Australian Public Assessment Report for Regorafenib

Proprietary Product Name: Stivarga

Sponsor: Bayer Australia Ltd

February 2014

About the Therapeutic Goods Administration (TGA)

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· The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

· The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

· The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

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About AusPARs

· An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.

· AusPARs are prepared and published by the TGA.

· An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.

· An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.

· A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Initial decision: Rejected Final decision: Approved
Date of decision:	Date of initial decision: 25 June 2013; Date of final decision: 26 November 2013
Active ingredient:	Regorafenib
Product name:	Stivarga
Sponsor's name and address:	Bayer Australia Limited 875 Pacific Highway Pymble NSW 2073
Dose form:	Tablet
Strength:	40 mg
Container:	Bottle
Pack sizes:	28 and 3 x 28
Approved therapeutic use:	Stivarga is indicated for the treatment of patients with 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.[1]
Route of administration:	Oral
Dosage (abbreviated):	Four Stivarga (40 mg) tablets daily for three weeks on therapy (21 days) followed by one week off therapy (7 days) to comprise a cycle of four weeks (28 days).
ARTG Number:	200553

Product background

This AusPAR describes the application by Bayer Australia Ltd (the sponsor) to register tablets containing 40 mg regorafenib (Stivarga) for the following indication:

> *Stivarga is indicated for the treatment of patients with metastatic colorectal cancer (CRC) irrespective of KRAS mutational status who have been previously treated with,*

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[1] Abbreviations: VEGF: vascular endothelial growth factor; KRAS: Kirsten rat sarcoma viral oncogene homolog (protein), member of the RAS family of GTPases (guanosine triphosphate hydrolases); EGRF: epithelial growth factor receptor.

or are not considered candidates for, fluoropyrimidine based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti EGFR therapy.

Regorafenib is an oral anti-tumour agent that inhibits a variety of kinases using biochemical and cellular kinase phosphorylation. It blocks kinases associated with the regulation of tumour vasculature (vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, tyrosine kinase with immunoglobulin, and epidermal growth factor (EGF) homology domain 2), oncogenesis by mutant kinases (KIT, RET, RAF1, BRAF, and BRAFV600E), and tumour microenvironment (platelet-derived growth factor receptor-β (PDGFRB) and fibroblast growth factor receptor 1 (FGFR1)) (Wilhelm *et al.*, 2011[2], Demetri *et al.*, 2013).

Most colorectal cancers (CRCs) are adenocarcinomas. Carcinomas are the result of sequential accumulation of mutations in various genes (oncogenes, tumour suppressor genes and mismatch repair genes), that initially cause adenomatous polyps, some of which then acquire additional mutations and become malignant. Differentiation may range from tall, columnar cells resembling the adenomatous lesions (but invading the submucosa and muscularis propria) to undifferentiated, anaplastic masses. The following stages can be distinguished: normal mucosa, small adenoma, larger adenoma, invasive adenocarcinoma, metastases.

Regulatory status

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

At the time this application was considered by the TGA, a similar application was approved in the USA, Canada and Switzerland and was under review in the European Union (EU).

Product Information

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

II. Quality findings

Drug substance (active ingredient)

Regorafenib is a synthetic urea derivative. The structure (Figure 1) is not closely related to registered drugs. Regorafenib is not chiral and does not show isomerism:

Figure 1. Structure of regorafenib monohydrate

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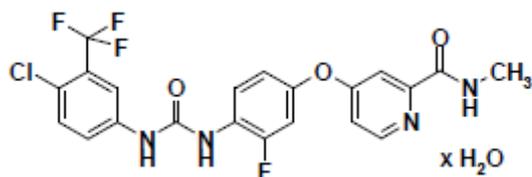
[2] Wilhelm SM, Dumas J, Adnane L *et al*. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011:129(1);245–255.

The molecular formula of regorafenib is $C_{21}H_{15}ClF_4N_4O_3.H_2O$ and it has a molecular weight of 500.83 (monohydrate) or 482.82 (free base).

The drug substance is regorafenib monohydrate. The water is lost during the formulation process for the drug product so the active drug substance present in the tablets is amorphous and anhydrous regorafenib.

Regorafenib is practically insoluble in water and only very slightly more soluble in acid. The drug is very lipophilic. Particle size and polymorphism controls are not relevant because the drug is dissolved in solvents during tablet manufacture.

Potential impurities in regorafenib monohydrate were investigated and are controlled in the drug substance.

Drug product

Bayer proposes registration of 40 mg, unscored, film-coated tablets. These are light-pink ovals (16 x 7 mm) marked "Bayer" and "40" on opposite sides. They are presented in an high density polyethylene (HDPE) bottle, with a child-resistant cap, of 28 tablets as a pack of 1 or 3 bottles (that is, 84 tablets). Bottles have a desiccant.

The tablets are stably formulated with amorphous drug, which enhances drug dissolution *in vivo*. Excipients are otherwise conventional.

Solid solution tablets (20, 40 and 100 mg, all direct scales) have been used in clinical trials. The 40 mg solid solution tablets were used in Phase III studies. The only notable change in the solid solution tablet formulation during development was a change of the film coating. This did not affect bioavailability (Study 12437).

Biopharmaceutics

No absolute bioavailability study has been done. Bayer argues that it is not feasible to make an intravenous solution acceptable for human use.

Two bioavailability studies were reviewed:

· Study 14656: Food effect

Study 14656 was a 3-way, cross-over, single dose study comparing the effects of a high-fat breakfast, a low-fat breakfast and fasting state on the bioavailability of 4 x 40 mg tablets (formulation for registration) in healthy volunteers. Food increased both exposure (area under the plasma concentration-time curve, AUC) and maximum plasma concentration (C_{max}) while slightly delaying the time of maximum plasma concentration (T_{max}), with high fat having the greatest effect. Point estimators (least-squares means) and two-sided 90% confidence intervals (CIs) of selected PK parameters after administration of regorafenib (in all subjects valid for PK (n = 24) are shown in Table 1.

Table 1. Point estimators for selected PK parameters

Analyte	Ratio	Parameter	Estimated Ratio (%)	90% confidence interval (%)
BAY 73-4506	Low Fat / Fasted	AUC	136.05	[123.12 ; 150.33]
		C_{max}	154.29	[137.88 ; 172.66]
	High Fat / Fasted	AUC	148.20	[134.12 ; 163.77]
		C_{max}	172.63	[154.26 ; 193.18]
	High Fat / Low Fat	AUC	108.93	[98.58 ; 120.37]
		C_{max}	111.88	[99.98 ; 125.20]

Interestingly, exposure to active metabolites (M-2 and M-5) is higher with the low fat meal rather than the high fat meal (details not shown here). The PI recommends that doses are taken after a light meal.

· Study 12437: bioequivalence

Study 12437 was a two-way, single dose, crossover bioequivalence comparison of the clinical trial solid solution tablets (1 x 100 mg + 3 x 20 mg) and the 40 mg solid solution tablets as proposed for registration (4 x 40 mg). The study showed bioequivalence.

Advisory committee considerations

The application was considered at 151st (May 2013) meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). A summary of the PSC advice is as follows:

1. The PSC endorsed all the issues raised by the TGA in relation to pharmaceutic and biopharmaceutic aspects of the submission by Bayer Australia Ltd to register Stivarga film coated tablet containing 40 mg of regorafenib. In particular, the PSC supported the issues raised in relation to labelling and advised that these should be resolved in line with best practice guidelines.

2. The PSC noted that no absolute bioavailability study had been undertaken. Such studies are considered a fundamental part of the pharmacokinetic characterisation of a drug. The PSC recommended that, if Stivarga was registered, this issue should be reconsidered if the use of the drug changed significantly in the future.

3. The PSC advised that the product should be stored with a maximum recommended temperature of 25°C.

There was no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the ACPM.

Quality summary and conclusions

Matters relating to chemistry, quality control and bioavailability have been resolved.

Registration is recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical findings

Introduction

General comments

The overall quality of the submission was good. Appropriate studies were conducted and pivotal studies were compliant with good laboratory practice (GLP). Toxicity studies were well supported by toxicokinetic data. Additional studies were conducted on the two major circulating metabolites in humans that were not adequately covered by the use of the rat and dog as the primary nonclinical species. However, some primary pharmacology studies that would appear to have been conducted by the sponsor but were not submitted.

Pharmacology

Primary pharmacology

Various growth factors and receptors are involved in the regulation of tumour growth. These include vascular endothelial growth factor receptor (VEGFR) and tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2), both of which are receptor tyrosine kinases (RTKs) that control tumour angiogenesis (see review by Yancopoulos et al., 2000[3]). VEGFR includes various members, with VEGFR-2 (previously known as KDR or Flk-1) believed to mediate the major growth and permeability actions of VEGF; other members of the family include VEGFR-1 (previously known as Flt-1) and VEGFR-3 (previously known as Flt-3) (Yancopoulos et al., 2000). Fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) are also involved in angiogenesis but have broader roles, such as regulation of cell proliferation, differentiation, growth, survival and migration (Turner and Grose, 2010[4]; Williams, 1989[5]). The oncogenic RTKs, KIT (also known as stem/mast cell growth factor), RET and BRAF are also targets for cancer therapy as they have been identified as driving oncogenic events in certain tumour types (Lanzi et al., 2009[6]; Fletcher and Rubin, 2007[7]; Lo, 2012[8]).

Regorafenib is a new chemical entity which inhibits multiple kinases that are involved in tumour growth, as well as in a wide range of normal cellular functions. Regorafenib and its two major circulating metabolites in humans, M-2 (N-oxide metabolite) and M-5 (N-oxide and N-desmethyl metabolite), were tested in biochemical and in cellular assays for inhibition of various kinases. In the biochemical assays, the kinases inhibited at the lowest concentrations of regorafenib included RET/RET variants, KIT/KIT variants, PDGFR (α and β/variants), VEGFR-1,-2, and -3, FGFR-1 and -2, TIE2 and BRAF/BRAF variants, as well as DDR1 and 2, ZAK, HIPK4, LOK, CSF1R, ABL1-nonphosphorylated, ERK8, EPHA6, p38β, FLT4, TIE1 and PTK5. In a number of *in vitro* biochemical assays investigating the inhibitory effect of regorafenib on various kinases, half maximal inhibitory concentration (IC_{50})/dissociation constant (K_d) values for VEGFR1, -2, and -3, TIE2, PDGFR, FGFR, RET/RET variants, Kit/Kit variants, RAF-1 and BRAF/BRAF variants often fell within the range 1 to 300 nM. It is, however, notable that there were some KIT, PDGFR and FGFR variants with IC_{50}/K_d values higher than this.

When tested against a number of kinases (including VEGFR, FGFR, PDGFR, Kit, Ret and BRAF and/or their variants, but not TIE2), the M-2 and M-5 metabolites showed inhibitory activity that was similar to, and sometimes higher than, the activity of regorafenib parent drug (studies SAG103 and SAG161), with IC_{50}/K_d values falling within a broadly similar range to those for regorafenib (1 to 300 nM).

The mean plasma maximum concentration (C_{max}) values of regorafenib, M-2 and M-5 at a dose of 160 mg/day were about 3.5, 3.3 and 4.0 µg/mL, respectively, corresponding to 7.2 µM, 6.6 µM and 8.3 µM (Study 11650). These values are well above the 1-300 nM range of the IC_{50}/K_d values for some of the critical kinases. A correction for protein binding can be made using a value of 0.488% for fraction unbound (fu) for regorafenib in pooled human plasma (Report PH-34096, although other values for fu were also obtained),

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[3] Yancopoulos GD, Davis S, Gale NW et al. Vascular-specific growth factors and blood vessel formation. *Nature* 2000:407;242-248.

[4] Turner N and Grose R. Fibroblast growth factor signalling from development to cancer. *Nat. Rev. Cancer* 2010:10;116-129.

[5] Williams LT. Signal transduction by the platelet-derived growth factor receptor. *Science* 1989: 243;1564-70.

[6] Lanzi C, Cassinelli G, Nicolini V and Zunino F. Targeting RET for thyroid cancer therapy. *Biochem Pharmacol* 2009:77;297-309.

[7] Fletcher JA and Rubin BP. KIT mutations in GIST. *Curr Opin Genet Dev* 2007:17;3-7.

[8] Lo RS. Receptor tyrosine kinases in cancer escape from BRAF inhibitors. *Cell Res* 2012: 22;945-947.

0.188% for fu for M-2 and 0.053% for fu for M-5. Correcting for protein binding, the concentrations of free regorafenib, M-2 and M-5 are about 35, 12 and 4.4 nM, respectively, which are still within the IC_{50}/K_d ranges, although towards the lower end. Thus, both these metabolites are likely to contribute to the clinical antitumour efficacy of regorafenib.

Regorafenib also showed inhibitory activity against kinases in cellular assays: in Chinese hamster ovary (CHO) cells transfected with human TIE2, in rat-1 cells transfected with BRAF-V600E and in M07e megakaryoblastic leukaemia cell line expressing high levels of cKIT. IC_{50} values for regorafenib in the cellular assays lay within the same range as those in the biochemical assays (24-41 nM for inhibition of TIE2 in the CHO cells, 23 nM for inhibition of KIT in M07e cells and 69 nM for inhibition of BRAF in rat-1 cells). As in the biochemical assays, the metabolites M-2 and M-5 were pharmacologically active, with both showing broadly similar activity to parent drug in all three test systems.

Regorafenib also inhibited the proliferation of various human colorectal and pancreatic cell lines. However, half maximal effective concentration (EC_{50}) values (in the range 2.7 to 9.7 µM for 23 of the 33 cell lines tested), while similar to the expected C_{max} for total drug, were considerably higher than the C_{max} for free drug, and 6 of the 25 colorectal cell lines tested had EC_{50} values >10 µM.

Orally administered regorafenib inhibited tumour growth in *in vivo* studies performed in nude mice transplanted with human xenografts and in mice transplanted with murine cancer cells. Activity was investigated against five human colorectal tumour xenografts (including three oxaliplatin-resistant xenografts) and one human breast tumour xenograft in nude mice, and against implanted H129 hepatoma and 4T1 breast cancer cells in syngeneic mice. The primary endpoint was inhibition of tumour growth, except in the hepatoma study in which it was survival. Toxicity was determined from mortality and body weight changes, and was acceptable (1/8 mice given the high dose (HD) died in the HT-29 colorectal xenograft study but there were no other deaths at the same dose in the other studies; body weights remained within an acceptable range).

Regorafenib showed moderate anti-tumour activity in the HT-29 colorectal tumour model, eliciting 34% and 67% reductions in tumour volume over the study at 3 and 10 mg/kg/day. The 10 mg/kg/day dose was comparable to (about 75% of) the maximum recommended human dose (MRHD) based on area under the plasma concentration-time curve from time of administration until 24 h post-dose ($AUC_{0-24\,h}$) (38.3 µg.h/mL after multiple dosing (Report A55575) compared with 51.3 µg.h/mL in humans), while the 3 mg/kg/day dose gave an AUC only about 20% of that at the MRHD. Protein binding is similar in mice and humans, so a correction is not required. In the oxaliplatin-resistant Co8183 and Co8435 colorectal models, regorafenib also showed moderate efficacy, eliciting respectively, 69% and 64% reductions in tumour volumes at 10 mg/kg/day. While a combination of regorafenib and irinotecan was of superior efficacy to either drug alone in both of these models tumour, inhibitory effects were less than additive. However, regorafenib was not effective in all colorectal models, having minimal activity in the oxaliplatin-resistant Co8434 and Co5896 models, while irinotecan was highly efficacious in both models.

Although not relevant to the indication for the current submission, regorafenib also demonstrated moderate efficacy in the MDA MB231 and 4T1 breast cancer models (inhibition of tumour growth) and improved survival of mice bearing H129 hepatomas. It significantly reduced lung metastases in the 4T1 breast cancer model.

Given that exposure (AUC) in nude mice was lower (75% at 10 mg/kg/day) than the expected regorafenib clinical AUC, and given that moderate efficacy was observed in several colorectal xenograft models, the primary pharmacology results are predictive of efficacy in some, but not all, colorectal tumour types.

In the HT-29 and MDA MB231 models, M-2 and M-5 were also tested at the same two doses (mg/kg/day basis) as regorafenib, and both metabolites showed similar activity to parent drug in both models, which is consistent with in vitro data. Both metabolites showed moderate efficacy at 10 mg/kg/day in the HT-29 model, a dose which achieved exposures comparable to those expected at the MRHD (for M-2, an exposure of 51.9 µg.h/mL can be estimated based on data from multiple dosing in Report A55575 comparable to the expected clinical exposure of 49.8 µg.h/mL; for M-5, an exposure of 52.8 µg.h/mL can be estimated based on data from multiple dosing in Report A55575, similar to the expected clinical exposure of 64.2 µg.h/mL). These data suggest that both metabolites will make a contribution to efficacy in patients, although it is noted that a correction for interspecies differences in protein binding for M-2 and M-5 would result in the mouse M-2 AUC being about 5 fold the expected human value and the mouse M-5 AUC being about 7 times the expected human value.

The antiangiogenic effects of orally administered regorafenib and M-2 were investigated in female Fischer rats bearing implanted gliomas in studies using nuclear magnetic resonance imaging (MRI) following Gadomer-17 injection to estimate tumour blood vessel volume and total permeability surface area of tumour vessels. Decreased MRI signals in tumours from rats treated with regorafenib and M-2 are indicative of *in vivo* antiangiogenic activity of both compounds. Tumour growth inhibition (no growth for 4 days after the last dose) after multiple (4) daily oral doses of 10 mg/kg regorafenib correlated with the antiangiogenic effect (significant reduction in MRI signal). At 10 mg/kg regorafenib which elicited significant decreases in MRI signals after both single and multiple doses, estimated $AUC_{0-24\,h}$ values are 48.1 and 86.9 ng.h/mL, respectively (data from the 2 week rat toxicity study in female Wistar rats; no adequate pharmacokinetic (PK) data available for Fischer rats). These AUC values are comparable to and 1.7 fold the expected clinical AUC for regorafenib, respectively, suggesting beneficial effects on tumour angiogenesis at the MRHD, although as the fraction of regorafenib unbound in rat plasma is slightly higher than in human plasma, a correction factor of 1.5 can be applied to this calculation, giving exposures of about 1.4 and 2.5 times those expected clinically.

An *in vivo* experiment examining potential anti-VEGF activity of regorafenib and the M-2 and M-5 metabolites was conducted in male Wistar rats. At 1 mg/kg intravenously (IV), regorafenib and both of its metabolites were able to block VEGF-induced hypotension. Extrapolation of PK data from Report PH-34034 gives an AUC0-24 h of about 6.8 µg.h/mL and plasma concentrations of about 1.2 µg/mL (when BP was measured) at this IV dose which are below the AUC (51.3 µg.h/mL) and C_{max} (3.5 µg/mL) expected at the MRHD. The plasma regorafenib concentration (1.2 µg/mL) was also below the expected clinical C_{max}. The findings suggest that regorafenib will be exhibiting anti-VEGF activity at the recommended clinical dose in patients.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamic (PD) studies did not reveal analgesic activity or pro-convulsive potential at oral doses of up to 50 mg/kg regorafenib in male Wistar rats. This dose achieved a C_{max} of 5.7 µg/mL (in the 2-week rat toxicity study), about 1.6 fold (2.4 fold corrected) the expected clinical C_{max} (AUC was 1.2 fold (1.8 fold corrected) the expected clinical value). Blood glucose concentrations were reduced in both fed and fasted rats after a single oral dose of 50 mg/kg regorafenib, and also in fasted rats at 2 and 10 mg/kg, but the magnitude of the reductions was small (<20%). No effects on plasma glucose levels were observed in the repeat dose toxicity studies in any species, although there were some reductions in liver glycogen levels in rodents.

Although drugs with antiangiogenic properties may suppress wound healing, this was not investigated in any specific nonclinical or clinical study. However, the proposed PI includes a statement relating to this issue and recommends interruption of treatment with Stivarga in patients undergoing major surgical procedures.

Specialised safety pharmacology studies for regorafenib and its metabolites M-2 and M-5 covered the core systems (central nervous system (CNS), cardiovascular and respiratory), although the *in vitro* cardiovascular safety studies on regorafenib were not GLP compliant. Regorafenib was also tested in supplementary systems (renal and gastrointestinal). At doses up to 50 mg/kg orally (PO) regorafenib or 20 mg/kg PO M-5, open field behaviour in male Wistar rats was not affected, but some effects (most notably prone position and stereotypic licking in 1/6 rats, and slightly elevated body temperature at 4 h post dose) were observed at 20 mg/kg M-2. C_{max} values at these doses were 1.6 fold, 2.3 (7.7/3.3) fold and 70% (2.78/4.0) of the expected clinical C_{max} for regorafenib, M-2 and M-5, respectively, but correction for interspecies differences in protein binding would increase these ratios by about 1.5, 3.6 and 5.4, respectively for regorafenib, M-2 and M-5. These results suggest that CNS effects are unlikely in patients. CNS safety studies were backed up by investigation of various CNS parameters in some of the repeat dose toxicity studies, including a functional observation battery and motor activity assessment in the 13-week rat study (which revealed a reduction in motor and locomotor activity in HD females (8 mg/kg/day, exposure ratio (ER) 1.3 or 2 after correction for protein binding)), and measurement of body temperature in the 4-, 13- and 52-week dog studies, testing of reflexes in the 13-week dog study, and testing of nervous system function in the 52-week dog study (no effects of treatment were observed in any of these tests). These results give further support to the conclusion that CNS effects are unlikely in patients.

Human Ether-à-go-go-Related Gene (hERG) current was reduced by regorafenib in transfected HEK293 cells in protein free medium (up to 38% compared to predrug values at 20 μM, significant at 10 and 20 μM; IC_{50} 27 μM). This IC_{50} value is 3.8 fold the C_{max} expected in patients of 7.2 μM (total drug) and 1000 fold taking into account protein binding (comparing free drug), so this inhibition is unlikely to be of clinical relevance. Metabolites M-2 and M-5 were more potent inhibitors of hERG current than parent drug, with IC_{50} values of 1.1 and 1.8 μM, respectively. These are below the C_{max} values at the MRHD, about 6.6 and 8.3 μM, respectively (17% and 22%, respectively of these C_{max} values). Although the comparison based on total drug suggests a risk associated with reduction in hERG current due to the metabolites, if protein binding is taken into account, there is no evidence of a risk. Using a mean value of 0.239% for the fu of M-2 in human plasma (Report PH-34096) gives an expected C_{max} for free M-2 in patients of 16 nM which is well below the IC_{50} for hERG inhibition by M-2. Using the value of 0.053% for the fu of M-5 in human plasma (Report PH-34096) gives an expected C_{max} for free M-5 in patients of 4 nM which is well below the IC_{50} for hERG inhibition by M-5. Further, regorafenib elicited a reduction rather than an increase in action potential duration (APD_{50} and APD_{90}) values in rabbit cardiac Purkinje fibres, which might be expected because of its weak hERG blocking activity.

No effects of regorafenib at intraduodenal doses of up to 100 mg/kg were observed for haemodynamic, electrocardiogram (ECG) or respiratory parameters in anaesthetised dogs. However, plasma regorafenib concentrations were very low with this route of administration (C_{max} values were up to 0.141 μg/mL which is about 4% of the expected regorafenib clinical C_{max} (3.5 μg/mL)). Due to these low exposures, the study was repeated using a 30-min IV infusion to achieve greater exposures (C_{max} values were up to 4.63 μg/mL at the high dose of 2.25 mg/kg; this is about 1.3 fold the expected clinical C_{max} (2.6 fold taking into account species differences in protein binding). Again, no effects of treatment were observed, although the exposure margin achieved was still relatively low. No effects on ECG/cardiovascular parameters were observed in the repeat dose toxicity studies in which these investigations were conducted (4-, 13- and 52-week dog studies).

Findings of the animal studies were consistent with the results of a dedicated clinical study on the QT interval[9] in cancer patients at 160 mg regorafenib, which did not reveal any QTc prolonging effects. Heart rate and blood pressure were also measured in some of the repeat dose toxicity studies (4-, 13- and 52-week dog studies) and no effects were observed.

Since M-2 and M-5 were major circulating metabolites in humans, but were only produced at low levels in plasma in dogs, separate but similar cardiovascular/respiratory studies using the IV route were conducted with administration of these metabolites. No effects were observed after administration of either M-2 or M-5. Achieved plasma M-2 C_{max} values were up to 5.63 μg/mL which is about 1.7 fold the expected M-2 clinical C_{max} of 3.3 μg/mL. Plasma M-5 C_{max} values were up to 5.54 μg/mL which is 1.4 fold the expected M-5 clinical C_{max} of 4.0 μg/mL. However, differences in protein binding between humans and dogs were quite high (a factor of 6.5 for M-2 and 7.8 for M-5), raising the exposure ratios for free drug to 11 for both M-2 and M-5.

Even though not predicted by the nonclinical studies, an increased incidence of arterial hypertension has been observed in patients treated with regorafenib and the proposed product information recommends monitoring of BP, treating hypertension according to standard medical practice and reducing the dose or interrupting or discontinuing treatment with Stivarga, depending on severity of reaction.

Although the kidney was a target organ for toxicity upon repeated dosing in all species investigated (including rats), there were no effects on renal function of single oral doses of regorafenib up to 50 mg/kg in male rats, a dose which achieved an AUC of 1.2 fold the expected clinical value (1.8 fold after correction for species differences in protein binding). Regorafenib was also tested for effects on contractions/relaxation responses to acetylcholine, barium chloride, serotonin (5-HT) and histamine in isolated guinea pig ileum. No effects were observed but concentrations tested were relatively low (up to 1 μg/mL, that is, about 30% of the expected clinical C_{max} of regorafenib). Regorafenib reduced gastrointestinal transit of a barium sulfate meal in male Wistar rats, with a significant effect at the lowest dose tested, 2 mg/kg, which would be expected to achieve a C_{max} of about 0.68 μg/mL (Report PH-3034) or about 20% (30% after protein binding correction) of the expected clinical C_{max}. This suggests that gastrointestinal transit might be reduced at patients at the MRHD.

Pharmacokinetics

Absorption

The extent of absorption of a radioactive oral dose was estimated as 79% after a dose of 2 mg/kg in rats and 71% after a dose of 2.5 mg in dogs. Estimates of oral bioavailability were similar to estimates of absorption in rats, and only slightly lower in dogs, suggesting little first pass effect. Estimates in rats ranged from 77-89%, while in dogs, oral bioavailability declined with increasing dose, from 67% at 1 mg/kg to 29% at 10 mg/kg, suggesting saturation of absorption with increasing dose. Oral absorption was reasonably rapid, with mean T_{max} values in rats being 4-6 h (over the dose range 0.5-8 mg/kg) and in dogs being 1.6-2.7 h (over the dose range 1-10 mg/kg), while in humans T_{max} was 3-4 h at the 160 mg dose. Oral absorption was also reasonably rapid in mice (T_{max} 1-2 h over the dose range 3-10 mg/kg) and rhesus monkeys (T_{max} 2.6 h at a dose of 1 mg/kg), but extent

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[9] QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. QTc is QT interval corrected for heart rate.

of absorption and absolute bioavailability were not estimated in these species, nor in humans.

Clearance was estimated to be 0.15 L/h/kg in rats, 0.21-0.27 L/h/kg in dogs, but was not estimated in humans. Volume of distribution was moderate to high, being about 0.9 L/kg in rats and about 1.8 L/kg in dogs, but was not estimated in humans. Mean half-life ranged from 3.4 to 4.0 h in mice, 4.1 to 7.3 h rats, 5.3 to 8.1 h in dogs which was considerably shorter than in rhesus monkeys (32.6 h) or humans (20-30 h).

In single dose studies, AUC was dose proportional over the dose range 3 to 10 mg/kg PO in mice, 0.5 to 2 mg/kg IV in rats, 0.5 to 8 mg/kg PO in rats, but was less than dose proportional over the dose range 1 to 10 mg/kg PO in dogs. In humans, regorafenib PKs were generally linear up to a dose of 160 mg following a single dose, and up to 60 mg following multiple doses. At higher doses, AUC increased in a less than dose proportional manner, while C_{max} remained relatively constant. Repeat dose studies did not reveal any accumulation with multiple dosing in the mouse, but slight to moderate accumulation was observed in the rat studies, while in the dog, exposures tended to decline with multiple dosing. In humans, accumulation of regorafenib at steady-state was approximately 2-fold, as expected given the mean elimination half life of 20-30 h. Plasma concentration data in the repeat dose studies were pooled for both sexes to estimate PK parameters. This was acceptable in mice and dogs as there was no evidence of sex differences in these species, but in rats, exposures tended to be higher in females than males (for example in the 2-week study T6073132).

In Caco-2 cells, apparent permeability $P_{app\,A-B}$ and $P_{app\,B-A}$ were 124 nm/s and 104 nm/s, respectively, giving an efflux ratio of 0.835. Thus, regorafenib was considered to be highly permeable according to FDA guidelines for the biopharmaceutical classification system (BCS) and there was no evidence of involvement of an efflux transport protein for regorafenib.

Distribution

Plasma protein binding was very high in all species, but there were some species differences. Fraction unbound (mean values from several studies) was in the range 0.25-0.49% in humans; in the nonclinical species, fu was 0.58% in mice, 0.72% in rats, 0.97% in dogs, 1.68% in rabbits and 2.16% in rhesus monkeys. Human serum albumin and α-globulin were identified as important binding components in human plasma. Regorafenib was also bound extensively to the non-esterified fatty acids (oleic, palmitic and stearic). Regorafenib did not show a propensity to distribute into erythrocytes, as plasma concentrations of radioactivity were higher than those of blood or erythrocytes following incubation of blood with radiolabelled (^{14}C)-regorafenib and following administration of ^{14}C-regorafenib to rats.

In tissue distribution studies in rats, radioactivity was rapidly and widely distributed to the tissues. Consistent with the role of the liver in excretion of regofafenib in the rat, a high concentration of radioactivity was observed in this organ (6.6 tissue:blood ratio at the C_{max} (Report PH-35209)). The adrenals (particularly the cortex), adipose tissue and Harderian gland were also consistently highly labelled (tissue:blood ratios of 5.6 (6.3 for cortex), 2.8 and 3.6, respectively). The contents of the bile ducts and gastrointestinal tract were also highly labelled (Report PH-33804; no data for these in Report PH-35209), consistent with biliary excretion. Penetration across the blood/testes and placental barriers was low-moderate (tissue:blood ratio of 0.37 for testes and fetal blood:maternal blood ratio of 0.51) and across the blood/brain barrier was low (tissue:blood ratio of 0.19). Seminal vesicles also had a low concentration of radioactivity (tissue:blood ratio of 0.13), but other reproductive tissues had moderate concentrations. There was no evidence of retention of radioactivity in any organ/tissue, and in most tissues, the half life of radioactivity was

similar to that in blood. There was evidence of slight melanin binding as the eye-wall:blood ratio for radioactivity was higher in pigmented Long Evans rats than in Wistar albino rats (1.75 compared with 0.88 at 24 h post dose), but there were no differences in skin:blood ratio of radioactivity between highly pigmented and less pigmented skin in the Long Evans rats or between the skin of the two strains. An interesting feature of the tissue distribution of regorafenib/metabolites was the heterogeneity of labelling within some tissues, most notably the adrenals and kidneys (cortex>medulla in both organs).

Metabolism

Nine metabolites of regorafenib were identified in an *in vitro* study with rat, dog and human hepatocytes, although metabolite M-1 was only observed in incubations with human hepatocytes, and then only in trace amounts. The two glucuronidated metabolites (M-7 and M-8) were also only observed in incubations with human hepatocytes while the glutathione conjugate (M-9) was only observed in incubations with rat hepatocytes. An *in vitro* study with liver microsomes from mice (two strains, CD-1 and NMRI), rats, dogs, rabbits, rhesus monkeys and humans suggested that the metabolic profiles of regorafenib in mice and rabbits were the most similar to the metabolic profile in humans, but this study was limited by the fact that M-1/M-5 coeluted in the system used and combined results for these metabolites were presented. There were no differences in metabolic profile for the two mouse strains.

Results of investigation of the metabolic profile of regorafenib *in vivo* in mice, rats, dogs and humans were consistent with the *in vitro* data, although M-2, which was formed in significant amounts by mouse microsomes, was only observed as a minor circulating metabolite in mice (there were no data in this species for metabolic profiles in other matrices). The metabolism of regorafenib involves N-oxidation of the pyridine moiety leading to M-2 (a major pathway in humans, minor in mice, minimal in rats and dogs), N-methylhydroxylation leading to M-3 (major pathway in rats and dogs, minor in mice and humans), N-demethylation leading to M-4 (a substantial pathway in rats, minor in mice, dogs and humans), N-demethylation and hydrolysis leading to M-6 (major pathway in dogs, minor in rats (not detected in plasma, but significant in bile/faeces) and humans (not detected in plasma but significant in faeces)), N-glucuronidation (at the urea nitrogen adjacent to the trifluoromethyl-chloro phenyl moiety) leading to M-7 (minor pathway in humans (low levels in plasma, low to moderate levels in urine), not in rats or dogs)), glutathione conjugation leading to M-9 (minor pathway in rats in vitro, not in mice, dogs or humans) and combinations of these pathways leading to M-1, M-5 and M-8 (M-1 not detected *in vivo* in humans, not in mice, rats or dogs (trace in humans in vitro)), M-5 being a metabolite in humans, very minor in mice, rats and dogs, and M-8 being a minor metabolite in humans (detected in urine, not plasma), not in mice, rats or dogs).

Whether there were any sex differences in metabolism is not clear as metabolism was only investigated in male mice and rats, and in female dogs. There were no sex differences in tissue distribution of regorafenib, and rats were the only species in which a difference (relatively small) was observed in plasma concentrations of regorafenib.

In experiments using recombinant cytochrome P450 (CYP) isoforms and CYP isoform selective inhibitors, CYP3A4 was identified as the main CYP isoform responsible for the Phase I metabolism of regorafenib (pyridine N-oxidation leading to the formation of M-2, N-methylhydroxylation leading to the formation of M-3 and N-demethylation leading to the formation of M-4; other metabolites formed by Phase I reactions were the result of combinations of these pathways). CYP3A4 was the only recombinant isoform (except for slight activity of CYP3A5) producing M-2 and M-5, and this was confirmed in the case of M-2, by the finding that ketoconazole and azamulin (CYP3A4 selective inhibitors) abolished or almost abolished M-2 formation. Using recombinant isoforms, CYP2J2 was identified as an isoform of secondary importance to CYP3A4 in the N-methylhydroxylation reaction

leading to M-3 (a metabolite detected in human faeces but not plasma). The finding that ketoconazole and azamulin reduced M-3 formation to about 10-20% of control is consistent with a major role of CYP3A4 in M-3 formation.

In humans, although M-7 (N-glucuronidated regorafenib) was not a major circulating metabolite, about 18% of the dose was eliminated as M-7, while about 5% of the dose was eliminated as M-8 (N-glucuronidated pyridine N-oxide metabolite). In experiments with recombinant uracil diphosphate (UDP) glucuronosyltransferases (UGTs), UGT1A9 was identified as the main UGT isoform responsible for the glucuronidation of regorafenib to M-7 in human liver and kidney microsomes, with UGT1A7 forming trace amounts of M-7. This major role of UGT1A9 was confirmed by the finding that niflumic acid (an inhibitor of UGT1A9) reduced formation of M-7 by both liver and kidney microsomes by about 90%. In experiments with recombinant UGTs, UGT1A9 was identified as the only UGT isoform responsible for the glucuronidation of M-2 to M-8. The major role of UGT1A9 in this conversion was confirmed by the finding that niflumic acid reduced formation of M-8 by liver microsomes by 90%.

Unchanged drug was the dominant circulating moiety in all species investigated (mice, rats, dogs and humans) representing ≥47% of plasma radioactivity AUC (and up to 86% in mice). The dominant circulating metabolites in humans were M-2, followed by M-5 and M-7. This contrasts with the dominant circulating metabolites in rats (M-3 and M-4) and in dogs (M-3 and M-6, followed by M4). M-2, together with M-3 and M-4, were the major circulating metabolites in mice, so in this species at least, the major circulating metabolite in humans (M-2) was produced. However, metabolism was less extensive in mice than in the other species, so the concentrations of M-2 in mouse plasma were relatively low. Thus, even in the relatively short term (4 and 5 weeks) toxicity studies in mice, relatively low exposure ratios for M-2 (AUC for M-2 mouse/AUC M-2 in humans) were achieved (up to 0.9 at 80 mg/kg/day, the HD in the 4-week study, and up to 0.4 at 20 mg/kg/day, the HD in the 5 week study). M-5 was not measured in the 4 week study, but the exposure ratios achieved for M-5 in the 5-week study were very low (0.03 at the HD). Since rats and dogs, the two main species used in toxicity testing, produced little or none of the two major human metabolites, M-2 and M-5, it was appropriate that the sponsor conducted additional studies with these metabolites.

In faeces, parent drug, followed by M-6 were the major moieties in humans, while M-6 and M-3, followed by M-4, were the major moieties in rats, and M-6 followed by M-3 were the major moieties in dogs, after oral administration. Given the enterohepatic circulation observed in humans, the parent drug found in faeces could be derived from intestinal microbial breakdown of conjugated metabolites as well as (possibly) unabsorbed drug. Parent drug was not detected in urine in rats, dogs or humans (except in trace amounts in one IV study in rats). Renal excretion was minor in rats and dogs, but there was substantial renal excretion in humans, with the glucuronides, M-7, followed by M-8, being the major metabolites in human urine. In rat and dog urine, no identified metabolite was detected, but relatively large numbers (8-17) of unidentified metabolites were present, each representing a small fraction (generally <1%) of the dose.

Excretion

Faeces was the major route of excretion in rats and dogs, with 88.2% and 87.6% of an administered oral dose excreted in faeces over 0-168 h in rats and dogs, respectively. It was also the major route of excretion in humans, but faecal excretion over 0-288 h represented only 71.2% of the dose in humans. As noted above, urine was a more significant route of excretion in humans than in rats and dogs, representing 19.3% of the dose, compared with 5.5% and 0.75% in rats and dogs, respectively. Given the relatively low level of renal excretion, regorafenib exposures might not be expected to differ greatly between patients with impaired and normal renal function. Regorafenib/metabolites

showed marked excretion in rat milk, with the ratio of radioactivity for milk:maternal plasma being 6.8.

Faecal excretion after oral administration in the rat was due to biliary excretion, as no radioactivity was detected in faeces in bile duct-cannulated rats. Consistent with this conclusion is the finding of comparable proportions of the dose being excreted in faeces after IV and oral administration in the rat, and the same was the case in dogs. In bile duct-cannulated rats given ^{14}C-regorafenib IV, 8.2% of the administered dose was excreted in faeces, suggesting excretion of this proportion of the drug across the gut wall. In humans, enterohepatic circulation was observed, with the main contributors being regorafenib and M-2. The extent of enterohepatic recirculation in the nonclinical animal species was not specifically investigated.

In summary, there were marked differences in the biotransformation of regorafenib in humans compared with rats and dogs. M-2 formation was much more pronounced in humans than M-3 formation which was a major pathway in rats and dogs. M-5 was a significant metabolite in humans but was a very minor metabolite in mice, rats and dogs. Glucuronidation was a significant biotransformation pathway in humans, but not in rats and dogs, and this difference was reflected in a greater component of urinary excretion in humans than in rats and dogs.

Pharmacokinetic drug interactions

The potential for PK drug interactions involving regorafenib via a variety of mechanisms was investigated.

In an *in vitro* study (primary human hepatocyte cultures), regorafenib (up to 10 µg/mL (approximately 3 fold the expected clinical C_{max} for total drug and 580 fold the expected clinical C_{max} for free drug)) did not show any potential for induction of the major CYP isoforms, CYP1A2, 2B6, 2C19 and 3A4. The study included cell viability tests and positive controls. *In vivo* investigation of the potential for induction of liver enzymes was conducted in the repeat dose toxicity studies (2- and 4-week rat and 4-week dog), with a broader range of enzymes studied. A consistent effect was not observed, although there was a trend for increases in the 4-week rat study.

In studies with human liver microsomes and recombinant isoforms, regorafenib was demonstrated to inhibit some CYP isoforms at clinically relevant concentrations of total drug (about 7.2 µM), but at concentrations well above the expected level of free regorafenib (35 nM). Isoforms inhibited were CYP2C8 (IC_{50} 1.7 µM, K_i 0.6 µM), 2C9 (IC_{50} 2.7 µM, K_i 4.7 µM), 2B6 (IC_{50} 8.1 µM, K_i 5.2 µM) and 3A4 (IC_{50} 5.8/8.3/9.1/10.4 µM, K_i 11.1 µM), and possibly also 2C19 (K_i 16.4 µM), with similar results being obtained for the isoforms that were investigated in both studies. However, in a clinical study, regorafenib (160 mg for 14 days) when coadministered with a single dose of 4 mg rosiglitazone (a CYP2C8 substrate), did not alter exposure to rosiglitazone or its CYP2C8-selective metabolite. A preliminary clinical study in which the effect of regorafenib on the PKs of a single dose of 10 mg warfarin (a substrate of CYP2C9) was investigated, also suggested a lack of any inhibition by CYP2C9, but when a single oral dose of 2 mg midazolam (a substrate of CYP3A4) was co-administered with regorafenib, there was a slight (24%) increase in midazolam AUC, suggestive of weak CYP3A4 inhibition.

Metabolite M-2 showed a broadly similar CYP isoform inhibitory profile to the parent drug, although it was more active against CYP2D6 and less active against CYP2B6. It inhibited CYP2C8 and 2C9, and possibly also 3A4 and 2D6 at clinically relevant total drug concentrations (about 6.6 µM) (IC_{50} values 2.4, 6.1, 9.5/12/21/22, and 13 µM, respectively), while M-5 only inhibited CYP2C8 (IC_{50} 2.5 µM) at clinically relevant concentrations (about 8.3 µM). However, M-2 and M-5 were highly protein bound, even more so than parent drug (fu = 0.188% and 0.053%, respectively), so the concentrations

at which M-2 and M-5 showed inhibitory activity would be well above plasma levels of the free metabolites at the MRHD.

Regorafenib also inhibited two UDP-glucuronosyltransferases at clinically relevant total drug concentrations: UGT1A9 (Ki 2.1 μM) and UGT1A1 (Ki 0.7/3.1 μM). At clinically relevant concentrations, M-2 also inhibited UGT1A1 (IC50 1.6/1.9 μM) and UGT1A9 (IC_{50} 8.3 μM), while M-5 inhibited UGT1A1 (IC_{50} 1.8/2.0 μM). Again, the concentrations at which inhibition was observed would be well above the expected clinical free concentrations of regorafenib, M-2 and M-5.

Regorafenib (at concentrations up to 10 μM) was not found to be a substrate of Breast Cancer Resistance Protein (BCRP) when tested in BCRP over expressing and wild type L-MDCKII cells, as efflux ratios were 0.036 and 0.030 in these respective cells and compounds are considered to be substrates if the efflux ratio is ≥2 in cells that express the transporter (International Transporter Consortium). Similarly, regorafenib (up to 10 μM) was not found to be a substrate of P-glycoprotein (P-gp) when tested in P-gp transfected and wild type L-MDR1 cells, with efflux ratios again ≤2 (0.30 and 0.093, respectively). For both transporters, this conclusion was supported by the lack of an increase in $P_{app\ A-B}$ in the presence of the relevant inhibitors.

Regorafenib was found to be an inhibitor of both BCRP and P-gp. Estimated IC_{50} values were 44.8 and 67.7 nM (mean 56 nM) for BCRP. These values lie below the clinically relevant range (about 7.2 μM) for regorafenib based on total drug concentrations and are less than double the clinically relevant free concentration of regorafenib (35 nM). These calculations suggest that regorafenib might show clinically relevant inhibitory potential toward BCRP, increasing the plasma concentrations of concomitant medicines that are BCRP substrates, such as methotrexate. Estimated IC_{50} values were in the range 0.78-3.4 μM (mean 2.2 μM) for P-gp. These values lie below the clinically relevant range for regorafenib based on total drug concentrations but are about 60 fold above the clinically relevant free concentration of regorafenib, suggesting a possible but not probable interaction with P-gp substrates *in vivo*. Digoxin is a P-gp substrate with a narrow therapeutic index for which a drug-drug interaction might be of significance. Regorafenib may also have the potential to inhibit the intestinal absorption of a co-administered P-gp substrate, since at a dose of 160 mg regorafenib, a duodenal concentration of 1.3 mM can be estimated (based on an assumed duodenal volume of 250 mL), which is considerably higher than the IC_{50} value for P-gp inhibition at 2.2 μM.

Regorafenib (up to 10 μM) was found to be neither a substrate nor an inhibitor of organic anion transporter (OAT) OATP1B1 and was not a substrate of OATP1B3 when tested in OATP1B1 and OATP1B3 transfected and control HEK cells. Regorafenib showed 23% inhibition (non significant) of OAT1B3 transport at 5 μM. This is unlikely to be of clinical relevance. Pravastatin was used as a substrate positive control for both transporters, but there was no positive control inhibitor for either transporter. At concentrations up to 10 μM, regorafenib was also found not to be an inhibitor of OAT1, OAT3 or OCT2 in transfected and control HEK cells, whereas positive controls showed the expected activity.

Investigation of the potential for 129 compounds (mainly other drugs from a variety of drug classes) to increase exposure to regorafenib by reducing formation of M-2 via inhibition of CYP3A4 revealed, as expected, inhibition by many of the typical CYP3A4 substrates. Drugs with IC_{50} values below 1 μM included clotrimazole, ritonavir and ketoconazole, with IC_{50} values of 0.02, 0.10 and 0.11 μM, respectively. Ketoconazole was tested for drug interactions in a clinical study. Co-administration of regorafenib (160 mg on day 5) and ketoconazole (400 mg for 18 days) resulted in a 90% decrease in exposure to M-2 (AUC and C_{max}), but exposure to regorafenib was increased by only 30-40% suggesting that glucuronidation represented an important alternative pathway. Given that ketoconazole is one of the strongest inhibitors identified in this study, this increase in

exposure to regorafenib of 30-40% is likely to be the maximum extent of any interaction by this mechanism.

The same drugs were also investigated for the potential to increase exposure to regorafenib by reducing formation of M-7 via inhibition of UGT1A9. Several drugs inhibited regorafenib glucuronidation with IC_{50} values below 20 μM. Considering the therapeutic plasma concentrations of each of these, niflumic acid and possibly mefenamic acid may affect glucuronidation of regorafenib *in vivo*.

5-Fluorouracil is an anticancer drug that might potentially be prescribed concomitantly with regorafenib. Neither regorafenib nor its metabolites, M-2, M-4 and M-5, each at concentrations up to 20 μM (well above expected clinical concentrations of total or free regorafenib/metabolites) was found to inhibit dihydropyrimidine dehydrogenase, the enzyme that is responsible for 85% of the metabolism of 5-fluorouracil.

As regorafenib is highly protein bound, it may interact with other highly protein bound drugs via competition for protein binding sites. Such potential interactions were addressed by examining the regorafenib fu when ^{14}C-regorafenib was incubated with 11 other highly protein bound drugs at therapeutic and supratherapeutic (5 times) concentrations. Although the concentration of regorafenib used in this study was relatively low (0.2 μM), none of the drugs, when tested at therapeutic concentrations, elicited an increase in the fu for regorafenib.

Inducers of CYP3A4 might be expected to reduce exposure to regorafenib, although this may not reduce efficacy due to the comparable pharmacological activity of the main human regorafenib metabolites and parent drug. This drug interaction was not specifically investigated in nonclinical studies, but a clinical study with rifampicin (600 mg for 9 days, a strong inducer of CYP3A4) was conducted in which the AUC of regorafenib (160 mg on day 7) was reduced by about 50% and there was a 3-4 fold increase in exposure to M-5, but no change in exposure to M-2. The proposed PI recommends the avoidance of strong inducers of CYP3A4.

As regorafenib undergoes enterohepatic recirculation (at least in humans), co-administration of regorafenib with antibiotics may alter regorafenib exposure by altering the gut microbial flora, but no nonclinical or clinical studies were conducted to investigate this effect.

Toxicology

Due to the poor solubility of regorafenib in water and other solvents, a 10% coprecipitate formulation was developed in order to maximise systemic exposure. This formulation, which was not described in detail, was used in the majority of the pivotal toxicity studies.

Acute toxicity

Single dose toxicity studies were limited to investigation of a single dose level (250 mg/kg) given by the oral (clinical) route in mice and rats (females only). This dose was the maximum possible dose achievable with the formulation used and was non-lethal and did not elicit any clinical signs, and although there was no control group for comparison, animals gained weight over the standard 14 day observation period. Thus, regorafenib was of low acute toxicity by the clinical route. Although these studies were very limited (no control group, females only, oral route only, non-rodent not investigated), drugs from this class have generally been found to have low acute toxicity and further or more detailed studies are unlikely to have provided additional information of relevance in assessing the toxicity of regorafenib.

Repeat-dose toxicity

Studies of up to 5 weeks duration were conducted in mice, 6 months in rats and 12 months in dogs. All studies used the oral (clinical) route, with daily dosing, as is proposed clinically (although no 'off period' was included). Study designs, including species used, duration, group sizes and investigated parameters were consistent with the requirements in Guideline CPMP/SWP/1042/99, and toxicokinetic data were collected in all studies. Primary pharmacology studies in mice and rats revealed these species to be pharmacologically responsive to regorafenib, and judging by the toxic effects of regorafenib in dogs, this species is also pharmacologically responsive to regorafenib.

Relative exposure

Exposure ratios have been calculated based on animal:human plasma $AUC_{0-24\,h}$. Human reference values (regorafenib 51.3 µg.h/mL; M-2 49.8 µg/h/mL; M-5 64.2 µg/h/mL) are from Clinical Study 11650 (mean values from 3 cohorts of patients including those with CRC). As is typical for this class of drugs, exposure ratios were very low. Values have also not been corrected for the 3 week on-one week off cycle in humans compared with continuous dosing in the nonclinical species.

Table 2. Relative exposure in repeat-dose toxicity studies

Species; study	Study duration	Analyte	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)	Exposure ratio[#@]
Mouse (CD-1); study T3076262*	4 weeks	Regorafenib	5	15.5	0.3 (0.4)
			20	63.0	1.2 (1.5)
			80	186	3.6 (4.4)
		M-2	5	2.43	0.05
			20	11.7	0.2
			80	45.8	0.9
Mouse (CD-1); study T5079478*	5 weeks	Regorafenib	1	3.13	0.1 (0.1)
			5	18.4	0.4 (0.4)
			20	84.0	1.6 (2.0)
		M-2	5	2.97	0.1
			20	17.8	0.4
		M-5	20	2.02	0.03
Rat (Wistar); study T6073132^	2 weeks	Regorafenib	10	60.5	1.2 (1.8)
			25	145	2.8 (4.2)
			50	196	3.8 (6)
Rat	4 weeks	Regorafenib	1	5.8	0.1 (0.2)

Species; study	Study duration	Analyte	Dose (mg/kg/day)	AUC$_{0-24\,h}$ (µg·h/mL)	Exposure ratio[#@]
(Wistar); study T107462^			4	20.4	0.4 (0.6)
			16	81	1.6 (2.4)
Rat (Wistar); study T4075651^	13 weeks	Regorafenib	0.5	3.14	0.1 (0.1)
			2	10.8	0.2 (0.3)
			8	68.6	1.3 (2.0)
		M-2	8	0.431	0.01
Rat (Wistar); study T2078241^	26 weeks	Regorafenib	0.1	0.511	0.01 (0.01)
			0.5	3.15	0.1 (0.1)
			2	12.5	0.2 (0.4)
		M-5	2	0.130	0.002
Dog (Beagle); studies T2074704 and T3076046*$	4 weeks/13 weeks	Regorafenib	5	12.9	0.3 (0.5)
			20	32.2	0.6 (1.3)
			80	71.8	1.4 (2.8)
		M-2	5	0.094	0.002
			20	0.479	0.01
			80	1.07	0.02
Dog (Beagle); study TXST20070037*	52 weeks	Regorafenib	1	3.19	0.1 (0.1)
			4	13.9	0.3 (0.5)
			16	38.2	0.7 (1.5)
		M-2	4	0.235	0.005
			16	0.923	0.02
		M-5	16	<0.118	0.002

\# = animal:human plasma AUC$_{0-24\,h}$ (human AUC = 51.3 µg.h/mL); @ exposure ratios in parentheses are values corrected for differences between humans and the nonclinical species in protein binding, using correction factors of 1.2 for mice, 1.5 for rats and 2.0 for dogs; * AUC values are the mean of all sampling times as there was no accumulation (mice) or a decrease in AUC with repeated dosing (dogs); ^ AUC values are from the final sampling time as accumulation was evident; $ values for regorafenib are means of data from the 4 and 13 week studies

Major toxicities

The toxicological profile of regorafenib was characterised by degenerative and inflammatory changes in multiple tissues at exposures comparable to or less than those expected clinically. This is not unexpected for this class of drugs. ERs refer to values uncorrected for species differences in plasma protein binding.

Target organs were the liver, skin, kidney, teeth, bone/cartilage, heart, digestive system (stomach, intestine, pancreas, salivary glands), male and female reproductive organs (testes, epididymides, ovaries, uterus, vagina, cervix), haematopoietic/lymphoreticular system (spleen, thymus, bone marrow, Peyer's patches, and to a lesser extent, lymph nodes) and endocrine system (adrenals, pituitary, thyroid). Some (possibly many) of these target organ toxicities, most notably the skin changes in the dog and the dentine changes in both rats and dogs, may be related to the primary pharmacological activity of the drug. Gastrointestinal and skin effects are commonly observed with VEGF inhibition, and skin effects with KIT inhibition.

There were no consistently observed major haematological changes or effects on blood coagulation in any of the nonclinical species.

The liver was a target organ in mice, rats and dogs. In mice, changes were limited to a reduction in weight (also seen in rats and dogs) and a reduction in glycogen (also seen in rats). Some additional changes, seen in both rats and dogs, included bile duct proliferation, increased pigment storage in Kupffer cells, cytoplasmic changes, mononuclear cell infiltration and pigment deposition. Additionally, perihepatitis, increased apoptoses/mitoses and rounded hepatocytes were seen in rats and centrilobular hypertrophy and fat accumulation in dogs. In dogs, the gall bladder was also affected in the 52-week study (most notably, inspissation and epithelial hyperplasia). Most changes in the rat were observed at ≥2 mg/kg/day (ER 0.2). In dogs, the majority of findings were at ≥ 20 mg/kg/day (ER 0.6). A number of serum clinical chemistry changes were consistent with liver damage induced by regorafenib. These included increases in serum aspartate transaminase (AST) and alanine transaminase (ALT) in all the repeat dose rat and dog studies, with significant increases observed at ≥5 mg/kg/day in mice (ER 0.4), ≥ 0.5 mg/kg/day in rats (ER 0.1) and ≥ 16 mg/kg/day in dogs (ER 0.7). Lactate dehydrogenase (LDH), creatinine kinase (CK) and glutamate dehydrogenase (GLDH) were also measured in some studies and were increased. Increases were also observed in cholesterol (2-, 4- and 13-week rat studies) and bilirubin (2- and 4-week rat studies). Consistent with the nonclinical data, hepatotoxicity has been identified as an important adverse drug reaction in patients. It is appropriate that the proposed Product Information contains a statement recommending that close monitoring of overall safety is conducted in patients with moderate to severe hepatic impairment.

The skin was a major target organ in dogs, but no effects on the skin were observed in mice, while in rats, the only finding in skin was in the 2-week study in which apoptosis of hair follicles was observed in females mainly at ≥ 25 mg/kg/day (ER ≥2.8)(there were no findings in skin in the longer term studies at doses up to 16 mg/kg/day (ER up to 1.6)). Skin histological changes in the dog were characterised by folliculitis/perifolliculitis and hair growth arrest after 13 weeks dosing (but not after 4 weeks dosing at the same doses), and additionally, after 52 weeks, hyperkeratosis, follicular keratosis, hypergranulosis, comedo, fibrosis, crusts, pigment clumping, inflammation and lymphoid cell infiltration. These changes resulted in gross skin changes/clinical signs of alopecia or sparse coat after 13 weeks and additionally, skin reddening, thickening and swelling, formation of scabs, papules, pustules, abscesses, wounds and eczema after 52 weeks. Skin changes were observed at all doses in the 52-week dog study (ER ≥ 0.1). Consistent with the nonclinical data, dermatological adverse reactions have been observed in patients, with hand-foot skin reaction (HFSR)/plantar-plantar erythrodyesthesia syndrome being the most frequently observed skin reaction. The tongue was also affected in rats and dogs, but

findings were inflammatory changes (52-week dog study), reductions in mast cells (4- and 13-week rat studies) and interstitial oedema (4-week rat study) (as well as changes to the sublingual glands noted above), rather than epithelial changes.

The kidney was a target organ in mice, rats and dogs. Glomerulopathy and tubular dilation were observed in all these species. Additional changes were observed in rats and dogs, with many being common to both these species, including tubular degeneration (often accompanied by regeneration), interstitial fibrosis, increased PAS positive staining and casts. Additional findings in the 52 week dog study included glomerulosclerosis, Bowmans capsule hypertrophy and cortical mineralisation. Kidney changes were observed in rats mainly at ≥ 2 mg/kg/day (ER 0.2) and in dogs mainly at ≥ 4 mg/kg/day (ER 0.3). Kidney lesions were associated with urinalysis findings in some studies.

The teeth were affected in all species, with histological changes including dentine alterations (all species), and additionally in rodents, ameloblast and odontoblast degeneration, and in rats only, angiectasis/oedema of the periodontal ligament and inflammation/degeneration of the pulp. Grossly, discolouration was observed in rodents and additionally, broken, missing and spit teeth were observed in rats. Changes to the teeth were observed at doses ≥ 5 mg/kg/day in mice (ER ≥ 0.3), at ≥ 8 mg/kg/day in rats (ER ≥ 1.3) and at ≥ 20 mg/kg/day in dogs (ER ≥.0.6). The findings in rodents may not be of relevance in humans because rodent teeth are constantly growing, but dentine alteration was also observed in dog teeth, in both the 4- and 13-week studies in which the dogs were 6-7 months or 7-8 months old at treatment initiation, that is, relatively mature.

Bone was a target organ in mice, rats and dogs. Thickened growth plate was observed in all these species, and hypocellularity of the growth plate in rats, but these changes are likely to only be of relevance to young patients. Chondrodystrophy (cartilage maldevelopment) was also observed in all species, mainly at the higher doses in the shorter term studies in rodents (in mice, mainly at 80 mg/kg/day (ER 3.6) and in rats at ≥ 8 mg/kg/day (ER ≥ 1.3)), while in dogs, it was observed in the 2 week study, but surprisingly not at the same doses in the 13 week study in similarly aged dogs. Again, this is likely to be of relevance mainly to young patients.

Digestive system: Histological changes in the gastrointestinal tract were observed in mice, rats and dogs. Stomach changes were mainly in the rodent forestomach (hyperkeratosis/acanthosis) which does not have a counterpart in humans and therefore is not considered relevant for risk assessment. However, cell hypertrophy in the pyloric region of the glandular stomach was also observed in the 4- and 13-week rat studies mainly at 8 mg/kg/day (ER 1.3), while at the higher doses used in the 2 week rat study, changes included erosion/ulceration and mucosal degeneration (at ≥25 mg/kg/day, ER 2.8) and dys-/hyperkeratosis (at ≥10 mg/kg/day). In dogs, findings in the stomach (mucosal mineralisation and hypertrophy of zymogenic cells) were only seen at the higher doses used in the 4 week study (ER >0.6).

The duodenum was affected in rats, but not mice or dogs. The main findings were seen in the 4- and 13-week studies and included hypertrophy of the mucosa, musculature and blood vessels, as well as degeneration/regeneration and inflammatory cell infiltration at 8 mg/kg/day in the 13 week study (ER 1.3), with thickening observed grossly. The choleduodenal junction was also affected (degeneration/regeneration, inflammation, fibrosis and intraluminal debris) in the 13-week rat study. The ileum was only affected in dogs, with degeneration of villi observed in the 13-week study at 80 mg/kg/day (ER 1.4.). Findings in the colon, caecum and/or rectum were relatively minor (including submucosal oedema in the 4-week rat study and inflammatory cell infiltrate in the 13-week dog study).

Gastrointestinal clinical signs (increased incidence of diarrhoea and vomiting, discoloured faeces, mucus and/or blood in faeces) were observed in dogs at ≥ 1 mg/kg/day (ER 0.1).

Consistent with the nonclinical data, gastrointestinal adverse reactions were observed in patients, including gastrointestinal perforation.

Atrophy (general and acinar cells) was the main finding in the pancreas and was observed in mice, rats and dogs. It was associated with degeneration and apoptosis in rats and dogs (and there was a compensatory increase in mitosis in rats), as well as inflammatory interstitial oedema. Effects were observed at doses ≥ 20 mg/kg/day in mice (ER 1.2), ≥ 8 mg/kg/day in rats (ER 1.3) and mainly at 80 mg/kg/day in dogs (ER 1.4).

Salivary glands (parotid, submandibular and/or sublingual glands) were also affected (atrophy or hypertrophy, generally of acinar cells) in the 4- and 13-week rat and dog studies.

Reproductive organs: In males, testicular atrophic changes were observed. These were restricted to reduced weights in the mouse (4 week study), but histological changes (testicular atrophy, immaturity or tubular atrophy/degeneration) were observed in rats (4-, 13- and 26-week studies) and dogs (4- and 13-week studies). Spermatid giant cells were observed in both the 13- and 52-week dog studies. Rats were affected at doses ≥ 2 mg/kg/day (ER ≥ 0.2) and dogs at 20 mg/kg/day (ER 0.6). Some histological changes were observed in the epididymides, most notably cellular debris in rats and dogs, and additionally, aspermia, lymphocytic cell infiltration, tubular mineralisation and epithelial vacuolar degeneration in dogs, but were not always clearly dose-related.

In females, histological changes were observed in the ovaries in mice, rats and dogs. Reductions in ovary weight and/or atrophic changes were observed in rats and dogs, while changes to the numbers of follicles (reduced developing follicles, atrophic, cystic or degenerative) and/or corpora lutea (cystic or necrotic) were seen in all species. Some of these changes are likely to be secondary to hormonal changes, although there was no investigation of these. Findings in the ovaries were observed at doses ≥ 5 mg/kg/day (ER 0.4) in mice, mainly at ≥ 8 mg/kg/day (ER 1.3) in rats, and mainly at ≥ 4 mg/kg/day (ER 0.3) in dogs. The most notable change in the uterus was atrophy/juvenile appearance accompanied by a reduction in organ weight in the 4- and 13- week rat studies (at ≥ 8 mg/kg/day (ER 1.3)), but other changes included stromal atrophy and oedema (in mice), luminal dilatation (rats) and cystic glandular dilatation (dogs). Similarly, the most notable changes in the vagina and cervix were atrophy/juvenile appearance in rats (in the 4- and 13-week studies at ≥ 8 mg/kg/day (ER 1.4)). There was also an increase in the proportion of rats in prooestrus (decrease in proportion in met/dioestrus and in vaginal mucification) in the 4-, 13- and 26-week studies. Other changes included vaginal keratinisation in mice, epithelial exfoliation in rats and a mononuclear cell infiltrate and increased vaginal discharge in dogs. Homogeneity of corpora lutea in rats suggested irregular oestrous cycling.

Haematopoietic/lymphoreticular system: A reduction in spleen weight, reduced haematopoiesis and marginal zone atrophy were observed in the spleen of mice and reduced haematopoiesis in the spleen of rats, but largely at relatively high doses (the HD in the 4-week studies in both species). Reduced thymus weights and thymic atrophy were observed in mice, rats and dogs at doses of 80 mg/kg/day in mice (ER 3.6), ≥ 8 mg/kg/day in rats (ER 1.3) and ≥ 16 mg/kg/day in dogs (ER 0.7). Lymphoid depletion (depletion of follicular centres, single cell necrosis and/or atrophy/degeneration) was observed in Peyer's patches in rats (at ≥ 16 mg/kg/day (ER 1.6)) and dogs (at ≥ 20 mg/kg (ER 0.6)).

There were also changes in bone marrow, which included hyperaemia in rodents, hypocellularity and/or increased fat in all species, and increased myelopoiesis/increased ME ratio in mice and dogs, although these changes did not have a major impact on peripheral blood cell numbers. Bone marrow changes were observed in mice at ≥ 20 mg/kg/day (ER 1.4), in rats at ≥ 10 mg/kg/day (ER 1.2) and in dogs at ≥ 1 mg/kg/day (ER 0.1).

Endocrine system: The most notable findings in the adrenals were degenerative changes at relatively low incidences in rats (necrosis mainly at ≥ 8 mg/kg/day (ER 1.3) in the 4- and 13-week studies; peliosis was observed at high incidence in females in the same studies at ≥ 8 mg/kg/day) and in dogs (vacuolar degeneration of the cortex in the 52-week study mainly at ≥ 4 mg/kg/day (ER 0.3)). Changes in the pituitary were relatively minor, and were different in rats (increased pale cells in the 4- and 13-week studies) and dogs (most notably, mononuclear cell infiltration in the pars nervosa in the 13- and 52-week studies). The same was the case with the thyroid. In rats, a flattened epithelium was observed in the 4-, 13- and 26-week studies (in the latter study, in HD males only) at ≥ 2 mg/kg/day (ER 0.2), and was associated with a reduction in thyroxine (T4) and an increase in thyroid stimulating hormone (TSH) in the 4- and 13-week studies, and an increase only in TSH in HD males in the 26-week study. Thyroid atrophy was observed in dogs, but only in the 13-week study, while mineralisation was observed in the 52-week study, but was not clearly dose-dependent. In dogs, some thyroid hormone changes were seen (a small increase in TSH at the HD (male and female combined) in the 52 week study; thyroid hormones were not measured in the other dog studies).

Some changes were observed in the heart of rats, most notably, perivascular oedema (4- and 13-week studies at ≥8 mg/kg/day (ER 1.3)) and thickening of the atrioventricular valves (26-week study at 2 mg/kg/day (ER 0.2)).

Ophthalmological examinations were conducted in the 13- and 26-week rat studies and the 4-, 13- and 52-week dog studies and did not reveal an effect of treatment.

Recovery was examined following a 4 week recovery period in three of the repeat dose toxicity studies: the 4- and 13-week rat studies and the 4-week dog study. In the 4-week rat study, recovery was poor and mortality high in the treated group. In the dog study, data interpretation was difficult due to the low animal numbers (3/sex/group in the treatment period and 2/sex/group in the recovery period), however, with the exception of dentine alterations in the teeth, there was evidence for recovery of many of the drug-induced changes (including diarrhoea), although some histological changes still remained in the liver (increased serum transaminases resolved), skin, testes and ovaries in the recovery animals. The 13-week rat study provided good data on recovery and it was clear that, with the exception of the teeth (and in particular, dentine alterations), partial or complete recovery was observed for the majority of findings seen during/at the end of the treatment period.

Since rats and dogs, the two main species used in toxicity testing, produced little or none of the two major circulating human metabolites, M-2 and M-5, the sponsor conducted repeat dose toxicity studies (4-week mouse) with these metabolites. M-2 and M-5 showed lower toxicity than parent drug. The histological changes induced by M-2 and M-5 were limited to incisor dentine alterations and, additionally for M-2, hepatic haematopoiesis, and additionally for M-5, dilated bone marrow sinuses (indicative of hypocellularity). Changes elicited by regorafenib were more extensive. The ER achieved for $AUC_{0-24\,h}$ at the HD of M-2 in the 4-week mouse study was 1.4 (69.4 (mean of day 1 and day 30 values)/49.8), although this would increase to 7 (1.4 x 4.7) if corrected for interspecies differences in protein binding. The ER achieved for $AUC_{0-24\,h}$ at the HD of M-5 in the 4-week mouse study was 1.5 (98.5 (mean of day 1 and day 30 values)/64.2), although this would increase to 12 (1.5 x 7.8) if corrected for interspecies differences in protein binding.

In conclusion, the nonclinical data suggest a substantial clinical risk of changes in the liver, skin, kidneys, digestive system and male and female reproductive organs.

Genotoxicity

A standard set of genotoxicity studies was submitted: a bacterial reverse mutation study, an *in vitro* chromosome aberration study in Chinese hamster V79 cells and an *in vivo*

mouse micronucleus test. All studies were GLP compliant, adequately conducted, used appropriate concentrations/doses and included positive controls. Although concentrations scored in the chromosome aberration study in the presence of S9 did not elicit reductions in mitotic or survival indices of >50%, the reductions in survival indices were substantial (>40%).

The bacterial reverse mutation study included *Salmonella typhimurium* strain TA102 which detects mutations at A-T sites and was conducted using both the standard plate incorporation assay, as well as the preincubation assay. Males only were used in the micronucleus test. This is acceptable 'unless there are obvious differences in toxicity and metabolism between male and female rodents' (International Conference on Harmonisation (ICH) Guideline 3B6a). Although the metabolism of regorafenib was only investigated in male mice and rats, so no comparison of metabolism between the sexes could be made, all repeat dose toxicity studies in both mice and rats included both sexes, with no major sex differences evident. Although the toxicity studies were conducted in the CD-1 strain of mice and the genotoxicity studies in the NMRI strain, metabolism in these two strains was similar (Study PH-33760). Overall, the use of males only is considered acceptable. The results of all genotoxicity studies were negative.

Given that rat hepatocytes produced minimal or no M-2 and M-5 (Study A57473), and that the S9 mix used in the *in vitro* genotoxicity studies on regorafenib was from rat liver, it was appropriate that specific genotoxicity studies (bacterial reverse mutation assays and *in vitro* chromosome aberration studies) were conducted on M-2 and M-5. These studies were also GLP compliant, adequately conducted, used appropriate concentrations (although in the chromosomal aberration studies, a 50% reduction in mitotic index/survival index was not achieved in all instances), and positive controls (in most instances), and were conducted in the presence and absence of metabolic activation (rat liver S9). Results were negative except for the chromosome aberration study with M-2 (4 h exposure) in which the percentage of abnormal metaphases was significantly increased at the 30 h harvest (±S9) and at the highest concentration scored following the 18 h harvest (+S9). For the 30 h harvest, the result in the absence of S9 (6.5%) fell within the historical control range (0-8.5%), but the result in the presence of S9 fell considerably outside the historical control range (17.5% compared with 0-5.5%). The result for the 18 h harvest (+S9) fell only marginally outside the historical control range (10.5% compared with 0-8.5%). While M-2 is the major circulating human metabolite of regorafenib and represented nearly 30% of plasma radioactivity in study A59022, the positive clastogenicity finding is not considered a major concern because it was only marked after the later harvest in the presence of S9 and it is not known whether the metabolism of M-2 by rat liver S9 mix reflects the human metabolism of M-2. Further, the short lifespan of the patient population needs to be taken into account.

Carcinogenicity

Carcinogenicity studies on regorafenib were not conducted and are not required for drugs to be used for the treatment of advanced cancers where the predicted life expectancy of the patients is short.

Reproductive toxicity

No fertility and early embryonic development or pre-/postnatal development studies were submitted. This is acceptable given the proposed indication (see ICH S9). Given the mode of action of regorafenib and the effects on the reproductive system in both males (most notably, testicular atrophy or tubular atrophy/degeneration) and females (atrophic changes in the ovaries, and degenerative or necrotic changes to follicles and/or corpora lutea, and probably perturbations to oestrous cycling) seen in the repeat dose toxicity studies, effects on fertility and on pre-/postnatal development might be expected.

Two embryofetal development studies were submitted: one in rats and one in rabbits, both using oral administration. The rabbit study was a full GLP compliant study with 20 females/group and toxicokinetic assessment, but the rat study was a non-GLP pilot study, with 7 females/group, and included 7 dose levels (and control). Both studies were adequately conducted, with standard treatment periods and parameters investigated (in the rat pilot study, fetal examination included visceral and skeletal examination, as well as external examination). Dose selection was appropriate in the rabbit study, as was the dose range covered in the rat pilot study. Pharmacokinetic studies in pregnant and lactating rats showed that regorafenib/metabolites crossed the placenta (ratios of fetal/maternal tissues ranging 0.1-1.6) and was excreted in milk (milk/plasma AUC ratio 6.8).

In the rat, teratogenic effects were observed at doses of ≥0.8 mg/kg/day, while fetal weights were significantly decreased at 1.6 mg/kg/day and the number of viable fetuses/litter was significantly reduced at 2 mg/kg/day. Although there were no toxicokinetic data for this study, available toxicokinetic data from the repeat dose toxicity studies in rats suggest that major reproductive toxicity occurred at exposures well below those that might be expected at the MRHD (a dose of 2 mg/kg/day was associated with an ER of 0.2).

In rabbits, at the high dose (1.6 mg/kg/day, ER 0.4 for regorafenib), there were significant increases in postimplantation loss, decreases in number of live fetuses/litter and increases in fetal and/or litter incidences of various malformations. The main malformations were in the urinary system (rabbits only), the heart and major vessels, and the skeleton.

Relative exposure in the rabbit embryofetal development study

Exposure ratios have been calculated based on animal:human plasma $AUC_{0-24\,h}$. Exposure ratios were very low (Table 3).

Table 3. Exposure in rabbit reproductive toxicity study

Species	Analyte	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)^	Exposure ratio#
Rabbit (NZW)	Regorafenib	0.4	3.2	0.1
		0.8	8.76	0.2
		1.6	18.5	0.4
	M-2	1.6	0.396	0.01
	M-5	1.6	0.132	0.002

^ AUC values are from the final sampling time as accumulation was evident; # = animal:human plasma AUC_{0-24} h (51.3 µg.h/mL from Clinical Study 11650).

Pregnancy classification

The sponsor has proposed Pregnancy Category D[10] which is appropriate and consistent with the category for other kinase inhibitors.

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[10] Use in pregnancy Category D is defined as: *Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.*

Local tolerance

Specific local tolerance studies were not conducted and are not required for a tablet formulation. The toxic effects of regorafenib on the gastrointestinal tract have been noted above, with some (in particular, the gastrointestinal clinical signs observed in dogs) probably due to a local effect.

Immunotoxicity

Immunotoxicity assessment was incorporated into the 4- and 13-week repeat dose rat studies and included splenic cell counts and FACScan analyses of splenic cell subpopulations and determination of serum immunoglobulin (Ig) IgG, IgA and IgM titres. Additionally, a plaque forming cell assay was conducted in the 13-week study. There were no effects of regorafenib in the plaque forming cell assay and minor effects on splenic cell counts. While there were effects on splenic cell subpopulations (most notably, decreases in $CD4^{total}$, $CD45^{high}$ and $CD8^{total}$) and in serum antibody titres (most notably, increases in IgM and decreases in IgG), mainly at the HD in both studies, these did not overtly affect the susceptibility of the animals to infection and are not considered of major toxicological significance.

Phototoxicity

Phototoxicity studies were required as regorafenib and its metabolites M-2 and M-5 absorb the ultraviolet/visible light at the wavelength range 290 -700 nm and are distributed to the skin following systemic administration. Phototoxicity was initially studied in the *in vitro* 3T3 NRU phototoxicity test, which has been validated by the Organization for Economic Cooperation and Development (OECD) and is recommended in the European Medicines Agency (EMA) photosafety testing guideline (CPMP/SWP/398/01). The study was adequately conducted and included positive controls which gave the expected responses. However, the results for regorafenib (3 assays) were variable, with photoirritation factor (PIF) values of 0.73, 1.8 and 6.12 obtained. PIF values of <2 are considered to predict no phototoxicity, values between 2 and 5 to predict probable phototoxicity and values >5 to predict phototoxicity. Thus, two values predicted no phototoxicity while one predicted phototoxicity. This study was therefore followed by an adequately conducted *in vivo* study. Based on toxicokinetic data from the 4- and 5-week mouse studies, the highest dose used in the *in vivo* study would have achieved an exposure above that expected clinically. Results of this study were negative suggesting that regorafenib is unlikely to have phototoxic potential.

Metabolic activation was not used in the *in vitro* study (it is not recommended by the OECD), but a separate 3T3 NRU phototoxicity study was conducted with metabolites, M-2 and M-5. The results for M-2 (PIF of 2.86) weakly predicted probable phototoxicity, while the results for M-5 (PIF of 7.82) predicted phototoxicity. This study was therefore followed by an *in vivo* study on M-5 which gave negative results suggesting that M-5 does not have phototoxic potential. These studies, both *in vitro* and *in vivo*, were again adequately conducted and used positive controls which gave the expected responses. Based on toxicokinetic data from the 4-week mouse study with M-5, the highest dose used in the *in vivo* study would have achieved an exposure above that expected clinically.

Impurities

Impurities/degradants in the drug substance/product are either below the ICH qualification thresholds or can be considered adequately qualified.

Metabolites

Studies conducted on the two major metabolites in humans that were formed only in small quantities in rats and dogs (the major species used in the repeat dose toxicity studies) were quite extensive and included *in vitro* cardiovascular and *in vivo* CNS and cardiovascular/respiratory safety studies, absorption studies in nude mice and rats, plasma protein binding studies (range of species), CYP and UGT inhibition studies, *in vitro* genotoxicity studies (bacterial reverse mutation and chromosome aberration studies) and repeat dose oral toxicity studies (4 weeks in mice, supported by toxicokinetic data) and phototoxicity studies (*in vitro*, and additionally, an *in vivo* study with M-5).

Paediatric use

Regorafenib is not proposed for paediatric use and no specific studies in juvenile animals were submitted. The repeat dose toxicity studies revealed toxicities that would be of concern if regorafenib was to be used in juveniles. These toxicities were to the teeth (most notably dentine alterations, and ameloblast and odontoblast degeneration) and in bone (most notably thickening of the growth plate and chondrodystrophy).

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for regorafenib detailed in the sponsor's draft Risk Management Plan are in general concordance with those of the nonclinical evaluator. Some comments are made regarding proposed PI statements. Details of these are beyond the scope of the AusPAR.

Nonclinical summary and conclusions

·   The overall quality of the submission was good. Appropriate studies were conducted and pivotal studies were GLP compliant.

·   In biochemical assays, regorafenib inhibited multiple kinases that are involved in tumour growth, most notably antiangiogenic (VEGFR-2 and TIE2), stromal (FGFR and PDGFR) and oncogenic (KIT, RET and BRAF). IC_{50}/K_d values for inhibition of many, but not all, were in a clinically relevant range. In cellular assays, regorafenib inhibited TIE2, cKIT and BRAF-V600E with clinically relevant IC_{50} values. However, EC_{50} values for inhibition of proliferation of colorectal and pancreatic cell lines lay in a higher range (clinically relevant for total but not free drug). In nude mice bearing human colorectal xenografts, regorafenib showed moderate efficacy in 3 of 5 models at a clinically relevant dose, while little efficacy was observed in 2 models. Antiangiogenic activity was demonstrated in a rat tumour (glioma) model at a clinically relevant dose. Regorafenib reduced lung metastases in a breast cancer model. The major circulating metabolites in humans (M-2 (N-oxide) and M-5 (N-oxide and desmethyl)) showed similar pharmacological activity to the parent drug and are likely to contribute to pharmacological activity.

·   Secondary pharmacology studies revealed no analgesic activity or pro-convulsive activity, and little effect on blood glucose concentrations at exposures above those expected clinically. Safety pharmacology studies revealed little potential for CNS or respiratory effects of regorafenib, M-2 or M-5. Regorafenib did not show potential for effects on renal function but showed potential to inhibit gastrointestinal motility that may be clinically relevant. Regorafenib, M-2 and M-5 inhibited hERG current in *in vitro* studies, with the metabolites showing greater potency than parent drug, but IC_{50} values were considerably higher than free fraction plasma concentrations in patients, suggesting a low risk of QT interval prolongation. No findings (ECG findings/QT

prolongation) were observed in the *in vivo* safety studies or in the repeat dose dog toxicity studies. No other cardiovascular risks were identified.

· The PKs of regorafenib in rats were characterised by rapid and extensive absorption, high oral bioavailability, low first pass effect, moderate to high volume of distribution, and extensive tissue distribution, with liver, adrenals and adipose tissue being relatively highly labelled. There was no evidence of retention of regorafenib/metabolites in any specific tissue, and only slight evidence of melanin binding. Plasma protein binding was high in all species (but with some species differences). Major metabolic pathways included N-oxidation, N-methylhydroxylation and N-demethylation, but metabolism varied between species, with M-2 formation being more pronounced in humans than M-3 (N-methylhydroxylated) formation which was a major pathway in rats and dogs. M-5 was a significant metabolite in humans but was a very minor metabolite in mice, rats and dogs. Glucuronidation was a significant metabolic pathway in humans, but not in rats and dogs, and this difference was reflected in a greater component of urinary excretion in humans than in rats and dogs, although faecal excretion was the main route of excretion in all species. Marked excretion of regorafenib/metabolites was seen in rat milk. In humans, CYP3A4 was the main CYP isoform responsible for the oxidative metabolism of regorafenib, while UGT1A9 was the main UGT isoform responsible for regorafenib glucuronidation.

· Regorafenib showed potential for drug interactions via inhibition of various CYP isoforms (particularly CYP2C8, 2C9 and 2B6) and UGT1A1 and UGT1A9, as well as inhibition of P-glycoprotein and BCRP. Regorafenib showed no inhibitory potential towards OATP1B1, OATB1B3, OAT1, OAT3 and OCT2. No significant enzyme induction was observed with regorafenib.

· Regorafenib did not show any acute toxicity following a single oral dose of 250 mg/kg in mice and rats. Repeat dose toxicity studies of up to 5 weeks duration were conducted in mice, 6 months in rats and 12 months in dogs. The toxicological profile of regorafenib was characterised by degenerative and inflammatory changes in multiple tissues at exposures (based on AUC) comparable to or less than those expected clinically. The nonclinical data suggest a substantial clinical risk of changes in the liver, skin, kidneys, gastrointestinal system and male and female reproductive systems. Major target organs were the liver (increased serum transaminases and a range of histological changes), skin (particularly hair growth arrest and folliculitis in dogs) and kidney (particularly tubular degeneration and glomerulopathy) and major target organ systems were the gastrointestinal system (stomach, intestine, pancreas and salivary glands, with diarrhoea marked in dogs) and the male and female reproductive systems (in particular, the testes, ovaries and uterus, (mainly atrophic changes), but also epididymides, vagina and cervix)). The haematopoietic/lymphoreticular system (spleen, thymus, bone marrow and Peyer's patches) and endocrine system (adrenals, pituitary and thyroid) were also affected. Teeth (particularly dentine alterations) and bone/cartilage (particularly growth plate thickening and chondrodystrophy) were target organs that would be of particular relevance to children/adolescents (the current indication is for adults). Some changes were also observed in the heart. Metabolites M-2 and M-5 showed lower toxicity than parent drug in 4-week studies in mice.

· Regorafenib was negative in a standard set of genotoxicity studies (a bacterial reverse mutation study, an *in vitro* chromosome aberration study in Chinese hamster V79 cells and an *in vivo* mouse micronucleus test). M-2 and M-5 were also tested in the same *in vitro* studies, with negative results except for M-2 in the chromosome aberration study. An impurity, 4-amino-3-fluorophenoxy-picolinmethylamide (present at up to 0.01% in the active ingredient and 0.10% in the finished product) showed weak

genotoxic activity. These findings are considered of relatively minor concern given the patient population. Carcinogenicity studies were not conducted and are not required.

- Embryofetal development studies in rats (pilot study) and rabbits (full study) revealed embryofetal toxicity and teratogenicity at exposures (based on AUC) lower than those expected clinically. The main malformations were in the urinary system (rabbits only), the heart and major vessels, and the skeleton. Neither a fertility and early embryonic development study nor a pre-/postnatal development study was conducted and this is acceptable. Given the mode of action of regorafenib and the findings in the reproductive systems in males and females in the repeat dose toxicity studies, effects on fertility and pre-/postnatal development might be anticipated in patients.

- Regorafenib, M-2 and M-5 were considered to lack phototoxic potential given the results of the *in vivo* phototoxicity studies, despite some positive results in the *in vitro* studies for all three compounds.

Conclusions and recommendation

An acceptable package of nonclinical data was submitted, with no major deficiencies.

- The primary pharmacology studies demonstrated efficacy and support the use of regorafenib for the proposed indication, although some limitations were evident, most notably, antiproliferative effects on colorectal cell lines were only observed at relatively high concentrations (about clinical C_{max} for total drug) and *in vivo*, a clinically relevant dose of regorafenib showed efficacy in only 3 out of 5 human colorectal xenografts in nude mice.

- No clinically relevant hazards were identified by the secondary and safety pharmacology studies.

- Several potential drug interactions were predicted and there are adequate statements relating to these in the proposed Product Information.

- The toxicological profile of regorafenib was characterised by degenerative and inflammatory changes in multiple tissues at exposures comparable to or less than those expected clinically. This is not unexpected for this class of drugs, and rather than establishing the safety of the drug, the focus is on identifying toxic effects and the exposures at which these effects are observed. Identified target organs/organ systems of particular clinical relevance were the liver, skin, kidney, gastrointestinal system and male and female reproductive systems. Teeth and bone/cartilage were important target organs of relevance to children/adolescents (not the currently proposed patient population). The haematopoietic/lymphoreticular system, endocrine system and heart were also identified as target organs/organ systems.

- Genotoxicity studies on regorafenib were negative and carcinogenicity studies were not conducted. A major circulating metabolite (M-2) was identified as having genotoxic potential, as was an impurity, but the risk associated with this is considered low for this patient population.

- Fertility and pre-/postnatal development studies were not conducted but effects on fertility and pre-/postnatal development might be anticipated given the mode of action of regorafenib and the findings in the reproductive systems in males and females in the repeat dose toxicity studies. In embryofetal development studies in both rats and rabbits, regorafenib was found to be embryofetotoxic (decreases in live fetuses/litter) and teratogenic at exposures lower than those expected clinically.

There are no nonclinical objections to registration of regorafenib for the proposed indication.

Recommended revisions to nonclinical statements in the draft PI are beyond the scope of the AusPAR.

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

Regorafenib is for the proposed indication:

> *the treatment of patients with metastatic colo-rectal cancer irrespective of KRAS mutational status who have been previously treated with, or are not considered candidates for, fluoropyrimidine based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti EGFR therapy.*

Regorafenib is provided in a 40 mg tablet formulation for oral administration. Proposed administration is 160 mg regorafenib (4 tablets) taken orally once daily for 3 weeks (21 days, on therapy) followed by 1 week (7 days) off therapy to comprise a cycle of 4 weeks.

The dosage regimen is also referred to as intermittent dosing: 3 weeks on / 1 week off.

Clinical rationale

The clinical development of regorafenib as a single agent was initiated in 2005 for patients with advanced solid tumours (Study 11650) and progressed to Phase III trials in patients with advanced cancers including CRC. The first indication was for treatment of patients with metastatic CRC irrespective of KRAS mutational status who have been previously treated with, or are not considered candidates for, fluoropyrimidine chemotherapy, an anti-VEGF therapy and, if KRAS wild type, an anti-EGFR therapy, which is the subject of this application.

Contents of the clinical dossier

A total of 15 clinical trials are submitted including full reports and appropriate summaries as summarised in Table 4.

Table 4. Overview of Phase I, II and III regorafenib studies.

Study no. Countries	Type of study	Tumor type	Dosing	No. of patients	Report no.
Phase 1: Regorafenib in healthy volunteers					
12435 USA	Effect of ketoconazole on PK of regorafenib	N/A	Regorafenib 80 and 160 mg single dose (4 x 40 mg tablets) Ketoconazole 400 mg	24	PH-36717, Module 5.3.3.4
12436 UK	PK, metabolism, excretion, mass balance	N/A	Single dose of 120 mg regorafenib solution containing approximately 1.5 mg of 14C-radiolabeled regorafenib	4	PH-36734, Module 5.3.3.1
12437 USA	Relative bioavailability	N/A	2 single doses of 160 mg 1 x 100 mg tablets + 3 x 20 mg tablets compared to 4 x 40 mg tablets	48	PH-36595, Module 5.3.1.2
14656 USA	Bioavailability, high-fat vs. low-fat breakfast vs. fasting state effect on PK	N/A	3 single doses of 160 mg (4 x 40 mg tablets)	24	PH-36525, Module 5.3.1.1
15524 USA	Effect of rifampin (rifampicin) on PK of regorafenib	N/A	Regorafenib 160 mg single dose (4 x 40 mg tablets) rifampin(rifampicin) dose 600 mg	24	PH-36716, Module 5.3.3.4
Phase 1: Regorafenib as single agent in cancer patients					
11650 Germany	Dose escalation, PK, PD, tumor response, safety	Advanced solid tumors	Regorafenib 10 – 220 mg od intermittent dosing schedule (3 weeks on / 1 week off)	76 (of which 39 CRC patients)	PH-36733, Module 5.3.3.2
11651 USA	Dose escalation, PK, safety	Advanced solid tumors	Regorafenib 20 – 140 mg od continuous dosing	84	PH-36741, PH-36742, Module 5.3.3.2
12434 Canada	Probe substrate, PK, safety	Advanced solid tumors	Regorafenib 160 mg, od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off) Group A: Warfarin 10 mg, Omeprazole 40 mg, Midazolam 2 mg Group B: Rosiglitazone 4 mg	Group A: 20 (planned) 6 (actual) Group B: 20 (planned), 10 (actual)	PH-36721, Module 5.3.3.4 Preliminary PK report
13172 Japan	PK, safety	Advanced and refractory solid tumors	Regorafenib 160 mg od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off)	16	A51164 Module 5.3.3.2
14814 USA	Cardiovascular safety (QT/QTc, LVEF), PK, safety	Advanced solid tumors	Regorafenib 160 mg od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off)	54	PH-36720, Module 5.3.4.2 Interim QTc report on 25 patients

Table 4 continued. Overview of Phase I, II and III regorafenib studies.

Study no. Countries	Type of study	Tumor type	Dosing	No. of patients	Report no.
14996 China	PK, safety	Advanced and refractory solid tumors	Regorafenib 160 mg od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off)	24	A51600, Module 5.3.3.2
Phase 1: Regorafenib combined with other medicinal products in cancer patients					
11656 Germany	PK, safety	Metastatic CRC 1st or 2nd line	Regorafenib 160 mg od on days 4–10 and 18–24 of every 4 week cycle Plus mFOLFOX6 or FOLFIRI	45	PH-36735, Module 5.3.3.2
Phase 2: Regorafenib in cancer patients					
11726 USA, France, Germany, Poland, UK, Finland	Uncontrolled, single-arm study, efficacy, safety, PK	Metastatic or unresectable renal cell cancer (previously untreated patients)	Regorafenib 160 mg od: (1 x 100 mg tablets + 3 x 20 mg tablets or 4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off)	49	A46572, Module 5.3.5.2 A55873, Module 5.3.5.2
14596 Germany, Italy, Spain, Korea	Uncontrolled, single-arm study, safety, efficacy, PK	Hepatocellular cancer	Regorafenib 160 mg od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off)	36	A51601, Module 5.3.5.2
Phase 3: Regorafenib in metastatic CRC patients					
14387 North America, Europe, Israel, Australia, Asia [a]	Randomized, double-blind, placebo-controlled study; regorafenib + BSC vs. placebo, efficacy, safety, PK, biomarkers	Metastatic CRC (progressed after standard therapy)	Regorafenib 160 mg od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off) Matching placebo	760 Regorafenib: 505 Placebo: 255	A53306, Module 5.3.5.1

[a] Countries: North America (Canada and USA), Europe (Belgium, Czech Republic, France, Germany, Hungary, Italy, Switzerland, Spain, The Netherlands), Israel, Australia, and Asia (China and Japan)

Abbreviations: BSC – best supportive care; CRC – colorectal carcinoma; PD – pharmacodynamics; PK – pharmacokinetics; UK – United Kingdom; USA – United States of America; mFOLFOX6 – FOLinic acid/Fluorouracil/OXaliplatin (m = modified, the number 6 indicates this is the sixth variation of the regimen developed); FOLFIRI – FOLinic acid/Fluorouracil/IRInotecan

In addition, the sponsor provided a clinical overview, summary of clinical efficacy, summary of clinical safety as well as literature references.

Paediatric data

Not applicable.

Good clinical practice

All aspects of good clinical practice were observed in the studies.

Pharmacokinetics and pharmacodynamics

Studies providing pharmacokinetic and pharmacodynamic data

Fifteen studies provide clinical pharmacological data for regorafenib as summarised in Table 5. Studies were categorised as studies in cancer patient, studies in healthy volunteers, dose escalation studies (which served as the basis for dose selection), biopharmaceutical studies, metabolism (and interaction) studies, special population studies and special studies (a cardiovascular study).

Table 5. Clinical pharmacology studies of regorafenib

Module no. (Protocol no.) Region	Design / Regorafenib Dose Duration	Study population	Number of patients		Main outcomes / Reference
			Total	CRC	
	Phase 1 Studies in Cancer Patients				
	Dose Escalation Studies				
PH-36733 (11650) Germany	Open-label; uncontrolled; Dose-escalation (10-220 mg OD); Intermittent dosing schedule: 3 weeks on / 1 week off	Cancer patients with advanced solid tumors	76	39	Safety profile; PK; PD, MTD; recommended Phase 2 dose 5.3.3.2.1, PH-36733
PH-36741 PH-36742 (11651) USA	Open-label; uncontrolled; Dose-escalation (20-140 mg OD); Continuous dosing schedule.	Cancer patients with advanced solid tumors	84	0	Safety profile; PK; MTD; recommended Phase 2 dose 5.3.3.2.3, PH-36741, 5.3.3.2.2, PH-36742
	Special Populations Studies				
A51164 (13172) Japan	Open-label; uncontrolled; 160 mg OD; Intermittent dosing schedule: 3 weeks on / 1 week off	Cancer patients with advanced refractory solid tumors	16	0	Safety; PK 5.3.3.2.4, A51164
A51600 (14996) Hong Kong Singapore	Open-label; uncontrolled; 160 mg OD; Intermittent dosing schedule: 3 weeks on / 1 week off	Cancer patients with advanced refractory solid tumors	12	8	Safety, PK 5.3.3.2.5, A51600
	Drug Interaction Studies				
PH-36735 (11656) Germany	Open label; uncontrolled 160 mg OD On days 4-10 and 18-24 of every 4-week cycle.	Patients with metastatic CRC	45	45	Safety, PK, PD of regorafenib with mFOLFOX6 or FOLFIRI 5.3.3.2.6, PH-36735
PH-36721 (12434) Canada	Open label; uncontrolled;, 160 mg OD; Intermittent dosing schedule: 3 weeks on / 1 week off	Cancer patients with advanced solid tumors	Grp.A = 6 Grp B = 10	Not Avail-able	PK of probe substrates, Safety, PK, PD of regorafenib 5.3.3.4.3, PH-36721 Study ongoing; preliminary PK report
	Special Studies				
PH-36720 (14814) USA	Open-label, uncontrolled; 160 mg OD; Intermittent dosing schedule: 3 weeks on / 1 week off	Cancer patients with advanced solid tumors	54	Not Avail-able	Safety; PK, QT/QTc intervals and LVEF. 5.3.4.2.1, PH-36720 Study ongoing; interim report

(Table continued)

Table 5 continued. Clinical pharmacology studies of regorafenib

Module no. (Protocol no.) Region	Design / Regorafenib Dose Duration	Study population	Number of patients Total	CRC	Main outcomes / Reference
		Phase 1 Studies in Healthy Volunteers			
	Biopharmaceutics Studies				
PH-36525 (14656) USA	Open label, randomized 3 single oral doses of 160 mg	Healthy volunteers	24	0	Bioavailability; high-fat vs low-fat breakfast vs fasting state effect on PK 5.3.1.1.1, PH-36525
PH-36595 (12437) USA	Open-label, randomized; 160 mg; 2 single oral doses: 1 x 100 mg + 3 x 20 mg; and 4 x 40 mg	Healthy volunteers	48	0	Relative bioavailability 5.3.1.2.1, PH-36595
	Metabolism (Drug interaction) Studies				
PH-36734 (12436) UK	Open label, single center, Single oral dose of 120 mg ^{14}C-radiolabeled regorafenib	Healthy male volunteers	4	0	Metabolism, excretion, mass balance, safety, tolerability and PK 5.3.3.1.1, PH-36734
PH-36717 (12435)	Open label Single oral dose of 160 mg	Healthy volunteers	24	0	Effect of ketoconazole on PK of regorafenib 5.3.3.4.1, PH-36717
PH-36716 (15524) USA	Open label Single oral dose of 160 mg	Healthy volunteers	24	0	Effect of rifampin on PK of regorafenib 5.3.3.4.2, PH-36716
	Phase 2/3 Studies With PK in Cancer Patients				
A51601 (14596) Germany, Italy, Spain, Korea	Uncontrolled, single-arm study 160 mg OD intermittent dosing schedule (3 weeks on / 1 week off)	Hepatocellular cancer	36	0	Efficacy, safety, PK 5.3.5.2.1, A51601
A46572 A55873 (11726) USA, France, Germany, Poland, UK, Finland	Uncontrolled, single-arm study 160 mg OD intermittent dosing schedule (3 weeks on / 1 week off)	Metastatic or unresectable renal cell cancer (previously untreated patients)	49	0	Efficacy, safety, Pk, biomarker 5.3.5.2.2, A46572 5.3.5.2.3, A55873
A53306 (14387) Europe, USA, Canada, Australia, Asia (table continued)	Randomized, double-blind, placebo-controlled study; regorafenib + BSC vs. placebo 160 mg OD intermittent dosing schedule (3 weeks on / 1 week off)	Metastatic CRC (progressed after standard therapy)	760 Regorafenib: 505	760 Regorafenib: 505	Efficacy, safety, PK, biomarker 5.3.5.1.1, A53306

CRC = colorectal cancer; MTD = maximum tolerated dose; FOLFOX = chemotherapy regimen consisting of FOLinic acid/Fluorouracil/Oxaliplatin; FOLFORI = chemotherapy regimen consisting of FOLinic acid/Fluorouracil/IRinotecan

Evaluator's conclusion on pharmacodynamics and pharmacokinetics

The pharmacological data from these 15 studies has determined the PK and PD profile of regorafenib. It clearly indicates that metabolism of regorafenib results in formation of two major metabolites, M-2 and M-5, which have clinically significant activity. Furthermore metabolism principally occurs in the liver and excretion occurs via the faeces.

There is no evidence from this data that various intrinsic factors play a role in influencing the metabolism of regorafenib. There is however some evidence that strong CYP3A4 inducers may increase the metabolism of regorafenib. This only appears to be a modest dose response to toxicity relationship which will need to be further evaluated.

There is no evidence of significant cardiovascular toxicity associated with regorafenib from this data. The food effect evaluation clearly shows that dosing of regorafenib after a

low fat or light meal maximizes exposure to parent drug as well as to the active metabolites.

Dosage selection for the pivotal studies

Two early Phase I studies were conducted in cancer patients to define the best dose and dose regimen to be carried into Phase II–III clinical development. Study 11650, with a 3 week on / 1 week off schedule, and Study 11651, with a continuous dosing schedule, were evaluated to compare the safety and tolerability, PK, anti-tumour activity and the various potential advantages and disadvantages with respect to subsequent clinical use.

In Study 11650, the maximum tolerated dose (MTD) of regorafenib was 160 mg daily on a treatment schedule of 3 weeks on 1 week off in repeated 28-day cycles.

In Study 11651, the MTD of regorafenib in the continuous dosing schedule was 100 mg daily.

The regorafenib 160 mg once daily in the treatment schedule 3 week on / 1 week off in repeating 28 day cycles was selected over the regorafenib 100 mg once daily in the continuous dosing schedule due to a number of considerations, including safety and tolerability.

Safety and tolerability at the MTD were similar when comparing the intermittent versus continuous dosing regimen. However for approximately the same potential toxicity a 20% higher total dose of regorafenib can be delivered using the intermittent schedule when compared to the continuous schedule. This may translate into greater tumour activity.

The intermittent dosing schedule provided an opportunity for patients to recover at least partially from toxicities such as skin and gastrointestinal effects. A potential down side of the intermittent dosing schedule might be tumour flare up during the treatment break period. However the relatively robust disease control rate in patients treated with 160 mg of regorafenib with the intermittent dose schedule from Study 11650 suggests that this may not be a disadvantage in actual clinical use.

In the intermittent dosage schedule patients could receive regorafenib 160 mg, as compared to 100 mg in the continuous dosing schedule, and thus would be exposed to a higher steady state $AUC_{0-24\,h}$ and C_{max} of regorafenib and its two pharmacologically active, equally potent metabolites, M-2 and M-5. The higher exposure during the dosing days in the 3 weeks on / 1 week off schedule may prove advantageous with respect to anti-tumour activity for some tumours.

An intermittent dosing schedule may offer advantages in terms of combining with other agents which are dosed intermittently and decrease the chances of any possible PK drug-to-drug interactions.

Accordingly for the pivotal studies a dose schedule of 160 mg taken for 3 weeks and a 1 week break period on a 4 week schedule has been chosen.

Efficacy

Studies providing efficacy data

Two clinical trials are provided in this submission to support efficacy for regorafenib in the proposed indication, as summarised in Table 6.

Table 6. Overview of clinical studies to demonstrate efficacy of regorafenib in metastatic CRC

Study no. (Report no.) Regions/ countries involved	Title	Study population	Dosing	Number of patients by treatment group	Main outcomes
Pivotal, randomized, controlled trial					
14387 (A53306) North America, Europe, Israel, Australia, Asia	A randomized, double-blind, placebo-controlled Phase 3 study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic CRC who have progressed after standard therapy	Patients with metastatic CRC	160 mg oral Intermittent: 3 weeks on /1 week off	Total: 760 Regorafenib + BSC: 505 Placebo + BSC: 255	Primary: OS Secondary: PFS, ORR, DCR Tertiary: DOR, DSD, PRO, PK, biomarkers Safety
Clinical pharmacology trial					
11650 (PH-36733) Germany	Open label, Phase 1 study to determine the safety, tolerability, MTD, PK, and biomarker status of BAY 73 4506 in patients with advanced malignancies	Patients with advanced solid tumors Metastatic CRC expansion cohort	10-220 mg; oral Intermittent: 3 weeks on /1 week off	Total 76 including 38 with CRC treated with ≥60 mg regorafenib od	PK PFS, Tumor response, DCR Biomarkers Safety

Abbreviations: BSC – best supportive care; DCR – disease control rate; DOR – duration of response; DSD – duration of stable disease; CRC – colorectal carcinoma; no. – number; MTD – maximum tolerated dose; ORR – objective response rate; OS – overall survival; PFS – progression free survival; PK – pharmacokinetics PRO – patient reported outcomes; RECIST – Response Evaluation Criteria in Solid Tumors.
Countries: North America (Canada and USA), Europe (Belgium, Czech Republic, France, Germany Hungary, Italy, Switzerland, Spain, The Netherlands), Israel, Australia, and Asia (China and Japan)

The pivotal study was Study 14387, a randomised double blind, placebo controlled, Phase III study involving a total of 760 male and female patients of at least 18 years of age with metastatic CRC. Patients were randomly assigned on a 2 to 1 ratio to 1 of 2 treatment groups: the experimental arm of regorafenib 160 mg once per day for 3 weeks on / 1 week off together with best supportive care (BSC), and the comparator arm of matching placebo plus BSC.

The primary objective variable for this study was overall survival (OS). The secondary efficacy endpoints were progression free survival (PFS), objective response rate (ORR), which was the percentage of patients with complete response (CR) or partial response (PR), and overall disease control rate (DCR), which included the percentage of patients whose best response was CR, PR or stable disease and excluded those patients with stable disease less than 6 weeks from randomisation. Tertiary end points of the study included duration of response (DOR), duration of stable disease (DUC), and health-related quality of life assessed by patient reported outcomes. Evaluation of disease response was based on the RECIST version 1.1 criteria[11].

The second study, Study 11650, was a supportive, Phase I, open label, single agent study assessing efficacy, safety, PK, and MTD for regorafenib in patients with progressive solid tumours. Secondary objectives were to evaluate biomarker status, PD parameters and tumour response of patients treated with regorafenib. A dose escalation phase included regorafenib doses from 10 to 220 mg once per day given on an intermittent dosage schedule. At the end of the dose escalation phase an expansion cohort of 23 patients with CRC was evaluated at a dose level of 160 mg per day regorafenib given on a 3 weeks on / 1 week off schedule.

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[11]Response Evaluation Criteria for Solid Tumors (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.

Evaluator's conclusions on efficacy

Study 14387

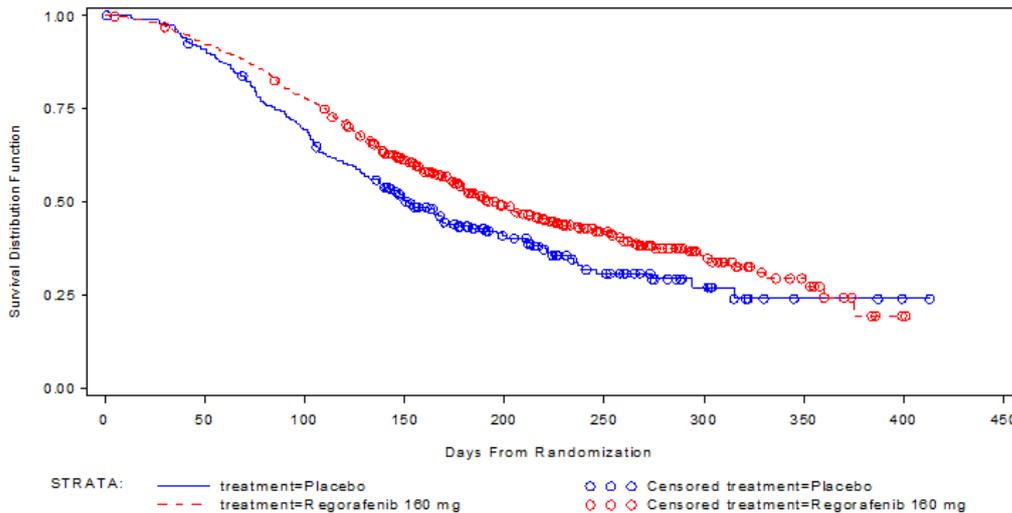Summary data for the primary endpoint, OS, are shown for the intent to treat (ITT) population in Table 7 and Figure 2.

Table 7. Overall survival in Study 14387 (primary analysis; ITT)

	Placebo + BSC (N = 255)	Regorafenib + BSC (N = 505)
Number of patients (%) with event	157 (61.6)	275 (54.5)
Number of patients (%) censored	98 (38.4)	230 (45.5)
Median overall survival (days)	151	196
95% CI for median	134, 177	178, 222
Range (days, without censored values)	13-315	5-375
Range (days, including censored values)	(1**-413**)	(5-401**)
Hazard ratio (regorafenib/placebo)	0.774	
95% CI for hazard ratio	0.636,0.942	
One-sided p-value from log rank test	0.005178	

** = censored observation; CI = confidence interval; ITT = intent-to-treat population
Note: Stratification based on CRF data. A hazard ratio < 1 indicates superiority of regorafenib over placebo. The hazard ratio and its 95% CI was based on Cox Regression Model, stratified by prior treatment with VEGF drugs (yes/no), time from diagnosis of metastatic disease (≥18 months or <18 months) and geographical region 1 (North America, Western Europe, Israel and Australia) versus region 2 (Asia) versus region 3 (Eastern Europe, South America, Turkey).

Figure 2. Kaplan-Meier curves of Overall survival in Study 14387 (ITT)

Summary data for the secondary end point PFS are shown for ITT population in Table 8 and Figure 3.

Table 8. Progression-free survival in Study 14387 (ITT)

	Placebo + BSC (N = 255)	Regorafenib + BSC (N = 505)
Number of patients (%) with event	241 (94.5)	430 (85.1)
Number of patients (%) censored	14 (5.5)	75 (14.9)
Median PFS (days)	52	59
95% CI for median	(51, 53)	(57, 65)
Range (days, without censored values)	6-277	5-333
Range (days, including censored values)	(1**-277)	(1**-336**)
Hazard ratio (regorafenib/placebo)	0.494	
95% CI for hazard ratio	0.419, 0.582	
One-sided p-value from log rank test	<0.000001	

** = censored observation, CI = confidence interval; ITT = intent to treat; PFS = progression-free survival

Note: PFS was based on the investigator's assessment.

Note: Median PFS and 95% CIs computed using Kaplan-Meier estimates. A hazard ratio < 1 indicates superiority of regorafenib 160 mg over placebo. Hazard ratio and its 95% CI was based on Cox Regression Model, stratified by prior treatment with anti-VEGF drugs (yes/no), time from diagnosis of metastatic disease (≥18 months or <18 months) and geographical region 1 (North America, Western Europe, Israel and Australia) versus region 2 (Asia) versus region 3 (Eastern Europe, South America, Turkey). Stratification was based on CRF data.

Figure 3. Kaplan-Meier curves of progression-free survival in Study 14387 (ITT).
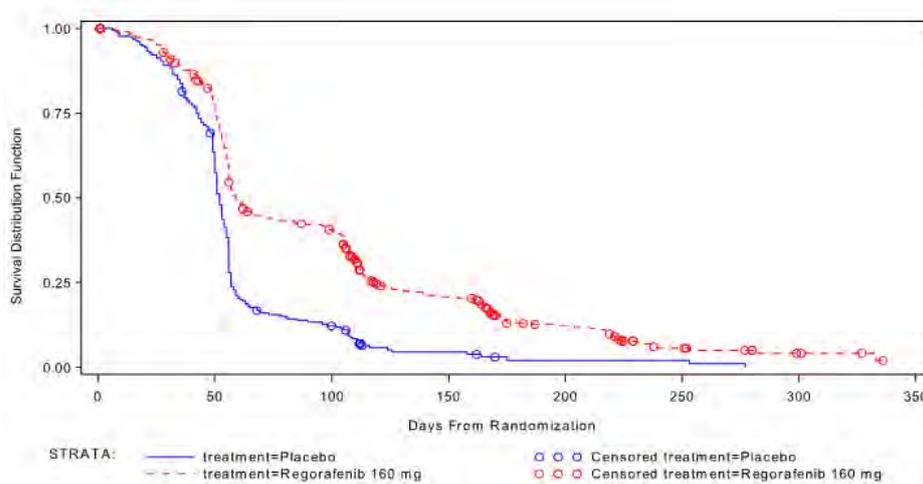
The data from this large, heavily pretreated population of patients with metastatic CRC has shown a comprehensive benefit for regorafenib in terms of both OS and PFS. The primary endpoint benefit for overall survival of 22.6% reduction in hazard is clinically meaningful and a 29.2% improvement in overall survival is confirmation of this. Similarly, the PFS data adds weight to the significant benefits for OS.

Further indication of the value of regorafenib is indicated by the fact that patients irrespective of KRAS mutation status benefited, with the subgroup analyses confirming a benefit.

Study 11650

Median PFS for the 38 patients who received at least 60 mg of regorafenib in this study was 107 days with a range of 1 to 279 days. Data on PFS of CRC patients receiving at least 60 mg regorafenib including information about their tumour KRAS mutation status, and Kaplan-Meier curves showed no clear difference in progression free survival between the two KRAS groups.

The data from the Phase I trial presents very limited information regarding the degree of modest efficacy for regorafenib in these heavily pretreated patients. This data cannot be really considered strongly supportive of the pivotal study because of the small number of patients and the nature of the Phase I trial together with the limited number of patients receiving 160 mg of regorafenib therapy.

Safety

Studies providing evaluable safety data

Safety data for this evaluation is based on the safety data derived from various Phase I, II, and III clinical studies as indicated in Table 9.

Table 9. Clinical development program: overview of clinical studies to demonstrate efficacy and/or safety of regorafenib

Study Report no. (Protocol no.) Region	Design / Regorafenib Dose Duration	Study population	No. of treated patients Total	No. of treated patients CRC	Main outcomes / Reference
		Pivotal Phase 3 Study in Colorectal Cancer Patients			
A53306 (14387) (Pool 3) Europe, North America (incl USA), Israel, Australia, Asia (Japan,China)	Randomized; double-blind; placebo-controlled; 160 mg; intermittent dosing: 3 weeks on / 1 week off	Colorectal cancer patients (after failure of standard therapy)	753 (all CRC) 253 placebo 500 regorafenib		Efficacy; safety, PK, biomarkers Module 5.3.5.1, A53306
		Phase 2 Studies in Cancer Patients			
A46572 (11726) (Pool 1) USA, France, Germany, Poland, UK, Finland A55873 (addendum for 11726)	Uncontrolled; open-label; 160 mg; intermittent dosing: 3 weeks on / 1 week off	Renal cell cancer patients with advanced cancer (previously untreated, metastatic or unresectable)	49	0	Efficacy, safety. Module 5.3.5.2, A46572 Module 5.3.5.2, A55873
A51601 (14596) (Pool 1) Germany, Italy, Spain, Korea	Uncontrolled; open-label; 160 mg; intermittent dosing: 3 weeks on / 1 week off	Hepatocellular cancer patients	36	0	Safety profile; efficacy Module 5.3.5.2, A51601
		Phase 1 Studies in Cancer Patients			
PH-36733 (11650) (Pool 1) Germany	Uncontrolled, open-label; multicenter; Dose-escalation (10-220 mg); Intermittent dosing: 3 weeks on / 1 week off	Cancer patients with advanced solid tumors	76	39	Tumor response; Safety profile; PK; MTD; recommended Phase 2 dose Module 5.3.3.2.1, PH-36733
PH-36742 (11651) (Pool 2) USA	Uncontrolled, open-label; multicenter; Dose-escalation (20-140 mg); continuous dosing schedule.	Cancer patients with advanced solid tumors	84	6	Safety profile; PK; MTD; recommended Phase 2 dose Module 5.3.3.2.2, PH-36742
PH-36735 (11656) (not pooled) Germany	Open label 160 mg once daily days 4-10 and 18-24 of every 4-week cycle.	Patients with metastatic CRC	45	45	Safety, PK/ PD of regorafenib with mFOLFOX6 or FOLFIRI Module 5.3.3.2.6, PH-36735
A51164 (13172) (Pool 1) Japan	Uncontrolled; open-label; 160 mg; intermittent dosing: 3 weeks on / 1 week off	Cancer patients with advanced refractory solid tumors	16	0	Safety profile; PK Module 5.3.3.2.4, A51164

Table 9 continued. Clinical development program: overview of clinical studies to demonstrate efficacy and/or safety of regorafenib

Study Report no. (Protocol no.) Region	Design / Regorafenib Dose Duration	Study population	No. of treated patients Total	CRC	Main outcomes / Reference
A51600 (14996) (Pool 1) Hong Kong Singapore	Uncontrolled; open-label; 160 mg; intermittent dosing: 3 weeks on / 1 week off	Cancer patients with advanced refractory solid tumors	12	8	Safety profile; PK Module 5.3.3.2.5, A51600
TOTAL	Exposed to regorafenib Exposed to placebo	Cancer patients	818 253	598 253	
Phase 1 Studies in Healthy Volunteers					
PH-36595 (12437) (not pooled) USA	Two way, randomized, open label study; 160 mg tablets 2 single oral doses: 1 x 100 mg + 3 x 20 mg; and 4 x 40 mg	Healthy volunteers	48	0	Relative bioavailability Module 5.3.1.2.1, PH-36595
PH-36525 (14656) (not pooled) USA	Open label 3 single oral doses of 160 mg	Healthy volunteers	24	0	Bioavailability; high-fat vs low-fat breakfast vs fasting state effect on PK Module 5.3.1.1.1, PH-36525
PH-36734 (12436) (not pooled) USA	Single center, open label Single oral dose of 120 mg ^{14}C-radiolabeled regorafenib	Healthy male volunteers	4	0	Metabolism, excretion, mass balance, safety, tolerability and PK Module 5.3.3.1.1, PH-36734
PH-36717 (12435) (not pooled) USA	Open label Single oral dose of 160 mg	Healthy volunteers	24	0	Effect of ketoconazole on PK of regorafenib Module 5.3.3.4.1, PH-36717
PH-36716 (15524) (not pooled) USA	Open label Single oral dose of 160 mg	Healthy volunteers	24	0	Effect of rifampin on PK of regorafenib Module 5.3.3.4.2, PH-36716
TOTAL	Exposed to regorafenib	Healthy volunteers	124	0	
TOTAL	Exposed to regorafenib Exposed to placebo	Cancer pts + healthy volunteers	942 253	598 253	

CRC = Colorectal cancer; MTD = maximum tolerated dose; FOLFOX = chemotherapy regimen of FOLinic acid/Fluorouracil/OXaliplatin; FOLFIRI = chemotherapy regimen consisting of FOLinic acid/Fluorouracil /IRInotecan, PK = pharmacokinetics, UK = United Kingdom; USA = United States of America

The main analyses are based on safety data pooled from completed company sponsored monotherapy trials in patients with cancer. Data from the pivotal Study 14387 forms Pool 3; data from the Phase I Study 11651 of regorafenib administered continuously once daily forms Pool 2; and pooled data from the Phase I and II studies in cancer patients with intermittent dosing (3 weeks on / 1 week off) forms Pool 1. A total of approximately 1,145 cancer patients with all types of cancer have been treated with regorafenib, of whom 621 were CRC patients.

Adverse events (AEs) of pooled data were coded using the Medical Dictionary for Regulatory Activities (MedDRA) recognised clinical dictionary and severity of AEs were categorised by National Cancer Institute (NCI) criteria.

Extent of exposure

The extent of exposure in the various 3 pools is indicated in Table 10.

Table 10. Extent of exposure to regorafenib and placebo treatments in pools 1 to 3 (Safety Analysis Set)

	Pool 1	Pool 2	Pool 3	
	Regorafenib N = 188	Regorafenib N = 84	Regorafenib N = 500	Placebo N = 255
Overall time under treatment [a]				
Mean ±SD (weeks)	25.79 ± 33.47	19.74 ± 29.99	12.08 ± 9.74	7.78 ± 5.19
Median	14.79	11.43	7.27	6.98
Range	0.1 – 179.4	0.1 – 145.0	0.28 – 47.01	0.57 – 38.61
Actual time under treatment [b]				
Mean ±SD (weeks)	18.86 ± 24.38	18.01 ± 27.14	8.85 ± 6.78	6.29 ± 3.79
Median (range)	9.64	9.93	5.98	5.98
Range	0.1 – 132.3	0.1 – 134.1	0.28 – 35.9	0.57 – 29.92
Actual daily dose (mg) [b]				
Mean ±SD	137.38 ± 39.41	88.82 ± 29.06	147.13 ± 18.64	159.25 ± 4.85
Median	160.00	100.0	160.00	160.00
Range	10 - 220	20.0 – 140.0	85.7 – 160.0	107.00 – 160.0
Any dose modification, n (%)	112 (59.6%)	83 (98.8%)	378 (75.6%)	97 (38.3%)
Dose reduction per patient, n (%) [c]				
Any dose reduction	79 (42.0)	5 (6.0)	100 (20.0)	8 (3.2)
1	45 (23.9)	5 (6.0)	82 (16.4)	8 (3.2)
2	26 (13.8)	0	14 (2.8)	0
≥3	8 (4.2)	0	4 (0.8)	0
Dose interruptions per patient, n (%)				
Any dose interruption	148 (78.7)	83 (98.8)	352 (70.4)	95 (37.5)
1	70 (37.2)	22 (26.2)	178 (35.6)	70 (27.7)
2	27 (14.4)	32 (38.1)	94 (18.8)	19 (7.5)
≥3	51 (27.1)	29 (34.5)	80 (16.0)	6 (2.4)

Abbreviations: N – number of patients (in total); n – number of patients with the event; SAF – safety analysis set; SD = standard deviation

[a] Including time off drug/interruptions
[b] Excluding time off drug/interruptions
[c] Dose reduction was re-calculated in Pool 2 and differs from that originally presented in the CSR for 11651. If a subject had a dose interruption (a dose of 0 mg), the next non-zero dose was considered a 'reduction' in the CSR, but in this summary it was counted as re-challenge at lower than protocol dose.
The percent of planned dose was calculated consistently for all studies (Pool 1 and 2) and consistently with calculation rules in Pool 3 on the data mapped to the new CDISC standard.

Evaluator's conclusions on safety

The data clearly indicates that there is a significant incidence of toxicities in association with regorafenib administration. Adverse events were noted in 95% of all patients receiving this therapy. Although the majority of AEs were mild to moderate in severity a proportion was Grade 3 and higher. The most common AEs noted included palmar-plantar erythrodysesthesia syndrome, diarrhoea, fatigue, dysphonia, decreased appetite, hypertension and nausea. The most common Grade 3 events were hypertension, fatigue, diarrhoea, palmar-plantar erythrodysesthesia syndrome, pain in the extremity, abdominal pain hyperbilirubinemia, hypophosphatemia and increased transaminases.

In terms of significant toxicities, there was a definite risk associated with potential for severe drug induced liver injury, haemorrhage, myocardial ischaemia/infarction, arterial hypertension and hypertensive crisis, and palmar-plantar erythrodysesthesia syndrome. Also to be assessed carefully is the potential for gastrointestinal perforation and fistula.

These AEs are in general terms consistent with the mechanism of action of regorafenib and the AE profiles associated with other tyrosine kinase inhibitor. While requiring careful monitoring, these AEs are in general terms managed adequately with early intervention and in the appropriate circumstances with prophylactic treatment.

First round benefit-risk assessment

First round assessment of benefits

Data from the pivotal Study 14387 is the principal determinant of evidence of benefit in relation to regorafenib for the proposed indication. This study was a multi-national randomised, placebo controlled, Phase III trial involving 760 patients who were randomised on a 2 to 1 basis to regorafenib plus BSC versus placebo plus BSC.

The results showed a statistically significant benefit in OS for regorafenib over placebo. The estimated hazard ratio (HR, risk of death with regorafenib + BSC versus placebo + BSC) was 0.774 [0.636, 0.942] (one sided p-value = 0.005178). This represents an improvement in OS of 29% for regorafenib treated patients, with a median increase of 6.4 months versus 5 months in the placebo group, corresponding to a 23% reduction in hazard over placebo. This represents a clinically significant improvement in outcome for patients who have otherwise failed all standard therapies as no evidence-based therapy has been available up to the present time that has clearly demonstrated a prolongation of overall survival as has occurred in this trial.

Progression free survival data were consistent with the OS results, with an estimated HR of 0.494 (p-value < 0.000001) representing a 50.6% reduction in hazard with regorafenib compared to placebo.

Sensitivity and subgroup analyses confirmed the benefit for regorafenib in this pivotal trial, both in terms of OS and PFS.

First round assessment of risks

The data presented in the evaluation clearly demonstrates a quite high incidence of AEs associated with regorafenib treatment. More than 95% of patients experienced at least one treatment emergent AE. While the majority of these were Grade 1 and 2, nearly 50% were Grade 3 or greater in severity. The most frequent of these included palmar-plantar erythrodysesthesia, diarrhoea, fatigue, dysphonia, decreased appetite, hypertension and nausea. The majority of these adverse events could be managed either prophylactically or with adequate intervention.

Nevertheless results reveal a definite incidence of more severe complications requiring careful monitoring, in particular those events related to hepatotoxicity, myocardial ischaemia/infarction, gastrointestinal perforation and fistula. These require relevant monitoring as well as early intervention.

While accepting the fact that there is a definite toxicity profile for regorafenib it is commensurate with that observed with other tyrosine kinase inhibitors which are generally adequately managed with appropriate monitoring and early intervention.

First round assessment of benefit/risk balance

The data from this evaluation has shown an impressive evidence of benefit from the pivotal trial in relation to OS improvement and PFS improvement in this heavily pre-treated patient population with metastatic colorectal carcinoma. Nevertheless this is off-set to some extent by the significant toxicity profile associated with regorafenib, although in general terms the vast majority of these AEs would be adequately managed in modern oncology settings.

Accordingly, the clinical evaluator considered that the balance favours the benefit of regorafenib for the treatment of patients with metastatic CRC irrespective of KRAS mutational status who have previously been treated with and who are not considered

candidates for fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and, if with KRAS wild type, an anti-EGFR therapy.

Clinical questions

None

Recommendation regarding authorisation

The evaluator considered that the benefit/risk balance favours approval of regorafenib for the proposed indication, namely *treatment of patients with metastatic colorectal cancer irrespective of KRAS mutational status who have been previously treated with or are not considered candidates for fluoropyrimidine-base chemotherapy, an anti-VEGF therapy and, in KRAS wild type, an anti-EGFR therapy.*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (Core Safety Risk Management Plan (in EU-RMP format) Version 1.1 (dated 14/05/2011, DLP 31/12/2011)) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 11):

Table 11. Summary of Ongoing Safety Concerns

Important identified risks	• Severe drug-induced liver injury • Cardiac ischemic events • Hypertension and hypertensive crisis • Hemorrhage • Hand-foot skin reaction (HFSR) • Reversible posterior leukoencephalopathy syndrome (RPLS)
Important potential risks	• Stevens-Johnson-Syndrome (SJS) /Toxic epidermal necrolysis (TEN) • Wound healing complications • GI perforation and fistula • Interstitial lung disease
Important missing information	• QTc prolongation

Notwithstanding the evaluation of the nonclinical and clinical aspects of the SS, some safety concerns are missing. The sponsor should add the following as safety concerns:

· Interactions with substrates of CYP2C8, CYP2C9, CYP3A4 and CYP2C19.

· Important missing information: severe renal impairment, severe hepatic impairment.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information (as stated above). Furthermore, an open-label

Phase IIIb study is planned for the risk of severe drug-induced liver injury (DILI) and a cardiac safety study was planned for the risk of QTc prolongation.

Risk minimisation activities

The sponsor states that no additional risk minimisation activities are necessary. The sponsor's conclusion is acceptable.

Summary of round 1 recommendations

The OPR provides these recommendations in the context that the submitted RMP (Core Safety Risk Management Plan (in EU-RMP format) Version 1.1 (dated 14/05/2011, DLP 31/12/2011)) is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft product information and consumer medicine information documents should not be revised until the Delegates Overview has been received:

Further safety considerations

1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, 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.

Unless the sponsor can provide compelling justification against any of the following recommendations, the following should be considered:

Recommendations in regard to the proposed indication

2. The sponsor should define the criteria used to determine whether a patient is not a candidate for fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. The sponsor should provide a justification for the proposed Australian indication that differs from the US indication, especially given that the provided evidence does not seem to support it.

    The FDA approved indication is as follows:

    Stivarga is indicated for the treatment of patients with 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.

Recommendations in regard to safety concerns

3. The sponsor should add the following as safety concerns:

    a. Interactions with substrates of CYP2C8, CYP2C9, CYP3A4 and CYP2C19.

    b. Important missing information: severe renal impairment, severe hepatic impairment.

Recommendations in regard to pharmacovigilance activities

4. The sponsor should consider relevant pharmacovigilance activities for the additional safety concerns recommended above.

5. The sponsor should consider conducting a drug interaction study in regard to substrates of CYP2C8, CYP2C9, CYP3A4 and CYP2C19. It is noted that the sponsor has agreed to provide results of a similar study to the FDA by the end of 2012.

6. Given that the sponsor has identified several important potential risks, the sponsor should provide a justification why no additional pharmacovigilance activities have been planned to investigate these further. The sponsor should consider additional pharmacovigilance activities for the identified potential risks to characterise them further, or at least assign them to an existing study.

Recommendations in regard to risk minimisation activities

7. In regard to the proposed routine risk minimisation activities, revisions were recommended to several statements in the draft PI. Details of these are beyond the scope of the AusPAR.

Second round review

The RMP evaluator considered the sponsor's response to the recommendations above adequately addressed all of the issues identified in the RMP evaluation report, except for some statements in the draft PI which were drawn to the attention of the Delegate.

In addition, the sponsor provided an updated RMP: EU-RMP Version 1.3 (dated 01/02/2013, DLP 31/12/2012) with Australian Specific Annex Version 1 (dated February 2013).

Final recommendation to the Delegate

Approval of this application should include the implementation of EU-RMP Version 1.3 (dated 01/02/2013, DLP 31/12/2012) with Australian Specific Annex Version 1 (dated February 2013) and any future updates as a condition of registration. Usual conditions regarding provision PSURs should also be imposed.

VI. Overall conclusion and risk/benefit assessment

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

Background

Regorafenib tablets (Stivarga) are proposed for the following:

> *Stivarga is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.*

Regorafenib inhibits multiple protein kinases including those involved in oncogenesis, tumour angiogenesis and maintenance of the tumour microenvironment.

Current treatment options for patients with metastatic CRC include fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

A relevant European Guideline adopted by TGA is the *Guideline on the Evaluation of Anticancer Medicinal Products in Man* (CPMP/EWP/205/95/Rev.3/Corr.2, 14 December 2005).

Quality

There were no objections to registration on the grounds of chemistry, quality control and bioavailability aspects.

Nonclinical

- *In vitro* studies in human tissues showed that regorafenib is metabolised with CYP3A4 being the main enzyme involved in oxidative metabolism and UGT1A9 in glucuronidation. There is potential for drug interactions. This is adequately covered in the PI.

- In mice, rats and dogs, regorafenib was toxic in multiple organs at exposures (based on AUC) similar to those expected clinically. Degenerative and inflammatory changes were seen mostly in the liver, skin, kidneys, gastrointestinal system and male and female reproductive systems. Regorafenib is expected to adversely affect fertility in humans.

- In rats and rabbits, regorafenib was teratogenic at exposures (based on AUC) lower than those expected clinically. There were malformations in the urinary system (rabbits), the heart and major vessels and the skeleton and embryofetal deaths. Pregnancy category D is recommended.

The evaluator supported registration.

Clinical

Pharmacokinetics

- Absorption of regorafenib after oral administration is relatively rapid (median T_{max} 3-4 h) and about 70-80% complete. Regorafenib is predominantly eliminated through metabolism with mean elimination half-life of 20-30 h. The main metabolites M-2 and M-5 have similar pharmacological activity to regorafenib. M-5 is eliminated more slowly (elimination half-life 60 h) than the parent drug and M-2. The plasma concentrations of M-2 and M-5 are initially low; however, they accumulate non-linearly so that at steady-state the plasma concentrations are similar to the parent drug. Accumulation of drug and metabolites at steady-state is about 2-fold with dosing from day 1 to day 21.The bioavailability of regorafenib and metabolites is increased with low and high fat breakfasts. It is recommended that regorafenib be administered with a low fat light meal to maximise exposure.

- Regorafenib, M-2 and M-5 exposure based on AUC is not increased to a clinically significant extent in mild to moderate renal or hepatic impairment. Exposure has not been studied in severe renal or hepatic impairment. Close monitoring is recommended in hepatic impairment.

- Concomitant ketoconazole (a strong CYP3A4 inhibitor) increased regorafenib exposure by a mean 33% and decreased M-2 and M-5 exposure by a mean 90%. It is recommended that strong CYP3A4 inhibitors be avoided with regorafenib since the impact on the efficacy and safety of regorafenib is unclear.

- Concomitant rifampicin (a strong CYP3A4 inducer) significantly decreased regorafenib exposure by a mean 50% and increased exposure to M-5 by 3-4-fold. There was no change in M-2 exposure. It is recommended that strong CYP3A4 inducers be avoided with regorafenib since the impact on the efficacy and safety of regorafenib is unclear.

Pharmacodynamics

· Biomarker studies are ongoing.

· There was no evidence of a clinically significant prolongation of the QTcF interval in advanced cancer patients.

· The maximum tolerated dose of regorafenib was 100 mg/day with continuous dosing (Study 11651) and 160 mg/day with 3 weeks on, 1 week off dosing (Study 11650). The latter dosing schedule was chosen for the pivotal trial. The dose-limiting toxicity was hand-foot syndrome.

Efficacy

· Efficacy was assessed in a multinational, randomised, double-blind, placebo-controlled Study 14387 (referred to as CORRECT, published in *Lancet*[12]). Subjects were randomly assigned 2:1 to regorafenib 160 mg/day (3 weeks on / 1 week off) plus BSC or placebo plus BSC and treated until disease progression or unacceptable toxicity.

· Subjects with metastatic CRC whose disease progressed during or within 3 months of the last dose of standard therapy including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, bevacizumab and cetuximab (if KRAS wild type) were enrolled. The median age of subjects was 61 years, range 22-85. 60% of subjects were male.

· The primary efficacy endpoint was overall survival. Based on the second preplanned interim analysis, the data monitoring committee considered that the primary efficacy endpoint had been met, so the study was unblinded and crossover from placebo to regorafenib allowed.

· Regorafenib increased OS by a median of 1.4 months which was statistically significant (Table 12). In subgroup analyses, the OS increase was statistically significant in subjects with KRAS wild type but not KRAS mutant cancer. The increase in PFS was smaller but also statistically significant. Few subjects achieved a tumour response; however, regorafenib stabilised the disease based on better disease control rate than placebo. Quality-of-life worsened to a similar extent in both groups.

Table 12. Pivotal trial results. Interim at 21 July 2011. Intent-to-Treat

	Regorafenib n=505	Placebo n=255	Hazard Ratio[1]/ Difference [95% CI] log-rank p[2]
Duration of Treatment median (range) months	1.7 (0.1-10.8)	1.6 (0.1-8.9)	-
Overall Survival – median months	6.4	5.0	0.77 [0.64, 0.94] p=0.0052
KRAS wild type (n=299)	7.2	4.9	0.65 [0.48, 0.90]

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[12] Grothey A, Van Cutsem E, Sobrero A *et al*. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381: 303–312.

	Regorafenib n=505	Placebo n=255	Hazard Ratio[1]/ Difference [95% CI] log-rank p[2]
KRAS mutant (n=430)	6.1	5.1	0.87 [0.67, 1.12]
Progression-Free Survival[3] – median months	1.9	1.7	0.49 [0.42, 0.58] p<0.0001
KRAS wild type (n=299)	1.9	1.7	0.48 [0.36, 0.62]
KRAS mutant (n=430)	1.9	1.7	0.53 [0.43, 0.65]
Overall Response Rate[4]	1.0%	0.4%	0.6%[6] [-1.7, 0.5]
Disease Control Rate[5]	41.0%	14.9%	-25.9%[6] [-32.1, -19.8]
EORTC QLQ-C30 (0-100) QOL[13] – mean change from baseline	-14.9	-16.1	+1.2[7] [?, ?]

[1] Cox Regression Model stratified by prior VEGF treatment, time from diagnosis of metastatic disease and geographical region. [2] Stratified one-sided log rank test – met O'Brien-Fleming boundary for the interim analysis: p<0.0093. [3] Investigator assessment. [4] Complete response (CR) + partial response (PR) according to Response Evaluation Criteria for Solid Tumors (RECIST) criteria. All are PR. [5] CR + PR + maintenance of stable disease (SD). SD earlier than 6 weeks after randomisation not counted. [6] Cochran Mantel-Haenszel Test adjusted for stratification factors. [7] Difference of 10 required for clinical significance. EORTC: European Organization for Research and Treatment of Cancer; QLQ: quality of life questionnaire.

Safety

·   The safety data was presented in three pools. Pool 3 contained the pivotal CORRECT trial only. Across all Pools, a total of 1,145 cancer patients received regorafenib of whom 621 were CRC patients. The pattern of AEs was similar in the three Pools. The focus is on Pool 3 in which 500 patients received regorafenib and 253 placebo. The median regorafenib dose was 160 mg/day (range 86-160 mg) and the median time on treatment 1.4 months (range 0.1-8.3 month) excluding interruptions. Of regorafenib subjects, 76% had dose modifications, either dose reduction or interruption.

·   Most subjects experienced AEs. The incidence of severe AEs (≥ Grade 3) was greater with regorafenib (78%) than placebo (49%). The incidences of serious AEs and AEs

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[13] The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health related quality of life (QoL) of cancer patients participating in international clinical trials. The core questionnaire is the QLQ-C30.

leading to drug discontinuation were similar in the two groups: 44% versus 40% and 18% versus 13% respectively.

· Common AEs with a notably higher incidence with regorafenib (> 10 percentage points) included (regorafenib versus placebo): fatigue (63% versus 46%), decreased appetite (47% versus 29%), palmar-plantar erythrodysaesthesia syndrome (47% versus 8%, diarrhoea (43% versus 17%), decreased weight (32% versus 11%), dysphonia (32% versus 6%), hypertension (30% versus 8%), mucositis (29% versus 5%), rash (29% versus 5%), pyrexia (28% versus 15%), infection (25% versus 14%), haemorrhage (20% versus 7%), increased serum bilirubin (20% versus 10%), stomatitis (17% versus 3%) and thrombocytopenia (16% versus 2%) (Table 13). An increased incidence of hypophosphataemia with regorafenib of uncertain significance was also noted (57% regorafenib versus 11% placebo).

Table 13. Incidence (%) of treatment-emergent adverse events (any grade) occurring in at least 10% of the patients in any treatment group.

Event	Placebo (n = 253)	Regorafenib (n = 500)
Any	96.8	99.6
Blood/bone marrow	14.6	30.0
Hemoglobin	11.9	14.4
Platelets	2.4	15.6
Cardiac general	11.5	33.0
Hypertension	7.9	30.4
Constitutional symptoms	62.8	84.6
Constitutional symptoms - NOS	13.0	10.6
Fatigue	46.2	63.4
Fever	15.4	28.4
Weight loss	11.1	32.0
Dermatology/skin	22.9	71.2
Dry skin	4.0	10.0
Hand-foot skin reaction	7.5	47.0
Rash/desquamation	5.1	29.0
Gastrointestinal	65.6	83.2
Anorexia	28.5	46.8
Constipation	19.0	23.8
Diarrhoea	17.0	42.8
Mucositis (symptomatic), oral cavity	4.7	28.8
Nausea	21.7	22.4
	16.2	16.0

Event	Placebo (n = 253)	Regorafenib (n = 500)
Vomiting		
Haemorrhage/bleeding	6.7	20.4
Infection	14.2	25.2
Lymphatics	7.1	12.2
Metabolic/laboratory	24.5	45.6
Bilirubin (hyperbilirubinaemia)	9.5	20.0
Neurology	24.9	27.0
Neuropathy: sensory	9.9	10.0
Pain	53.0	65.6
Pain, abdomen NOS	18.6	24.4
Pain, back	10.3	15.0
Pain, head/headache	7.1	10.4
Pulmonary/upper respiratory	27.7	50.4
Cough	11.1	11.0
Dyspnoea (shortness of breath)	13.0	18.2
Voice changes	6.3	32.0

For patients experiencing the same adverse event several times, the adverse event has been counted only once by the worst severity grade. NOS – not otherwise specified

· In relation to deaths assessed as being related to regorafenib, the PI states: *The rate of death due to adverse events not associated with disease progression was slightly higher with regorafenib (1.6% vs 1.2%). Five deaths were considered to be regorafenib-related: one case each of liver dysfunction; sudden death; cerebrovascular incident; pulmonary haemorrhage, bronchus; haemorrhage, gastrointestinal, anus and haemorrhage, genitourinary, vagina (the last two occurred in one patient).*

· The PI has appropriate precautionary statements related to hepatic effects, haemorrhage and cardiac ischaemia.

Clinical evaluator's recommendation

The evaluator supported registration.

Risk management plan

The sponsor satisfactorily addressed issues raised by the RMP evaluator.

The evaluator recommended the RMP and PSURs as conditions of registration.

Risk-benefit analysis

Delegate considerations

In preclinical models, regorafenib inhibited protein kinases involved in oncogenesis, tumour angiogenesis and maintenance of the tumour microenvironment. However, further research is needed to define its exact mechanism of action.

In the pivotal CORRECT trial in subjects with metastatic CRC who received all currently recognised treatments, regorafenib produced a statistically significant but small increase in overall survival (median 1.4 months). Overall survival was the primary endpoint. Based on this analysis, the trial data monitoring committee considered that the primary endpoint had been met and allowed unblinding and crossover from placebo to regorafenib which would confound any future analysis.

The Delegate did not agree with the clinical evaluator that the increase in OS is clinically significant. The benefit was small and not supported by the recognised secondary endpoints, PFS (median 0.2 months increase), tumour response rate (1.0%) and quality-of-life (decreased). Some patients may benefit from regorafenib but it is not clear who they might be. A biomarker study is underway which may clarify the optimal patient population.

Regorafenib has significant toxicity including skin, gastrointestinal, hepatic, cardiovascular, immunological and haematological adverse effects. There were deaths due to hepatotoxicity, haemorrhage and cardiovascular events related to the pharmacology of the drug. Close monitoring of patients would be required.

In view of the small survival benefit and significant toxicity, the benefit-risk balance of regorafenib is negative in the trial population. In most patients, the small increase in survival is likely to be accompanied by significant risk and discomfort due to adverse reactions.

The sponsor seeks a broader indication than the trial population, *treatment of patients previously treated with or who are not considered candidates for fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy*. Such an indication would allow the use of regorafenib before oxaliplatin- and irinotecan-based chemotherapy had been tried. The Delegate did not support this indication on the grounds of negative benefit-risk in the trial population

Proposed actions

The Delegate proposed to reject this application for regorafenib (Stivarga) for *treatment of patients previously treated with or who are not considered candidates for fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy*, for reasons stated above.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request the committee also advise on the following specific issues:

1. What is the committee's opinion of the median 1.4 month increase in OS with regorafenib?

2. Should the indication be restricted to last-line treatment?

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

The committee was 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's response to matters raised in the Delegate's Overview has not been included in this AusPAR.

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 pharmaceutical quality, safety and efficacy agreed with the delegate that this product has an overall negative benefit-risk profile for the proposed indication.

The ACPM advised that the evidence submitted demonstrated efficacy that was not clinically significant while toxicities reported were severe.

Initial decision

Regarding the submission by Bayer Australia Ltd dated August 2012 to register Stivarga (regorafenib) tablets 40 mg for the following indication:

> *Stivarga is indicated for the treatment of patients with metastatic colorectal cancer (CRC) irrespective of KRAS mutational status who have been previously treated with, or are not considered candidates for, fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.*

which was subsequently amended in the Bayer *Pre-ACPM Response* dated May 2013 to:

> *STIVARGA is indicated for the treatment of patients with 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.*

Pursuant to section 25 of the *Therapeutic Goods Act 1989* ("the Act") the Delegate of the Secretary notified the sponsor of the decision **not to register Stivarga (regorafenib) tablets 40 mg** for this indication on the grounds that the efficacy and safety of the product have not been satisfactorily established for the purposes for which it is to be used. The summary of the reasons for this decision is as follows:

The efficacy of regorafenib in the indication was not satisfactorily established for the following reasons:

· In the single efficacy trial (trial 14387), a placebo-controlled trial, regorafenib did not increase overall survival by a clinically relevant amount. The median increase was 1.4 months. There was no clear separation of the Kaplan-Meier survival curves.

· Regorafenib did not provide clinically relevant increases in the recognised[14] secondary endpoints of progression-free survival (median increase 0.2 months) and overall tumour response rate (increase of 0.6 percentage points).

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[14] Guideline on the evaluation of anticancer medicinal products in man CPMP/EWP/205/95/Rev.3/Corr.2 London, 14 December (adopted by the TGA).

- Regorafenib did not improve quality-of-life, assessed by the EORTC LQ-C30 – quality-of-life worsened to a similar extent in both regorafenib and placebo-treated patients.

The safety of regorafenib in the indication was not satisfactorily established for the following reasons:

- Regorafenib had significant toxicity including skin, gastrointestinal, hepatic, cardiovascular, immunological and haematological adverse effects.

- The incidence of severe adverse events (grade 3 or greater) was higher with regorafenib (78%) than placebo (49%).

- There were deaths due to hepatotoxicity, haemorrhage and cardiovascular events related to the pharmacology of regorafenib.

Review of initial decision

Following the initial decision described above, the sponsor (under cover of correspondence dated 18 September 2013) sought a review of the decision under the provisions of Section 60 of the Act.

The Delegate of the Minister for the review noted that section 9A of the Act, which deals with the creation of the ARTG, and paragraph 25(1) of the Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, are of particular relevance.

Findings of fact

A summary of the Delegate of the Minister's main findings of fact as a result of the review is as follows:

There was one pivotal study, 14387 (CORRECT), which was a randomised, double-blind, placebo controlled, Phase III trial where adult patients with metastatic CRC who had disease progression during or within 3 months after administration of standard therapy were enrolled and randomised on a 2:1 basis to receive either regorafenib plus best supportive care or placebo plus best supportive care. The primary endpoint was overall survival and the secondary endpoints were progression free survival, objective response rate and disease control rate.

Regorafenib was administered as 4 x 40mg oral tablets at = 160mg once daily for three weeks followed by one week off therapy with a four week period constituting a cycle. The treatment was stopped for disease progression and unacceptable toxicity with dosage reduction allowed for reintroduction after toxicity.

The design of the study was intended to detect a hazard ratio of 0.75 for overall survival after 582 deaths using assumed median survival times of 6 months and 4.5 months for the regorafenib and placebo treated arms respectively. There were two planned reviews, for futility review after 174 deaths and an interim efficacy analysis and futility review at 408 deaths. The study was appropriately powered.

The study was stopped at the interim efficacy analysis. In the ITT group the hazard ratio (regorafenib to placebo) at the cut off was 0.774 (CI 0.636, 0.942), one sided p-value from log rank 0.005178. Updated at the time of crossover for placebo patients the hazard ratio was 0.790 (CI 0.664, 0.939), p-value 0.003791.

Median Overall survival was 196 days in patients receiving regorafenib and 151 days in patients receiving placebo with a difference of around 1.5 months.

Median progression free survival at cut off was 52 in the placebo group and 59 in the regorafenib group with CI of 51, 53 and 57, 65 respectively. The range in days (without censored values) was 6-277 and 5-333 respectively and at each of months 3, 6 and 9 progression free survival rate was greater in the regorafenib than the placebo group.

There was a retrospective analysis of 3 genetic biomarkers (KRAS, PIK3CA, BRAF) and 15 non-genetic biomarkers. The analysis of results by biomarker was unplanned and exploratory only. However, the analysis did show some benefit in all sub- groups and no group to which activity of the drug could be limited.

There were no complete responses but 5 patients in the regorafenib group and 1 in the placebo group had partial responses. The differences in objective response rates between the two groups were not statistically significant.

In terms of disease progression, at cut off 85.1 percent of patients in the regorafenib group and 94.5 percent of patients in the placebo group had experienced an event.

Quality of life was measured using two instruments, EORTC QLQ-C30 and EQ-5D, at baseline, and on day 1 of alternate cycles form Cycle 2 onwards. There were no differences between patients receiving regorafenib and those receiving placebo, despite the observed toxicity from treatment with regorafenib (see below).

Whilst adverse events were experienced by the majority of patients in the pivotal trial on either regorafenib or placebo and in the supporting studies on regorafenib, drug related and serious adverse events were more common in patients on regorafenib than placebo with the most frequent drug related adverse events including decreased appetite, palmar-plantar erythrodysesthesia, diarrhoea, fatigue, decreased weight, hypertension, pyrexia, asthenia, constipation and rash. Dose interruption due to adverse event occurred in 61% of regorafenib and 38% of placebo recipients and discontinuations due to drug related adverse events occurred in 8.2% of regorafenib and 1.2% of placebo recipients. The incidence of Grade 3 (56% versus 26.5%) and Grade 4 (8.6% versus 7.9%) adverse events were higher amongst those on regorafenib than on placebo. There were 138 deaths in patients on regorafenib, the majority of which (111 were due to disease progression. The most common causes of death other than disease progression were haemorrhage (4), cardiac arrest (3) and pneumonia (3).

Reviewers in the USA, EU and Australia noted that the drug adverse reaction profile from regorafenib is similar to that observed with other drugs approved for the treatment of metastatic solid tumours.

In the USA, the summary review includes the assessment that;

> 'The CORRECT trial demonstrated a statistically persuasive and clinically meaningful increase in overall survival in patients for whom there is no FDA-approved treatment. The effects were supported by consistent trends in improved survival in relevant patient subgroups and evidence of a significant improvement in progression-free survival. Specifically the benefits of regorafenib are longer overall survival and longer progression-free survival. While both effects are modest, judged in the context of the very short survival and progression-free survival expected these improvements are clinically meaningful in this population for which there are currently no FDA-approved treatments. Furthermore, the clinical benefits re meaningful in light of the adverse drug reaction profile. The adverse drug reaction profile of regorafenib is qualitatively similar to that observed with drugs previously approved for the treatment of metastatic solid tumours an which have been deemed acceptable by the patient and medical community in light of the potential benefits.'

The EMA convened a Scientific Advisory Group (SAG) in Oncology in March 2013 to consider the clinical benefit of regorafenib. The advice of that group is reported to include:

'A statistically significant difference was observed in the primary analysis of OS in study 14387 in the overall population. The difference in median OS between regorafenib and placebo was modest (45) days. The clinical relevance of this magnitude of treatment effect is considered to be minimal. The rapid onset of progression in the majority of patients suggests that a favourable effect is limited to a minority of patients.

Importantly, however, regorafenib was associated with significant toxicity in the majority of patients.....

Due to the significant toxicity and the minimal efficacy the SAG was uncertain that the balance of benefits and risks is positive.'

Following the advice of the SAG a second list of outstanding issues was provided to the applicant who responded with material also included in this appeal, including on sub group analysis and biomarker work. Following assessment of the company response the CHMP issued a positive opinion for granting a Marketing Authorisation to Stivarga (regorafenib).

In Australia the reviewers of the clinical, toxicological and risk management plan (RMP) had supported approval but the Delegate, as is usual practice, sought the view of the Advisory Committee on Prescription Medicines (ACPM). The Delegate brought the following issues to the ACPM: the clinical significance of the overall survival benefit, the appropriateness of the indication and the benefit-risk balance. ACPM was consulted on the application for registration or regorafenib at its June 2013 meeting and issued the following resolution:

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agree with the delegate that this product has an overall negative benefit-risk profile for the proposed indication.

The ACPM advised that the evidence submitted a demonstrated efficacy that was not clinically significant while toxicities reported were severe.

At the time of the meeting neither the Delegate nor the committee had access to the final European assessment report, the CHMP outcome, and the biomarker data that had been submitted in Europe.

The biomarker data and sub group analyses are briefly summarised above. To repeat a benefit in terms of overall survival was seen consistently in all subgroups.

Summary

Regorafenib has been shown to have a statistically significant and consistent, albeit modest, benefit in terms of overall survival and progression free survival in heavily pre-treated patients with metastatic CRC where there is no approved treatment alternative.

Significant toxicities occurred that were consistent with those seen in other similar drugs approved for use in metastatic solid tumours. The effect of these toxicities can be mitigated, but not eliminated, through skilled management of treatment cycles by expert oncologists.

Materials on which the findings of fact were based

In conducting the review, the Delegate of the Minister considered the following documents:

· Application by Bayer Australia Ltd for registration of Stivarga (the Application);

· TGA evaluation reports of the application;

- Delegate of the Secretary's overview, recommendations and request for ACPM advice;

- Response from the sponsor to the Delegate of the Secretary's overview, recommendations and request for ACPM advice;

- Extract of Minutes of ACPM of 6-7 June 2013;

- Delegate of the Secretary's initial decision letter dated 25 June 2013;

- Appeal against the initial decision by Bayer Australia Ltd, dated 18 September 2013, and all attached documents (Volumes 1 to 5);

- FDA Summary review of Stivarga dated 20 September 2012, as published on FDA website;

- EMA Assessment report dated 27 June 2013, as published on EMA website;

- CPMP/EWP/205/95/Rev.3/Corr. (Guideline on the Evaluation of Anticancer Medicinal Products in Man); and

- EMEA/CHMP/EWP/27994/2008 (Methodological Considerations for Using Progression-Free Survival (PFS) as Primary Endpoint in Confirmatory Trials for Registration).

Reasons

The Delegate of the Minister considered the arguments of the applicant and information on the evaluation of Stivarga (regorafenib) in Australia, by the EMA and US FDA and the information on biomarkers and sub group analyses and expert opinions within the appeal document.

There is evidence of statistically significant and consistent, albeit modest, benefit in terms of overall survival and progression free survival in heavily pre-treated patients with metastatic CRC where there is no approved treatment alternative.

Significant toxicities occurred that were consistent with those seen in other similar drugs approved for use in metastatic solid tumours. The effect of these toxicities can be mitigated, but not eliminated, through skilled management of treatment cycles by expert oncologists.

In considering the reasons given by the initial decision maker for the decision not to register Stivarga (regorafenib) there is evidence that there is a modest, statistically and clinically relevant effect on overall survival and progression-free survival. There is no improvement in quality of life measures, but also no deterioration despite treatment. Significant toxicities were observed but these were similar to those seen with other drugs approved for use in metastatic solid tumours which have been considered acceptable in the light of the conditions to be treated and the potential benefit of treatment.

Conclusion

For the reasons referred to above, the Delegate of the Minister decided to revoke the decision not to approve the registration of Stivarga (regorafenib) 40 mg tablets. The section 60 Appeal's Delegate replaced the "the initial decision" for Stivarga (regorafenib) 40 mg tablets under Section 60 (2) of the Act.

Final outcome

The Delegate was of the view that the requirements of efficacy and safety in the Act have been met to include the Stivarga (regorafenib) 40 mg tablets in the ARTG. The reasons for

the Delegate's decision and results of the reconsiderations of the initial decision are set out above.

Accordingly, pursuant to Section 60 of the Act, the Delegate notified the sponsor of the decision to approve the registration of Stivarga regorafenib 40 mg tablet bottle for the indication:

> *Stivarga is indicated for the treatment of patients with 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.*

This approval was based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application including additional information submitted with the sponsor's appeal of 18 September 2013.

Specific conditions of registration applying to these therapeutic goods

The Stivarga EU-RMP Version 1.3 (dated 01/02/2013, DLP 31/12/2012) with Australian Specific Annex Version 1 (dated February 2013) and any future updates, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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