontaneous reports are an underestimation of the true number of cases, there is a relatively high number of reports of hepatic

disorders with regorafenib in the postmarketing data and this reaffirms the association of this adverse effect with regorafenib use.

- 8 cases of cardiac ischemia, of which 6 were assessed as related to regorafenib. One was a spontaneous report, and the remaining 7 were from studies. Sponsor action: no immediate action.
- 190 cases of hypertension, 78 of which were spontaneous reports and 112 related to studies. No cases of hypertensive crisis were received. 83 of the total reports were considered serious but there were no cases with a fatal outcome. Sponsor action: cases of hypertension conform with its current description as a common AE and no action warranted.
- 123 cases of haemorrhagic events, of which 33 were spontaneous reports and 90 related to studies. 8 cases were reported with fatal outcome, of which 5 were related to cerebral haemorrhage. The most common site for bleeding was the GI tract (37%), followed by the central nervous system (CNS) (11%), urogenital (9%) and respiratory (8%). Sponsor action: cases in keeping with current knowledge, and no action warranted.
- 394 cases of HFSR, of which 237 were spontaneous reports and 157 were from studies. Notably, 231 (59%) cases were from Japan. 184 cases were reported as non-serious, 210 were reported as serious and 18 cases required hospitalisation. There was one relevant literature publication (a meta-analysis) during the reporting period<sup>9</sup> which found that the incidence and risk of development of HFSR with regorafenib is high (overall incidence 60.5%, 95% CI 48.3-71.6%) and may vary significantly with tumour type (71.4% for RCC, 60.2% for GIST, 50.5% for HCC, and 46.6% for mCRC). Sponsor action: Cases in keeping with current knowledge, no action warranted.
- 2 cases of reversible posterior leukoencephalopathy syndrome (RPLS), both spontaneous reports, one of which assessed as possibly related to regorafenib treatment and insufficient information to make an assessment for the other. Sponsor action: RPLS already contained within reference safety information, no further action warranted, continue to monitor.
- 38 case reports of GI perforation and fistula, of which 7 were spontaneous reports and 31 were from studies or compassionate use. For 18 cases of GI perforation, 5 were fatal and 6 were considered related to regorafenib treatment. Of 14 cases of GI fistula, 1 was fatal and 3 were considered related to regorafenib; while of 6 cases of GI abscess/peritonitis, none were fatal and one was considered related to regorafenib. Sponsor action: no further action warranted.
- 26 cases of severe cutaneous events including 3 cases of potential Stevens-Johnson Syndrome (2 of which considered related to study treatment) and 1 case of Toxic epidermal necrolysis. 9 cases were from spontaneous reports and 17 were from studies. Sponsor action: cases in keeping with known information, no action warranted.

As of 17 June 2014, there were 2 ADR reports for regorafenib in Australia on TRIM (4 reports in total, but both replicated), both related to clinical trials. These included 1 episode of Grade 2 pericarditis and 1 episode of Grade 5 liver failure. Both events were considered by the investigators to be related to study treatment but were considered unrelated by the sponsor.

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<sup>9</sup> Belum VR, Wu S, Lacouture ME. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis. *Invest New Drugs*. 2013 Aug;31(4):1078-86

**Comment:** There are no additional safety concerns arising from the post-marketing data that have not already been identified and addressed, other than the need to further monitor for a possible increased susceptibility of Japanese patients to hepatic toxicities with regorafenib treatment.

### **Safety related to clinical indication (GIST versus mCRC)**

In the sponsor's Summary of Clinical Safety, an analysis was presented comparing AEs between the two indications of GIST (study 14874, n=132) and mCRC (Study 14387, n=500). The overall safety profile was comparable between the two studies for Cardiac disorders, Renal and urinary disorders, Thrombo-embolic events, Gastrointestinal events (including diarrhoea and nausea/vomiting), Respiratory, thoracic and mediastinal disorders (including dysphonia), Metabolism and nutrition disorders (including decreased appetite) and Infections and infestations.

An increased rate of adverse events was observed in mCRC patients compared to GIST for hepatobiliary disorders (19.8% versus 6.1% respectively), haematological and biochemical toxicities (hyperbilirubinaemia 13.0% versus 1.5%), and haemorrhage (21.4% versus 11.4%).

An increased rate of adverse events was observed in GIST patients compared to mCRC for HFSR (66.7% versus 45.0% respectively), alopecia (24.2% versus 7.6%) and hypertension (59.1% versus 30.4%).

**Comment:** The safety profile of regorafenib was generally comparable across the current indication in mCRC and the proposed indication of GIST. Generally the evidence suggests that the safety profile may be slightly more favourable in GIST, with a reduced frequency of the potentially serious AEs of hepatobiliary disorders and haemorrhage, although a higher frequency of less serious AEs including HFSR, alopecia and hypertension. Caution is required in drawing conclusions from these comparisons across studies however.

### **Evaluator's conclusions on safety**

The new data presented with this submission is generally consistent with the known safety profile of regorafenib. The overall rate of adverse events is high in patients treated with regorafenib, with 100% of regorafenib treated patients in pivotal Study 14874 and 99.4% of subjects in the pooled global analysis experiencing any AE. The most common AEs are consistent across the studies and include HFSR, fatigue, diarrhoea and hypertension. A high proportion of patients (65% in pooled studies) required their dose to be modified in response to these AEs.

The most common cause of death across the submitted studies was disease progression, as would be expected in cancer patient populations. However, potential regorafenib related deaths include those from hepatic impairment, cardiovascular and thromboembolic events, renal impairment, infections, perforations and bleeding, and these should be considered adverse events of treatment.

It is agreed with the overall statement of the sponsor that although the proportion of patients who experience TEAEs is high, most of these AEs can be managed with dose modifications with a relatively low proportion of patients discontinuing treatment due to AEs.

There is some indication that the safety profile for patients treated with regorafenib for GIST may be more favourable than for patients with metastatic CRC or other indications. In treatment of GIST, there appeared to be a reduced frequency of the potentially serious AEs of hepatobiliary disorders and haemorrhage, although a higher frequency of less

serious AEs including HFSR, alopecia and hypertension. In addition the discontinuation rate in pivotal Study 14874 (8.5%) for all treated patients with GIST was lower than that for the pooled studies (20.5%) or for patients with HCC (50%). Caution is required however in drawing conclusions from cross-study comparisons.

Based on the analysis of results from Study 14874 and the pooled safety results, the following safety issues were considered:

- The study designs of all studies evaluated excluded subjects with hepatic or renal impairment from inclusion. Therefore, the ability of results to assess the safety of regorafenib in subjects with hepatic and renal impairment is limited. It is the opinion of this evaluator that no definitive conclusions or recommendations can be made about the use of regorafenib in subjects with moderate hepatic or renal impairment, in contrast to the sponsor's assessment that no dosage adjustments are required in patients with moderate hepatic impairment.
- The data confirmed the risk of liver toxicity and acute hepatic failure with regorafenib use. This evaluator agrees with the assessment of the sponsor that early recognition and management of liver function abnormalities with drug withdrawal will help to prevent episodes of acute hepatic toxicity. However, due to the potential seriousness of this adverse effect, there is potential scope for increasing the hepatic monitoring recommendations from fortnightly as stated in the current PI to weekly as occurred in the pivotal trial.
- Although rates of renal failure observed with regorafenib treatment to date remain low, given the known association between treatment with regorafenib and proteinuria and documented cases of Grade 5 renal failure attributed to regorafenib treatment, further monitoring for renal failure in patients treated with regorafenib is warranted.
- It is recommended that an additional precaution be added in the PI alerting to the increased risk of hypothyroidism.
- Other important adverse events documented that are in keeping with the known risks of regorafenib use include: sudden cardiac death; GI perforation due to anti-tumour effect; bleeding risk and hypophosphataemia.
- This evaluator does not agree with the assessment of the sponsor that there is a similar safety profile among the race subgroups. The data indicates there may be a different safety profile in patients of Asian race compared to other races, particularly with respect to serious AEs, hepatic impairment/toxicity and skin reactions as was discussed in other sections. Therefore, it is questioned whether alternative dosing schedules or monitoring requirements may be warranted for patients of Asian descent.
- Study 14596 in subjects with HCC generally supported the safety findings of the pivotal study however there was a suggestion of more frequent and severe incidences of hepatic dysfunction, which included 2 Grade 5 events. This could be explained due to the underlying cause of disease, however, it is uncertain as to the extent that treatment with regorafenib may have increased the likelihood and severity of these events. It is noted that all subjects enrolled in this study had Child Pugh A classification and therefore were assessed as having adequate baseline hepatic function, yet experienced an increased incidence of hepatic adverse events. Therefore, experience of regorafenib with moderate to severe hepatic impairment remains limited and it is therefore prudent that regorafenib be used with caution in these subjects.



## First round benefit-risk assessment

### First round assessment of benefits

The benefits of regorafenib in the proposed usage are:

- Improvements in progression free survival: The pivotal Study 14874 in patients with advanced or metastatic GIST previously treated with two tyrosine kinase inhibitors (TKIs) showed statistically and clinically significant improvements of median progression-free survival for patients treated with regorafenib of 4.8 months (95% CI: 4.0-5.7) over placebo of 0.9 months (95% CI: 0.9, 1.1), with a HR of 0.268 (95%CI 0.185, 0.388,  $p < 0.000001$ ). This result was supported by Study 14935.
- Suggested improvements in overall survival: The immaturity of OS data in Study 14874 means that no definitive conclusions can be drawn on the effect of regorafenib treatment on OS compared to placebo, although a beneficial effect of regorafenib was suggested with a HR of 0.772 (95% CI: 0.423, 1.408).
- There is possible variation in efficacy according to genetic biomarkers; this may affect the overall risk-benefit balance and further investigation is recommended.

### First round assessment of risks

The risks of regorafenib in the proposed usage are:

- The known common adverse effects including HFSR, fatigue, diarrhoea and hypertension that are already documented.
- Known serious adverse effect of acute hepatic toxicity with fatal occurrences, GI perforation and bleeding risk as already documented.
- Other adverse events of uncertain significance including acute renal failure and the impact of hepatic and renal impairment and racial characteristics (Asian origin) on the overall adverse effect profile which require further investigation and monitoring. The current data do not provide sufficient evidence to make definitive recommendations in these areas.

### First round assessment of benefit-risk balance

The benefit-risk balance of regorafenib is unfavourable given the proposed usage as outlined in the proposed PI but would become favourable if the changes recommended (particularly with regards to cautions in use with hepatic impairment) are adopted and the *Clinical questions* are satisfactorily addressed.

### First round recommendation regarding authorisation

The data submitted with this submission supports the use of regorafenib in the treatment of patients with advanced or metastatic GIST who have been previously treated with two TKIs. The median improvement in PFS in the pivotal study of 3.9 months is clinically significant in a patient population with advanced disease and no current approved treatment options. The adverse effect profile, although significant, is in keeping with that of other anticancer agents. However, there are some uncertainties with regards to the risk of acute kidney injury and the safety in patients with hepatic impairment and between different ethnic groups that warrants caution and further investigation.

Therefore, it is recommended that regorafenib be approved for the proposed indication: *treatment of patients with gastrointestinal stromal tumours (GIST) who have been*

previously treated with two tyrosine kinase inhibitors, subject to modification of the product documentation as recommended.

As reduced efficacy was observed in the small number of patients with KRAS and BRAF mutations, consideration should be given to reassessing the benefit-risk equation of regorafenib for biomarker subgroups as more information becomes available.

## Clinical questions

### Additional expert input

A separate evaluation was performed on the population PK analyses 14653 and 16282. The results of these evaluations were presented as separate reports with questions for the sponsor.

### Pharmacokinetics

1. Study 14996 (PH-37053): It is not clear from Tables 9-2 and 9-3 in the CSR how the Accumulation ratio (RAAUC) has been calculated. It is defined as the ratio of area under the concentration versus time curve (AUC<sub>∞</sub>) after multiple dosing and AUC<sub>τ</sub> after single dosing; AUC<sub>τ,md</sub>/AUC<sub>τ,sd</sub> (RAAUC). However, in Table 9-2 AUC is given as 67.4 mg.h/L (n=31) and in Table 9.3 AUC<sub>τ,ss</sub> is given as 45.4 mg.h/L (n=12), with RAAUC calculated as 2.11 which does not make sense. Presumably, RAAUC has been calculated using the single dose AUC of the 12 subjects who subsequently went on to receive the Cycle 1, Day 21 160 mg dosage for the steady state calculation but this value has not been provided. Could the sponsor please provide the Cycle 0, Day 1 PK values for the 12 subjects who subsequently went on to have the multiple dosing PK performed in Table 9-3 for comparative purposes?
2. Recommendations in patients with hepatic impairment: It is the opinion of this evaluator that the assessment of single dose PK in 4 patients with Child-Pugh B hepatic impairment in Study 11651 is insufficient to draw conclusions on the dosage recommendations and safety in patients with moderate hepatic impairment considering that drug accumulation has been found to occur on repeat dosing as per the proposed dosing regimen and regorafenib is primarily metabolised by the liver and has been associated with acute liver toxicity. Can the sponsor please address these reservations and indicate whether further studies in patients with moderate hepatic impairment are planned or in progress to support these claims?
3. Recommendations in patients with renal impairment: Can the sponsor please further justify use of the results of the physiology-based pharmacokinetics modelling to support the statements regarding the PK of regorafenib in patients with renal impairment in the PI given that this was an exploratory analysis performed on virtual populations. In addition, the PBPK model does not take into account renal elimination of glucuronidated forms of regorafenib and its metabolites, despite the PI stating that '*approximately 19% of the dose [is] excreted in urine as glucuronides*'. Particularly with regards to severe renal impairment, inclusion of this statement may be misleadingly reassuring.

### Pharmacodynamics

4. Can the sponsor please indicate when the longer term results on LVEF outcomes will be available for Study 14814?

## **Efficacy**

### **Pivotal Study 14874**

5. The handling of missing data was not pre-specified in the Study protocol for Study 14874 but was only introduced in the Statistical Analysis Plan released at the time of data cut-off. Can the sponsor please provide a justification for this omission and confirm that methods for handling missing data were determined prior to data analysis?
6. Can the sponsor please justify the methods used to handle missing data in Study 14874, including the effect that the selected methods have on the analysis of the results for PFS, which would seem to favour a prolonging of PFS (best-case scenario). Can the sponsor also please provide data on the number of subjects who missed a tumour assessment prior to disease progression in each treatment arm?
7. Can the sponsor please provide an explanation as to why a sensitivity analysis was not performed on the methods used to handle missing data?
8. The upper range of time since recent progression/relapse to randomisation is listed as being 421 weeks, which is equivalent to longer than 8 years. Can the sponsor please discuss the rationale for treatment in a patient who has not had disease progression for this length of time? Also, can the sponsor please provide data on the distribution of time since progression/relapse (preferably graphically) to randomisation for all patients enrolled in Study 14874 to allow for an assessment of the overall patient population?
9. In pivotal Study 14874, what is the status of further follow up of subjects regarding OS? Is more mature data available and if not, when is it anticipated that it will be?
10. What further studies or monitoring is planned to assess the impact of mutational biomarker status on the efficacy of regorafenib? In particular, it may be important to understand the efficacy in patients with KRAS and BRAF mutations in order to make informed decisions regarding overall risk-benefit.

### **Study 14935**

11. Can the sponsor please clarify the nature of the support and funding that were provided for the conduct of Study 14935?

## **Safety**

12. Can the sponsor please discuss the rationale for recommending 2 weekly monitoring of LFTs in light of the known risk of severe drug-induced hepatic toxicity, when weekly monitoring was recommended in the pivotal Study 14874?
13. Can the sponsor please discuss whether further monitoring for significant liver injury will be monitored in Japanese patients to assess whether there is increased susceptibility in this ethnic group, following on from the postmarketing findings in regorafenib PSUR No. 2?
14. Can the sponsor also please outline any risk management options for further investigating higher rates of hepatobiliary and skin adverse events in patients of Asian race, and whether further investigation is occurring and whether differing recommendations regarding monitoring, dose adjustment or dosage may be warranted?

15. Can the sponsor please explain the inconsistencies in the data for HFSR presented in the CSR of Study 14874 (where the incidence of HFSR is listed as being 56.8% in the regorafenib group and 13.6% in the placebo group), compared to the figures listed in the draft PI and presented from the pooled Safety analysis (Pool 2 representing Study 14874) in the sponsor's Summary of Clinical Safety (where the incidence of HFSR is listed as being 65.9% in the regorafenib group and 15.2% in the placebo group)?

### **Second round evaluation of clinical data submitted in response to questions**

The details of the sponsor's responses to the *Clinical questions* and the clinical evaluator's comments on the sponsor's responses are detailed in Attachment 2.

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

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

After consideration of the responses to clinical questions, the benefits of regorafenib in the proposed usage are unchanged from those identified in the First round evaluation.

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

After consideration of the responses to clinical questions, the risks of regorafenib in the proposed usage are unchanged from those identified in the First round evaluation.

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

The benefit-risk balance of regorafenib, given the proposed usage as described in the amended PI, is favourable.

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

It is recommended that regorafenib be approved for the proposed indication:

*Treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with two tyrosine kinase inhibitors.*

The first round clinical questions raised have been adequately addressed by the sponsor.

There remains one outstanding PI change that requires addressing, the details of it is however beyond the scope of this AusPAR.

## **V. Pharmacovigilance findings**

### **Risk management plan**

The sponsor submitted a Risk Management Plan (EU Risk Management Plan Version 2.0 (dated 18 July 2013, DLP 28 February 2013) and Australian Specific Annex (ASA) Version (Version 2, dated February 2014) which was reviewed by the TGA.

### **Safety specification**

The sponsor provided a summary of ongoing safety concerns which are shown at Table 6.

**Table 6: Sponsor's summary of Ongoing safety concerns**

<b>Important identified risks (confirmed by clinical data)</b>	<ul style="list-style-type: none"> <li>• Severe drug-induced liver injury (DILI)</li> <li>• Cardiac ischemic events</li> <li>• Hypertension and hypertensive crisis</li> <li>• Hemorrhage</li> <li>• Hand-foot skin reaction (HFSR)</li> <li>• Posterior reversible encephalopathy syndrome (PRES)</li> <li>• Gastrointestinal perforation and fistulae</li> <li>• Stevens-Johnson syndrome (SJS) /Toxic epidermal necrolysis (TEN)</li> </ul>
<b>Important potential risks (not refuted by clinical data or which are of unknown significance)</b>	<ul style="list-style-type: none"> <li>• Wound healing complications</li> <li>• Interstitial lung disease (ILD)</li> <li>• Atrial fibrillation</li> <li>• Reproductive and developmental toxicity</li> <li>• Renal failure</li> <li>• Phototoxicity</li> </ul>
<b>Important missing information</b>	<ul style="list-style-type: none"> <li>• Safety in severe hepatic impairment</li> <li>• Safety in children</li> <li>• Safety in patients with a cardiac history</li> <li>• Safety in severe renal impairment</li> <li>• Interaction with antibiotics</li> <li>• Interaction with BCRP substrates</li> <li>• Activity in KRAS mutated tumours or other biomarker-defined tumour subtypes</li> </ul>

### Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities.

### Risk minimisation activities

The sponsor proposes routine and additional risk minimisation activities.

There are no definite objections to the presentation of the submitted EU-RMP document and the ASA. The sponsor was advised to submit any missing protocols or protocol synopses, as soon as they become available.

### Reconciliation of issues outlined in the RMP report

Table 7 summarises the RMP evaluator's first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the RMP evaluator's evaluation of the sponsor's responses.

**Table 7: Reconciliation of issues outlined in the RMP Evaluation Report**

<b>Recommendation in RMP evaluation report</b>	<b>Sponsor's response (or summary of the response)</b>	<b>RMP evaluator's comment</b>
Safety considerations may	<i>The nonclinical evaluator</i>	The sponsor's response

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<p>be raised by the nonclinical and clinical evaluators through the consolidated TGA's 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 RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.</p>	<p><i>considered no additional safety concerns would warrant changes to the nonclinical safety specification of the Risk Management Plan. The clinical evaluator has raised some concerns regarding the clinical aspects of the safety specifications in the EU-RMP and these issues are addressed within this response. Please refer to M1.13.1 for the updated EU-RMP version 2.5.'</i></p>	<p>has been noted.</p>
<p>The sponsor should add 'Severe infections' as an Ongoing Safety Concern.</p>	<p><i>'As outlined and discussed in section 2.1.5.12 'Infections and Infestations' of M 2.7.4, an overall increased risk of infection in regorafenib-treated patients has been observed in the placebo-controlled Phase 3 trials in CRC (Study 14387) as well as GIST (Study 14874). However, the infections were generally of low severity and affected a variety of organ systems. No difference in the rate of infections with fatal outcomes was observed between treatment groups in the placebo-controlled trials. In addition, the rate of permanent study treatment discontinuations due to infection events was low with 1.6% (regorafenib) vs 0.8% (placebo) in Study 14387 and 0.8% (regorafenib) vs 0% (placebo) in Study 14874 (14387-CSR Table 14.3.2/2, 14874-CSR Table 14.3.9/15). Therefore, in the opinion of the applicant, there is currently no signal detected</i></p>	<p>This is considered acceptable in the context of this application.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>for an increased risk of clinically severe infection events with regorafenib treatment.</i></p> <p><i>Infection is listed as a very common ADR in Table 6 of the PI and also includes detailed information on frequency, severity and frequently observed sites of infection in section 'Description of selected adverse reactions'.</i></p> <p><i>Bayer considers the increased risk of infection associated with Stivarga use is adequately described in the Product Information and an inclusion of this safety concern as an important identified risk in RMP is not warranted.'</i></p>	
<p>The sponsor should add 'Safety in moderate hepatic impairment' as Missing Information.</p>	<p><i>'Use in patients with moderate hepatic impairment has been added to the section on missing information (Use in patients with moderate or severe hepatic impairment) in the Australian Specific Annex (ASA) v2.1 in M1.13.2.'</i></p>	<p>This is considered acceptable in the context of this application.</p>
<p>The sponsor should add 'Safety in moderate renal impairment as Missing Information.</p>	<p><i>'Use in patients with moderate renal impairment has been added to the section on missing information (Use in patients with moderate or severe renal impairment) in the ASA v2.1 in M1.13.2.'</i></p>	<p>This is considered acceptable in the context of this application.</p>
<p>The sponsor should add 'Asian patients with GIST' as Missing Information.</p>	<p><i>'In the pivotal Phase 3 trial in GIST (Study 14874), the safety profile of regorafenib has been determined in overall 49 Asian patients treated with regorafenib in double-blind (n=34) and/or open-label treatment (n=15) phases of this trial (14874-CSR Table 14.3.10/8).</i></p>	<p>This is considered acceptable in the context of this application.</p> <p>It is noted there is an increased proportion of palmar-plantar erythrodysesthesia in Asian patients. This should be reflected in the</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>For Study 14874, the adverse event profiles of Asians versus non-Asian GIST patients have been compared (see M.2.7.4, section 2.1.6.3, Table 2-109) with an increased rate of HFSR in Asian patients as the primarily observed difference. This finding is in line with the overall safety profile of regorafenib-treated Asian patients across all indications (see M2.7.4, section 2.1.6.3, Table 2-110).</i></p> <p><i>Current post-marketing adverse event data for Asian GIST patients is in line with the safety profile determined for Asian GIST patients in Study 14874. At present, no new safety signal have been observed: 166 adverse events (50 serious; 116 non-serious) have been reported in 66 Asian GIST cases in the post-marketing setting. The cases are from Japan (n=60), Australia (n=3), and one case each from Malaysia, New Zealand and Singapore. Bayer considers the current safety profile of regorafenib in Asian GIST patients is based on a sufficient number of regorafenib-treated Asian GIST patients, in line with overall regorafenib safety profile observed for Asian patients across indications and in line with the current postmarketing adverse event data for regorafenib-treated Asian GIST patients. Therefore, an inclusion of this safety concern as missing information in the RMP is not warranted.'</i></p>	proposed PI.
The sponsor is advised to submit any missing protocols or protocol	<i>'The respective study protocols (16674, 16675) as outlined in Part III</i>	This is considered acceptable in the context



Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
synopses, as soon as they become available.	<i>Pharmacovigilance Plan of the EU-RMP are provided with this submission and can be found in M1.13.1.'</i>	of this application.
The sponsor should provide a compelling justification for the inconsistencies between the information provided in the EU-RMP and the information in the proposed Australian PI document. The sponsor should remedy all inconsistencies, including inconsistencies not raised by the RMP evaluator.	<i>'The incidence rates of treatment-emergent medical events by MedDRA in the EU-RMP (Tables 31 – 57) are presented using both the number of patients experiencing the event and the corresponding percentage presented in brackets whereas Table 6 in the Adverse Effects section of the draft PI specifies the incidence rates of the ADRs in percentages only (as shown below).[...]'</i>	This is considered acceptable in the context of this application.
<p>In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows:</p> <p>In the 'Precautions' section, under the 'Patients with hepatic impairment' heading, the PI should include a more detailed statement on the information available on patients with moderate hepatic impairment (or a statement to that effect).</p>	<i>'Please refer to the responses in Questions 2, 32, 46. In response to Question 2, the sponsor has provided an explanation of the PK dataset and the approaches and conclusions taken. However, to address the concerns of the evaluator with respect to the limited clinical data from only 4 moderate (Child-Pugh B) hepatic impairment patients, Bayer agrees to retain the original text in the PI.'</i>	This is considered acceptable in the context of this application subject to approval by the Delegate.
In the 'Precautions' section, under the 'Patients with hepatic impairment' heading, the PI should include a statement that weekly LFT monitoring is necessary in patients with moderate hepatic impairment (or a statement to that effect).	<p><i>'Please refer to the response in Question 12.'</i></p> <p>Response to Q12: <i>'Discussions were held with key opinion leaders in the medical field by Bayer to address the feasibility of frequent monitoring in clinical practice outside of the clinical trial setting. Bayer was recommended to use the wording of 'at least</i></p>	<p>This is not considered acceptable.</p> <p>In the sponsor's response, it is unclear whether the sponsor refers to two weekly monitoring of patients without elevated LFTs or patients with elevated LFTs. For the former group two-weekly LFT monitoring may be appropriate unless there</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>every two weeks' in the PI to allow some flexibility for the treating physician and if deemed necessary, the treating physician was able to monitor more frequently based on his/her medical judgment in clinical practice.</i></p> <p><i>Current post-marketing data on severe liver injury is in line with label-defined liver monitoring schedule: as of August 2014, 6 cases (3 with fatal outcomes) compatible with regorafenib induced severe liver injury were identified during ongoing medical review of reported postmarketing cases of hepatic disorders. At the time point of this assessment, it was estimated that overall around 30,000 patients have been exposed to regorafenib (Stivarga) commercially. This post-marketing reporting frequency (6/30,000) is considered in line with 'Severe liver injury' being reflected as uncommon ADR (with reported fatal outcomes) within the label.</i></p> <p><i>An ongoing open-label Phase IIIb study in patients treated with metastatic CRC who have progressed after standard therapy (15967-CONSIGN) was developed to provide regorafenib to subjects diagnosed with metastatic colorectal cancer who have failed all approved standard therapies. The study with nearly 3000 enrolled CRC patients will also further evaluate the incidence and severity of liver function abnormalities, as well as label-defined liver function monitoring schedule and associated</i></p>	<p>is another reason for monitoring. However, the recommendation concerns patients with elevated LFTs.</p> <p>Weekly LFT monitoring in patients with hepatic impairment will allow any necessary dose modification or drug cessation to occur up to 1 week earlier. More severe hepatotoxic events may be detected and addressed earlier.</p> <p>It is recommended to the Delegate the PI contain a statement that weekly LFT monitoring should occur for any patient with elevated LFTs or any patient with any degree of hepatic impairment.</p> <p>This recommendation is in concordance with the FDA label and publications issued by Bayer and Onyx Pharmaceuticals.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>dose modification (dose interruptions and dose reductions) scheme to address the safety concerns for severe drug-induced liver injury as outlined in the EURMP v2.5 (see M1.13.1).</i></p> <p><i>So far, data on hepatotoxicity from the CONSIGN trial does not preclude the current label defined LFT monitoring recommendation. At present, one case of severe liver injury has been observed in this study only (see case [information redacted] in Appendix 6 of section 1 within Appendix B of Module 2.7.4 provided with the GIST submission).</i></p> <p><i>A hepatotoxicity profile comparable to the one observed in CRC was confirmed for the GIST indication (see also section 2.1.5.13.3 of Module 2.7.4 provided with the GIST submission). Severe liver injury reported from post-marketing data (6/30,000) and the ongoing Study 15967 (CONSIGN) (1/3000) indicate that the frequency of severe liver injury is not higher but rather lower compared to the time of first (CRC) submission (3 cases in around 1200 regorafenib-treated cancer patients; see M2.7.4 provided with the CRC submission).</i></p> <p><i>Therefore, the information presented in the Precautions – Hepatotoxicity and Dosage and Administration - Table 9 - Recommended measures and dose modifications in case of drug related liver function test abnormalities section of the PI provides adequate liver monitoring</i></p>	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>and dosing guidance for both indications, CRC and GIST. Experience with the label-defined</i></p> <p><i>LFT monitoring schedule indicates that this approach is acceptable.'</i></p>	
<p>In the 'Precautions' section, under a separate heading, the PI should include a statement on the association of tyrosine kinase inhibitors with infections (or a statement to that effect).</p>	<p><i>'Bayer considers the current approach in the PI describing infection as a very common ADR together with detailed information on the frequency, severity and most frequently observed sites of infection within section 'Description of selected adverse reactions' provides adequate guidance to physicians. No additional respective wording in the Precautions section is required – also taking into account that there is no associated specific monitoring or dose modification recommendation.'</i></p>	<p>This is considered acceptable in the context of this application subject to approval by the Delegate.</p>
<p>In the 'Precautions' section, under a separate heading, the PI should include a statement on the association of tyrosine kinase inhibitors with interstitial lung disease (ILD) (or a statement to that effect).</p>	<p><i>'A wide variety of drugs have been implicated among causes of interstitial lung disease (ILD), including VEGFR-targeting TKIs. At present there is no confirmed case of true ILD in regorafenib-treated patients or any other evidence for regorafenib-induced ILD.</i></p> <p><i>In the controlled Phase III trial population CRC/GIST, ILD was reported as AE term in 2 subjects in the regorafenib group corresponding to an incidence of 0.32% (95% CI [0.04; 1.14]), whereas 1 result was found in the placebo group corresponding to an incidence of 0.31% (95% CI [0.01; 1.73]). The exposure-adjusted incidence rate per</i></p>	<p>This is considered acceptable in the context of this application subject to approval by the Delegate.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>100 subject years for the regorafenib group was calculated to be 0.89 (95% CI [0.11; 3.23]) and 1.30 (95% CI [0.03; 7.25]) for the placebo group [Source: EU-RMP v2.5, section 3.2.2].</i></p> <p><i>Bayer considers the inclusion of a statement concerning interstitial lung disease (ILD) within the PI is not warranted. The EU-RMP outlines ILD as an Important Potential Risk and is being further investigated in Study 15967 CONSIGN. The ASA has also been updated accordingly (see M.1.13.2). All reports of ILD will continued [sic] to be monitored on a regular basis and presented in the respective PBRER/PSURs.'</i></p>	
<p>In the 'Precautions' section, under the 'Use in the Elderly' heading, the PI should include a statement on the available information on patients over 75 years (EU-RMP, p. 58) (or a statement to that effect).</p>	<p><i>'treated with regorafenib across clinical trials was considered sufficient to amend the sections and 5.2 of the SmPC as follows:</i></p> <ul style="list-style-type: none"> <li><i>• Removal of the wording 'There is only limited information for patients older than 75 years' in current SmPC section 4.2 ('Elderly population').</i></li> <li><i>• SmPC section 5.2 remains unchanged based on the fact that age did not affect the regorafenib pharmacokinetics over the studied age range (29 – 85 years) in clinical studies.</i></li> </ul> <p><i>Section 4.8 ('Description of selected adverse reactions') includes the following sentence:</i></p> <p><i>'Across all clinical trials, cardiac disorder events (all grades) have been more often (20.5% versus 10.4%)</i></p>	<p>The proposed change to the 'Adverse Effects' section is considered acceptable in the context of this application subject to approval by the Delegate.</p> <p>However, the proposed wording in the 'Precautions' section does not reflect the differences between the over 75 year age group as opposed to the under 75 year age group.</p> <p>It is recommended to the Delegate that, in the 'Precautions' section, under the 'Use in the Elderly' heading, the PI should state that there were relevant differences in safety when comparing patients over 75 years with patients under 75 years, e.g. the frequency of cardiac disorder events.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>reported in Stivarga-treated patients aged 75 years or older (N=78) as compared to Stivarga-treated patients below 75 years (N=995).'</i></p> <p><i>Therefore and in line with the current EU SmPC, Bayer proposes to amend the draft PI in the respective sections:</i></p> <p><i>Precautions section:</i></p> <p><i>Use in the Elderly</i></p> <p><i>In clinical studies, no relevant differences in exposure, safety or efficacy were observed between elderly (aged 65 years and above) and younger patients (see Adverse Effects).No dose adjustment is necessary in elderly patients (see Pharmacokinetics).</i></p> <p><i>Adverse Effects section:</i></p> <p><i>Description of selected adverse reactions Across all clinical trials, cardiac disorder events (all grades) have been more often (20.5% versus 10.4%) reported in Stivarga-treated patients aged 75 years or older (N=78) as compared to Stivarga-treated patients below 75 years (N=995).'</i></p>	
<p>In the 'Adverse Events' section, the sponsor should remove the inconsistencies in the adverse event table for the GIST population, as described above.</p>	<p><i>'Please refer to Bayer's response in Question 66. As outlined in our response, there are no inconsistencies in Table 6 of the draft PI.'</i></p>	<p>This is considered acceptable.</p>
<p>In the 'Adverse Events' section, the PI should present adverse events in a table that allows easy visualisation of the adverse events according to body system and frequency.</p>	<p><i>'Bayer contacted the Delegate from Prescription Medicines Clinical Unit 4 on 5 September 2014 to discuss the adverse drug reactions table in the draft PI. The Delegate advised that it was clinically relevant to include two separate tables</i></p>	<p>This is considered acceptable in the context of this application subject to approval by the Delegate.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>reporting the incidence rates for each indication.</i></p> <p><i>Each Adverse Effects tables specifies the body system and frequencies for all grades and grades greater than 3.'</i></p>	
<p>In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to accommodate the changes made to the product information document.</p>	<p><i>'The draft PI and CMI has been updated accordingly and can be found in M1.3.1 and M1.3.2.'</i></p>	<p>This is considered acceptable in the context of this application subject to approval by the Delegate.</p>

## Summary of recommendations

### *Outstanding issues*

It is considered that the sponsor's response to the TGA's request for further information has adequately addressed most of the issues identified in the RMP evaluation report. There are two outstanding issues and one additional recommendation.

### *Additional recommendation*

It is recommended to the Delegate that the PI contain a statement that the proportion of palmar-plantar erythrodysesthesia is increased in Asian patients.

### *Summary of outstanding issues (incorporating any additional recommendations)*

#### *Recommendations in regard to risk minimisation activities*

1. It is recommended to the Delegate that the PI contain a statement that weekly LFT monitoring should occur for any patient with elevated LFTs or any patient with any degree of hepatic impairment.
2. It is recommended to the Delegate that, in the 'Precautions' section, under the 'Use in the Elderly' heading, the PI should state that there were relevant differences in safety when comparing patients over 75 years with patients under 75 years, for example the frequency of cardiac disorder events.
3. It is recommended to the Delegate that the PI contain a statement that the proportion of palmar-plantar erythrodysesthesia is increased in Asian patients.

### **Advice from the Advisory Committee on the Safety of Medicines (ACSOM)**

Not applicable.

### **Key changes to the updated RMP**

EU Risk Management Plan Version 2.0 (dated 18 July 2013, DLP 28 February 2013) and Australian Specific Annex Version 2 (dated February 2014)



has been superseded by:

EU Risk Management Plan Version 2.5 (dated 12 August 2014, DLP 28 February 2013) and Australian Specific Annex Version 2.1 (dated September 2014).

Key changes to the EU-RMP and ASA are highlighted in Table 8 below.

**Table 8: Summary of key changes to the RMP and ASA**

<b>Key changes between EU-RMP Version 2.0 and EU-RMP Version 2.5</b>	
<b>Safety specification</b>	<ul style="list-style-type: none"> <li>• ‘Thrombotic microangiopathies’ (TMA) added as Important Potential Risk.</li> <li>• ‘Long-term safety in GIST patients’ added as Missing Information.</li> <li>• ‘Safety in severe or moderate hepatic impairment’ added as Missing Information (previously ‘Safety in severe hepatic impairment’).</li> <li>• ‘Safety in severe or moderate renal impairment’ added as Missing Information (previously ‘Safety in severe renal impairment’).</li> </ul>
<b>Pharmacovigilance activities</b>	<ul style="list-style-type: none"> <li>• Study 14814 (Category 3) completed; Result summary added to section 3 in Part III; Clinical Study Report added to Annex 9.</li> <li>• Study 14874 assigned to ‘Long-term safety in GIST patients’</li> <li>• Updates on due dates for study 15808 and 15967.</li> </ul>
<b>ASA</b>	<ul style="list-style-type: none"> <li>• ASA updated to accommodate EU-RMP changes.</li> </ul>

### ***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 Risk Management Plan Version 2.5 (dated 12 August 2014, DLP 28 February 2013) and Australian Specific Annex Version 2.1 (dated September 2014), and future updates, where approved 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**

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



## Nonclinical

The proposed dose and dosage regimen are the same as those for the current indication. There were no new safety concerns.

The evaluator recommended approval of the new indication.

## Clinical

After oral administration, the maximum regorafenib plasma concentration is reached within 4 hours. The drug is cleared primarily by metabolism in the liver. There are two main active metabolites M-2 and M-5. The mean elimination half-life of regorafenib and M-2 is 20-30 h and M-5 60 h. Serious adverse effects include hepatotoxicity, haemorrhage, myocardial infarction, reversible posterior leukoencephalopathy syndrome, gastrointestinal perforation, hypertension, complicated wound healing and palmar-plantar erythrodysesthesia syndrome (hand-foot skin reaction).

## Pharmacokinetics

- Population pharmacokinetic evaluations were undertaken separately to the clinical evaluation. There were no clinically relevant covariates affecting regorafenib exposure.
- The evaluations were considered and accepted as appropriate by the TGA's Pharmaceutical Subcommittee at their meetings in July and November 2014. There were some recommendations for the PI but the details of these are beyond the scope of this AusPAR.
- The clinical evaluator noted that the ability of the models to predict the pharmacokinetics of regorafenib in patients with hepatic or renal impairment was limited due to the small number of patients with such impairment.

## Efficacy

- There was one efficacy trial (Study 14874 or GRID). It was a multinational, randomised, double-blind, placebo-controlled trial in patients with unresectable or metastatic GIST after failure of imatinib and sunitinib. Failure of imatinib was either due to disease progression or intolerance. Failure of sunitinib was due to disease progression. Subjects presenting with intolerance to sunitinib were excluded due to the possibility of introducing bias to the primary endpoint PFS.
- Subjects were randomised 2:1 to either regorafenib 160 mg orally daily plus BSC (n=133) or placebo plus BSC (n=66) for three weeks on followed by one week off therapy per treatment cycle. The randomisation was stratified by line of therapy (third line versus fourth line or greater) and geographical region (Asia versus rest of world). The treatment was continued until disease progression or unacceptable toxicity. At progression, randomised placebo subjects were allowed to crossover to regorafenib and randomised regorafenib subjects were allowed to continue regorafenib.
- The majority of subjects were male (64%) and Caucasian (68%). The median age was 60 years, range 18 to 87 years. ECOG performance status was 0 or 1<sup>10</sup>.

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<sup>10</sup> ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used: 0 - Fully active, able to carry on all pre-disease performance without restriction, 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g.,

- PFS was assessed by a central blinded panel using modified RECIST 1.1 criteria<sup>11</sup>, in which lymph nodes and bone lesions were not target lesions and a progressively growing new tumour nodule within a pre-existing tumour mass was progression. Other endpoints were ORR, TTP, OS and health-related quality of life (EORTC QLQ-C30 version 3<sup>12</sup> and EQ-5D<sup>13</sup>).
- Regorafenib significantly increased PFS and TTP and there was a trend to increased OS (Table 9). The increase in PFS was independent of age, sex, geographic region, prior lines of treatment and ECOG performance status. The ORR was low in both groups (4.5% for regorafenib and 1.5% for placebo) and not significantly different between groups. Regorafenib did not improve quality-of-life.
- At progression, 56 subjects randomised to placebo (85%) crossed to regorafenib and 41 subjects randomised to regorafenib (31%) continued on regorafenib. The median secondary PFS (as measured by the investigator) was 5.0 months for those randomised to placebo and 4.5 months for those randomised to regorafenib.
- Updated OS results were provided in the sponsor's response to the TGA's request for further information. There were 139 death events compared with 39 in the previous analysis in Table 9. Regorafenib did not significantly increase OS. The median OS was 17.4 months in both groups. The hazard ratio was 0.85, 95% CI [0.60, 1.21] and the log-rank p-value 0.18. The result is confounded by crossover at progression. The final analysis is due in second quarter of 2015 when approximately 160 deaths will have been observed.

**Table 9: Efficacy results from Study 14874 or GRID Trial, Intent-to-Treat**

	Regorafenib + BSC n=133	Placebo + BSC n=66	Hazard Ratio [95% CI] p-value
Progression-Free Survival median months	4.8	0.9	0.27 [0.19, 0.39] p<0.000001
Time to Progression median months	5.4	0.9	0.25 [0.17, 0.36] p<0.000001
Overall Survival <sup>1</sup> median months	Not Reached	Not Reached	0.77 [0.42, 1.41] p=0.20

The hazard ratios were calculated using the Cox model stratified by line of treatment (third line versus fourth line or greater) and geographical region (Asia versus rest of world). The p-values were obtained

light house work, office work, 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours, 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours, 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair, 5 - Dead

<sup>11</sup> RECIST: The Response Evaluation Criteria in Solid Tumors (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.

<sup>12</sup> The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It is supplemented by disease-specific modules for e.g. Breast, Lung, Head & Neck, Oesophageal, Ovarian, Gastric, Cervical cancer, Multiple Myeloma, Oesophago-Gastric, Prostate, Colorectal Liver Metastases, Colorectal and Brain cancer which are distributed by the EORTC Quality of Life Department.

<sup>13</sup> Developed by EuroQol, EQ-5D™ is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

by the log-rank test stratified as above. The medians are Kaplan-Meier estimates. <sup>1</sup> Interim analysis based on 29% of the planned 160 events.

- An uncontrolled trial (14935) of regorafenib (n=33) in a similar population as the pivotal trial and treated at the same dose and treatment regimen supported the pivotal trial.

## Safety

- The safety of regorafenib in GIST was assessed in the pivotal Study 14874. The trial had two periods, a double-blind period and an open-label period. The safety population in the double-blind period consisted of 132 regorafenib subjects and 66 placebo subjects. The safety population for both periods consisted of 188 regorafenib subjects. The median duration of treatment with regorafenib was 5.3 months and the median daily dose was 153 mg. Dose modification for adverse effects was required in 70% of regorafenib-treated subjects.
- The safety of regorafenib in all trials in all indications was assessed in 1,073 subjects treated with regorafenib (Pool 1) for a median duration of 2.7 months (range 1 day – 3.4 years) and median daily dose of 157 mg (range 10 to 220).
- In the double-blind period of the pivotal trial (Pool 2), the incidence of severe (Grade 3-5) adverse events was 77% with regorafenib and 36% with placebo, the incidence of serious adverse events was 29% with regorafenib and 21% with placebo. The most common adverse events were palmar-plantar erythrodysesthesia syndrome (66% regorafenib versus 15% placebo), hypertension (59% vs 27%), diarrhoea (46% versus 9%), dysphonia (38% versus 9%) and fatigue (37% versus 29%). These events were also very common in the pooled analysis. In the double-blind period of the pivotal trial, common serious adverse events were related to the gastrointestinal system (14.4% regorafenib versus 4.5% placebo), infections and infestations (3.8% versus 0%) and nervous system (3.0% versus 0%).
- In the pivotal trial, there were six deaths (3.2%) reported as related to regorafenib and one (1.5%) to placebo within 30 days of last treatment. Two regorafenib deaths (1.5%) occurred in the double-blind period. The regorafenib deaths were due to cardiac arrest, acute hepatic failure, acute kidney injury, colonic perforation, adult respiratory syndrome and thromboembolism. The placebo death was due to fatigue.
- In the pivotal trial, dose modification (interruption, delay or reduction) due to adverse events was more common with regorafenib than placebo. In the double-blind period, 75% of regorafenib subjects and 26% of placebo subjects had dose modifications. Treatment discontinuations due to adverse events were similar in the two groups (6% regorafenib, 8% placebo).
- The pooled analysis of safety in all trials was consistent with that of the pivotal trial.
- The postmarket data was consistent with the known safety profile of regorafenib. However, 10 of 14 reports of severe liver injury were in Japanese patients and 59% of palmar-plantar erythrodysesthesia reports were from Japan suggesting possible increased susceptibility in these patients.

## Clinical evaluator's recommendation

The evaluator recommended approval of the new indication.

## Risk management plan

The sponsor addressed most RMP issues; however, there were three recommendations for the PI. The recommendations regarding use of regorafenib in the elderly and the incidence of palmar-plantar erythrodysesthesia in Asian patients are included in the recommendations for the PI. The recommendation for weekly liver function tests for any patient with elevated liver function test results or any patient with any degree of hepatic impairment is already adequately addressed in the proposed PI. *Under Precautions, Hepatotoxicity*, the proposed product information states 'Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the upper limit of normal or baseline'. The USA PI also contains a similar statement.

## Risk-benefit analysis

### Delegate's considerations

Efficacy was assessed in a randomised controlled trial (pivotal trial) and a small uncontrolled trial. In the pivotal trial, regorafenib produced a statistically and clinically significant increase in PFS of median 3.9 months. There was no significant increase in OS or QOL. The OS data is difficult to interpret due to confounding on crossover after disease progression. The effect on PFS is likely to be translated into a similar OS increase if the results were not confounded by crossover. The uncontrolled trial was supportive.

Patients treated with regorafenib had a high incidence of severe and serious adverse reactions, particularly hepatotoxicity, which warrant close monitoring. The majority of adverse events were managed with dose reduction. Seventy percent of subjects required dose modification due to adverse events. It is possible that Japanese patients are more susceptible than other races to some toxic effects of regorafenib, for example, hepatotoxicity and palmar-plantar erythrodysesthesia. Overall, the safety of regorafenib in GIST appeared similar to that for the registered indication. The sponsor has strengthened the safety advice in the product information in response to the evaluator's recommendations.

The Delegate recommends an indication similar to that in the European Union:

*STIVARGA is indicated for the treatment of patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.*

This is in line with the population treated in the trial. It is not possible to generalise to any two tyrosine kinase inhibitors because the efficacy of tyrosine kinase inhibitors other than imatinib mesylate and sunitinib malate in GIST is unknown. Imatinib mesylate and sunitinib malate are the only drugs registered for use in GIST.

There were no data in children. GIST is rare in children and the disease may be a different entity to that in adults<sup>14</sup>. The proposed PI states that the safety and efficacy of regorafenib have not been established in children. Use in children would be subject to clinical discretion on a case by case basis.

The recommended indication of regorafenib is last-line treatment of GIST. In this indication, the magnitude of the PFS benefit is likely to outweigh the significant toxicity of the drug. Therefore, the benefit-risk balance is positive.

<sup>14</sup> <<http://www.ncbi.nlm.nih.gov/pubmed/19194193>>

### Proposed action

The Delegate had no reason to say, at this time, that the application should not be approved for registration.

### Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. What is the committee's opinion of the clinical significance of the increase in progression-free survival with regorafenib in the efficacy trial? What is the committee's opinion of the support from the secondary endpoints?
2. Should the indication be restricted to the trial population as in the USA and EU?
3. What is the committee's opinion of the benefit-risk balance of regorafenib in the proposed indication?
4. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### Response from sponsor

The sponsor adopts the Delegate's recommendation to amend the proposed indication wording for last line treatment of gastrointestinal stromal tumours (GIST). The new wording is:

*'Stivarga is indicated for the treatment of patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib'.*

The sponsor agrees with the Delegate's preliminary assessment of proposed action.

The sponsor's comments regarding the 'Request for ACPM advice' and our response to the specific issues raised are presented below.

### Introduction

GIST is the most common form of mesenchymal tumour in the gastrointestinal tract. The estimated incidence of GIST in the total population is 11 to 20 million/year. In patients with unresectable and/or metastatic GIST, molecular targeted therapy has been the focus of the therapeutic approach over the past decade.

Imatinib mesylate, a selective tyrosine-kinase inhibitor of KIT, PDGFR, ABL kinase, and the chimeric BCRABL, was the first tyrosine-kinase inhibitor approved by health authorities worldwide for the treatment of patients with KIT positive unresectable and/or metastatic GIST. However imatinib therapy is limited by primary resistance in approximately 15% of patients<sup>15,16,17,18</sup> and over 80% of patients eventually exhibit disease progression driven by secondary-resistance mutations located in additional KIT exons.<sup>19,20,21,22 23</sup>

<sup>15</sup> Heinrich MC, Owzar K, Corless CL, et al. J Clin Oncol 2008a;26(33):5360-7.

<sup>16</sup> Debiec-Rychter M, Sciot R, Le Cesne A, et al. for EORTC Soft Tissue and Bone Sarcoma Group; Italian Sarcoma Group; Australasian Gastrointestinal Trials Group.

<sup>17</sup> Caram MV, Schuetze SM. J Surg Oncol 2011; 104:888-95.

<sup>18</sup> Antonescu CR, Besmer P, Guo T, et al. Clin Cancer Res 2005; 11:4182-90

<sup>19</sup> Antonescu CR, Besmer P, Guo T, et al. Clin Cancer Res 2005; 11:4182-90

<sup>20</sup> Chen LL, Trent JC, Wu EF, et al. Cancer Res 2004; 64:5913-9.

<sup>21</sup> Debiec-Rychter M, Cools J, Dumez H, et al. Gastroenterology 2005; 128:270-9.

<sup>22</sup> Liegl B, Kepten I, Zhu M, et al. J Pathol 2008; 216:64-74.

<sup>23</sup> Heinrich MC, Corless CL, Blanke CD, et al. J Clin Oncol 2006; 24:4764-74.

The first drug shown to provide clinical benefit in GIST following resistance to imatinib was sunitinib, which has more potent activity against the wild-type KIT kinase than imatinib and also inhibits a number of other tyrosine kinase-related signalling pathways through the vascular endothelial growth factor receptors (VEGFR1-3), Fms-like tyrosine kinase-3 (FLT3) and the receptor encoded by the proto-oncogene RET.<sup>24,25, 26, 27, 28</sup>

Currently there are only two approved therapies for the treatment of unresectable and/or metastatic GIST - imatinib, and upon imatinib failure, sunitinib. Despite the activity of sunitinib, the majority of patients with metastatic GIST will progress within 6 to 9 months and eventually die. There is no other therapy with any activity against this disease approved in Australia following failure of both these agents.

Thus, there is an unmet medical need for new therapies for patients with advanced GIST who have exhausted the current approved treatment options. The fast recruitment of patients with unresectable and/or metastatic GIST in the pivotal study (GRID), that is, 7 months instead of 11 months as originally planned is evident of the need for another effective treatment option in this patient group.

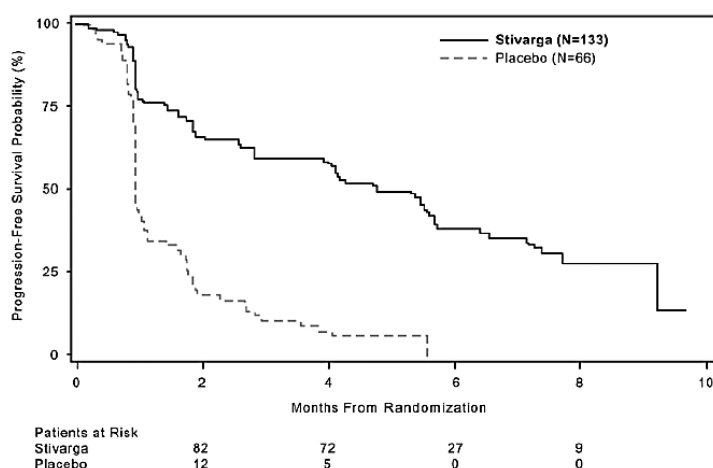
### ***Specific issues raised by the Delegate***

#### *Clinical significance of the increase in progression-free survival*

As acknowledged by the Delegate and the clinical evaluator, the pivotal Study 14874 (GRID) in patients with refractory unresectable and/or metastatic GIST demonstrated clinically and statistically significant benefits in favour of regorafenib for the primary endpoint of progression free survival (PFS). The GRID study was a robust, rigorously conducted large scale international study demonstrating that the median PFS time (per blinded central radiology review) was significantly longer in the regorafenib group with 147 days (4.8 months) compared to 28 days (0.9 months) in the placebo group (see Figure 1). These results were based on a primary efficacy analysis of 144 events.

The risk of progression (or death) was reduced by approximately 73.2% in the regorafenib group compared to the placebo group (Hazard ratio (HR): 0.268;  $p < 0.000001$ ). These results are considered clinically meaningful in patients with incurable disease not responding to currently approved therapies and for which there is no currently approved standard treatment.

**Figure 1: Kaplan-Meier curve of PFS**



<sup>24</sup> Abrams TJ, Lee LB, Murray LJ, Pryer NK, Cherrington JM. Mol Cancer Ther 2003; 2:471-8.

<sup>25</sup> Mendel DB, Laird AD, Xin X, et al. Clin Cancer Res 2003; 9:327-37.

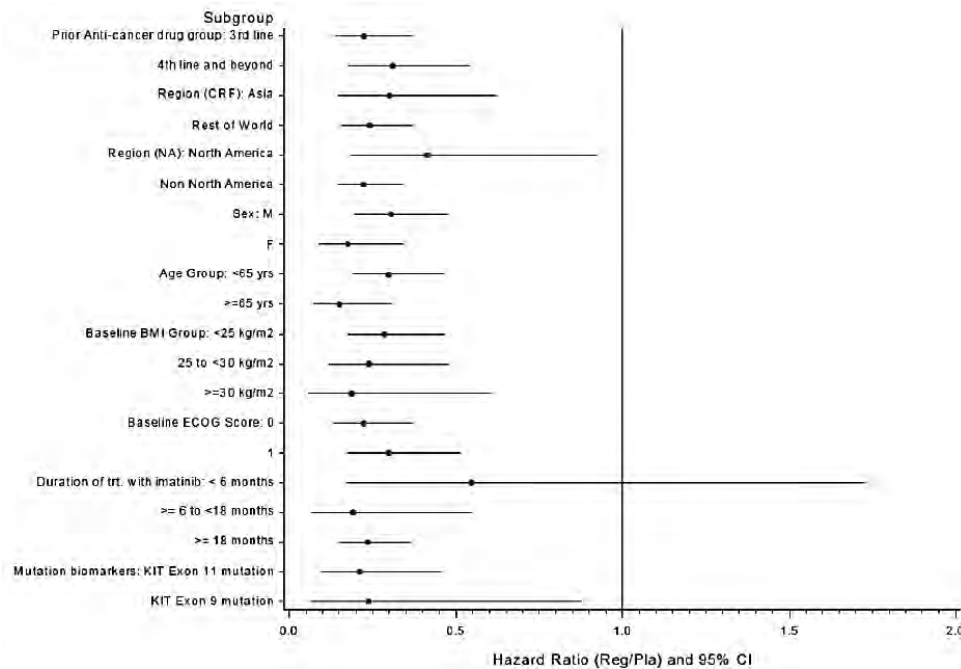
<sup>26</sup> O'Farrell AM, Abrams TJ, Yuen HA, et al. S Blood 2003; 101:3597-605

<sup>27</sup> Osusky KL, Hallahan DE, Fu A, Ye F, Shyr Y, Geng L. Angiogenesis 2004; 7:225-33.

<sup>28</sup> Broutin S, Ameer N, Lacroix L, et al. Clin Cancer Res 2011; 17:2044-54.

PFS was also evaluated in subgroups of geographic region, prior line of treatment, age, sex, baseline body mass index (BMI), duration of imatinib treatment, ECOG performance status and mutational status. Consistently across all subgroups and the primary analysis for PFS, median PFS was substantially longer in the regorafenib group than in the placebo group. A Forest plot depicting the HRs of the subgroup analyses for PFS is shown below in Figure 2. The HRs in the subgroups ranged from 0.150 to 0.546, which are all well below 1. The subgroup of patients treated with <6 months of imatinib is very small with a total 22 patients. These results demonstrate that regorafenib has a clinical benefit in a wide range of patients with unresectable and/or metastatic GIST.

**Figure 2: Forest plot of PFS by subgroup, central a 14874, FAS**



In addition, two sensitivity analyses were performed; that is, an unstratified analysis of centrally-assessed PFS data and a stratified analysis of investigator-assessed PFS data. Both sensitivity analyses were consistent with and supportive of the primary analysis of PFS and demonstrated a statistically significant lower risk of progression over time in the regorafenib group compared to the placebo group. For the investigator assessment, the median PFS time was longer in the regorafenib group, (224 days, 7.4 months), compared to the placebo group (52 days, 1.7 months). The risk of progression (or death) was lower in the regorafenib group than in the placebo group (HR: 0.221). This difference was highly statistically significant with  $p < 0.000001$ .

An important point to consider is the quality of life (QoL). In oncology, most therapies cause at least some early decrease in QoL due to their toxicity profile. In earlier lines of therapy, where there is a significant disease free interval, one would expect a patient's QoL to improve after completing therapy. However, in this pre-treated, refractory patient population, the disease-free interval is shorter and the natural course of the disease usually has a negative impact on the overall QoL. Generally, an improvement in QoL should not be expected in these patients with advanced GIST. The fact that regorafenib in this setting leads to a comparable QoL to placebo treatment while improving PFS in itself, is an important and clinically relevant finding.

### **Supporting secondary endpoints**

Consistency of the clinical benefit was observed among key secondary efficacy endpoints including time to progression (TTP), tumour response for which there was a statistically



significant difference in terms of disease control rate, largely attributable to disease stabilisation and overall survival.

#### *Tumour response*

While the objective response rate observed in the GRID study was low (4.5% in the regorafenib group versus 1.5% in the placebo group), the objective response rate per RECIST does not reflect the full beneficial effect of a medicinal product; patients with a slower tumour growth and disease stabilisation may also derive clinical benefit from treatment in terms of increased progression-free and overall survival. RECIST criteria are commonly used to assess response to anticancer therapies but in late line solid organ cancer therapy are not considered a major endpoint.

The point to note is that the overall disease control rate was significantly higher in the regorafenib group (52.6%) than in the placebo group (9.1%) (one sided  $p < 0.000001$ ). This result suggests that regorafenib was associated with clinically meaningful tumour control.<sup>29</sup> Results of the investigator assessment were consistent with those of the central assessment.

#### *Time to progression (TTP)*

The percentage of patients with disease progression was considerably higher in the placebo group (93.9%) compared with the regorafenib group (57.1%). Median TTP was longer in the regorafenib group (165 days, 5.4 months) than in the placebo group (28 days, 0.9 months). The risk of progression in the regorafenib group was lower than in the placebo group with a HR of 0.248, representing a 75.2% relative risk reduction of progression in the regorafenib patients compared to placebo patients. The difference in TTP between treatment groups tested with the stratified log rank-test was statistically significant with  $p < 0.000001$ .

#### *Overall Survival (updated analysis provided at Section 31 response)*

In the GRID trial, placebo patients were given the opportunity to cross-over to regorafenib. An updated OS analysis was provided to the TGA in the sponsor's response for further information. The analysis had a total of 139 events, 91 events (68.4% of patients) in the regorafenib group and 48 events (72.7%) in the placebo group. The final analysis is planned when 160 deaths have been observed.

The median OS was 17.4 months in the regorafenib group and 17.4 months in the placebo group (HR 0.85, 95% CI 0.597–1.206;  $p = 0.1799$ ). Despite 85% of placebo patients crossing over to open-label regorafenib treatment, after progression, a 15% relative risk reduction of death in the regorafenib patients compared with placebo patients was demonstrated.

In comparison to the interim OS analysis with data cut-off on 26 January 2012 (HR 0.772,  $p = 0.199$ ), regorafenib treatment of placebo arm patients was continued and as expected further diluted the treatment effect, evidenced by the slightly higher HR in this analysis.

To correct for the effect of crossover from the placebo to the regorafenib group, the data was additionally analysed using two different correction methods: a correction using the rank preserving structural failure time (RPSFT) model and an iterative parameter estimation (IPE) method (see Table 10). The results of the correction of the mature OS data show that the true OS treatment effect should be much greater (as shown by a smaller HR) than the treatment effect in the uncorrected (ITT) analysis.

<sup>29</sup> Demetri GD, Reichardt P, Kang YK, et al. Lancet 2013;381:295-302.



**Table 10: Hazard ratio and 95% CI intervals for uncorrected and corrected analysis**

OS crossover correction method	Hazard ratio	95% CI
ITT, uncorrected analysis (for reference)	0.849	(0.597, 1.206)
RPSFT with re-censoring	0.388	(0.259, 0.580)
IPE without re-censoring	0.508	(0.352, 0.734)

**Proposed indication**

The adopted indication wording is restricted to the trial population according to the pivotal GRID study and is in line with the approved European indication.

**Benefit-risk balance***Benefits*

As outlined above, the efficacy data from the GRID study demonstrated clinically relevant and statistically significant improvement of PFS. All survival and response endpoints analysed were supportive of the efficacy of regorafenib.

*Risks*

In the GRID study, the most frequently observed treatment-emergent AEs (TEAEs;  $\geq 30\%$ ) in the regorafenib group are outlined in Table 11. The majority of the most common TEAEs  $\geq 30\%$  was low in severity.

**Table 11: Most common TEAEs  $\geq 30\%$  in the regorafenib versus placebo arm in the GRID study (double blind)**

System Class/Preferred Term	Organ	All grades		Grade 3		Grade 4	
		regorafenib (N=132)	placebo (N=66)	regorafenib (N=132)	placebo (N=66)	regorafenib (N=132)	placebo (N=66)
Hand-foot reaction (HFSR)	skin	87 (65.9%)	10 (15.2 %)	29 (22.0%)	1 (1.5%)	0	0
Hypertension		78 (59.1%)	18 (27.3%)	36 (27.3%)	3 (4.5%)	1 (0.8%)	0
Dysphonia		50 (37.9%)	6 (9.1 %)	0	0	0	0
Fatigue		49 (37.1%)	19 (28.8 %)	4 (3.0%)	1 (1.5%)	0	0
Decreased appetite		41 (31.1%)	14 (21.2 %)	1 (0.8%)	2 (3.0%)	0	0

The incidence of Grade 3 TEAEs were reported at a higher incidence in the regorafenib treated patients compared to the placebo treated patients (57.8% versus 26.3%). The most common Grade 3 events ( $>5\%$ ) in the regorafenib group were hypertension (27.3%), HFSR (22.0%), diarrhoea (7.6%) and rash (5.3%).

The incidence rates for Grade 4 (6.8% versus 6.1%) and Grade 5 (5.3% versus 4.5%) TEAEs were reported at a similar incidence in both treatment groups.

One important risk identified for regorafenib is hepatotoxicity. The Delegate considered the recommendations in the proposed PI regarding monitoring of liver function tests (LFTs) in patients with elevated LFT results or any degree of hepatic impairment were addressed adequately. Routine and additional pharmacovigilance activities are outlined in the proposed Risk Management Plan (RMP) for hepatotoxicity.

It has been noted in the Delegate's overview that Japanese patients are more susceptible to certain toxicities associated with regorafenib treatment compared to other ethnicities that is, HFSR and hepatotoxicity. For HFSR, the sponsor has further strengthened this safety concern by including the incidence rates of Asians versus non-Asians in the Adverse Effects section of the proposed PI.

As outlined in the Delegate's overview, dose modifications (dose reduction, dose interruption, duration of dose interruption) due to an adverse event were more common among patients who received regorafenib (69.7%) than placebo (16.7%) in the double blind period. The difference in terms of AEs leading to permanent treatment

discontinuation was relatively low (regorafenib: 6.1% versus placebo: 7.6%), indicating that most AEs in the regorafenib group could be managed by dose modifications and did not result in permanent discontinuation of the study drug.

Despite the higher incidence of dose modifications in the regorafenib group, the median PFS times in patients in the regorafenib group who had dose modifications were also similar to those in the overall primary analysis (see Table 12). These results are clinically meaningful as these patients continue to benefit from treatment with regorafenib.

**Table 12: PFS in patients with dose changes, double blind period, central assessment (Study 14874, regorafenib subjects)**

Variable Subgroup	N	No. of subjects with events	Median (Days) [95% CI]	Median (Months)
Dose reduction (yes/no)				
Dose reduction	46	28 (60.9%)	168 [147, 218]	5.5
No dose reduction	86	52 (60.5%)	125 [57, 199]	4.1
Dose interruption (yes/no)				
Dose interruption	84	52 (61.9%)	166 [126, 199]	5.5
No dose interruption	48	28 (58.3%)	125 [44, A]	4.1
Duration of dose interruption				
≤5 days	25	16 (64.0%)	129 [56, 170]	4.2
5-10 days	42	23 (54.8%)	174 [126, 280]	5.7
>10 days	17	13 (76.5%)	147 [56, 217]	4.8

Abbreviations: CI = confidence interval  
CIs are based on the unstratified Cox Regression Model  
A: Value cannot be estimated due to censored data.

The incidence of Grade 3, Grade 4, and Grade 5 AEs leading to permanent discontinuation was similar between the regorafenib and the placebo group.

The incidence of the most common treatment-emergent SAEs was similar in the regorafenib group and the placebo group (28.8% versus 21.2%). The incidence of drug-related SAEs was 8.3% in the regorafenib group and 3.0% in the placebo group. Despite the higher incidence of SAEs, the incidence rate of AEs leading to permanent treatment discontinuation was low.

Overall, 10 deaths were reported in 198 GIST patients during the study (that died either during treatment or up to 30 days post permanent treatment discontinuation); 7 (5.3%) patients in the regorafenib group and in 3 (4.5%) patients in the placebo group. The majority of deaths were due to progression of the underlying disease: 4/132 (3.0%) for the regorafenib group and 3/66 (4.5%) for the placebo group. Three deaths were assessed by the investigator as drug related: 2 in the regorafenib group (acute hepatic failure, cardiac arrest) and 1 in the placebo group (asthenia).

The sponsor agrees with the Delegate that the safety profile in the GRID study is in line with that observed with the approved indication for regorafenib.

Further changes to the proposed PI have been made to strengthen the safety aspects of regorafenib as recommended by the Delegate.

In summary, regorafenib has a manageable and acceptable safety profile when administered according to the recommended dosage including proper monitoring of patients in line with the usual oncological standards and the recommendations set out in the proposed PI.

### **Conclusion**

Regorafenib provides an effective and safe oral medication in patients previously treated with imatinib and sunitinib where no treatment options exist. The PFS benefit observed in the GRID study is statistically significant and clinically meaningful and is supported by the key secondary efficacy endpoint results. The safety profile of regorafenib is acceptable and manageable when used according to the recommended PI.

The benefit-risk balance of regorafenib is favourable in patients with unresectable and/or metastatic GIST and supports the registration of regorafenib for the amended indication as last line therapy to address the unmet medical need in Australia.

### **Advisory committee considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Stivarga tablets containing 40 mg of regorafenib to have an overall positive benefit-risk profile for the delegate's amended indication;

*Stivarga is indicated for the treatment of patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.*

In making this recommendation the ACPM

- Noted the indication should reflect the trial population and needed to be more specific with regard to the tyrosine kinase inhibitors used.

### **Proposed conditions of registration**

The ACPM agreed with the Delegate on the proposed conditions of registration.

### **Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments**

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

### **Specific advice**

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *What is the Committee's opinion of the clinical significance of the increase in progression-free survival with regorafenib in the efficacy trial? What is the Committee's opinion of the support from the secondary endpoints?*

The ACPM advised that progression free survival (PFS) is a standard primary endpoint in cancer studies. This is because many cancer patients now receive multiple lines of cancer treatment, both before and after the clinical trials in which they participate, which makes assessment using PFS a pragmatic approach. Assessment using overall survival is ideal, but not feasible in this case with cross-over (which was ethically appropriate with a placebo controlled study).

The ACPM noted that a 3.9 months progression free survival is considered clinically meaningful.

Secondary endpoints were supportive with improved time to progression. Few responses were seen, but often responses are not seen with these targeted agents, so disease control may be a better marker of benefit. No quality of life (QOL) advantage was demonstrated, but QOL did not deteriorate markedly either. The ACPM commented that QOL could have been better assessed.

2. *Should the indication be restricted to the trial population as in the USA and EU?*

The ACPM supported the restriction of the indication to the third line of treatment after the use of the other TKIs (imatinib and sunitinib).

3. *What is the Committee's opinion of the benefit-risk balance of regorafenib in the proposed indication?*

The ACPM advised that there is a positive benefit-risk balance for the use of regorafenib for the proposed indication.

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

### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Stivarga tablets containing regorafenib for oral administration, indicated for:

*Stivarga is indicated for the treatment of patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.*

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

1. The Stivarga (regorafenib) Risk Management Plan (RMP) version 2.5 (dated 12 August 2014, DLP 28 February 2013) and Australian Specific Annex version 2.1 (dated September 2014), and future updates where approved by the TGA, will be implemented in Australia.

## **Attachment 1. Product Information**

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

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

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