Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Dabrafenib mesilate

Proprietary Product Name: Tafinlar

Sponsor: GlaxoSmithKline Australia Pty Ltd

January 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	21 August 2013
Active ingredient:	Dabrafenib mesilate
Product name:	Tafinlar
Sponsor's name and address:	GlaxoSmithKline Australia Pty Ltd Level 4, 436 Johnston St Abbotsford VIC 8003
Dose form:	Capsule
Strengths:	50 mg and 75 mg
Container:	Bottle
Pack sizes:	28 and 120
Approved therapeutic use:	Tafinlar is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma
Route of administration:	Oral
Dosage (abbreviated):	The recommended dose is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg)
ARTG numbers:	200922 and 200936

Product background

Advanced melanoma (unresectable Stage III or metastatic Stage IV) has a poor prognosis, with a 2008 meta-analysis of comparator arms in Phase II metastatic melanoma trials finding a median progression-free survival (PFS) of 1.7 months and a median overall

survival (OS) time of 6.2 months. [1] Mutations in BRAF (a member of the RAF kinase family) have been found to occur in approximately 50% of melanomas[2].

The RAS/RAF/MEK/ERK[3] pathway (also known as the MAP kinase (MAPK) pathway) is a critical proliferation pathway in many human cancers, including melanoma. This pathway can be constitutively activated by alterations in specific proteins, including BRAF, which phosphorylates MEK on two regulatory serine residues MEKI and MEK2.

Dabrafenib is an inhibitor of BRAF kinase activity. This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd (the sponsor) to register Tafinlar capsules containing 50 mg or 75mg dabrafenib for the following indication:

> *Tafinlar is indicated for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV) melanoma.*

Dabrafenib for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV) melanoma received Orphan drug designation by the TGA on 30 May 2012.

Regulatory status

Tafinlar capsules received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 27 August 2013.

At the time this application was considered by the TGA a similar application had been approved in the United States (US, May 2013) and was under consideration in the European Union (EU; a positive opinion was issued by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) in June 2013), Canada, Switzerland and 4 additional countries.

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)

Dabrafenib is a synthetic thiazole derivative. The drug is synthetic and achiral. The drug substance is the corresponding methanesulfonate salt or 'mesilate'.

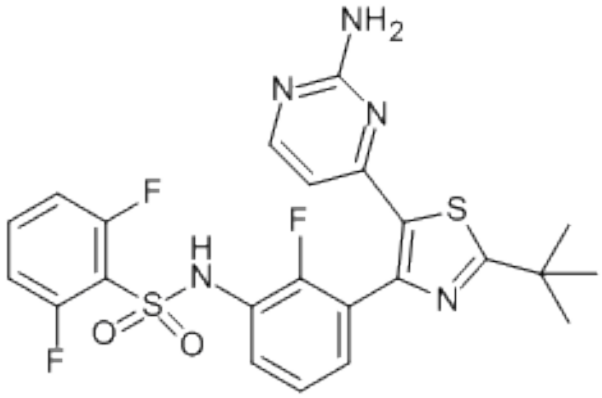
---

[1] Korn EL, Liu P-Y, Lee SJ, Chapman J-AW, Niedzwiecki D, Suman VJ *et al*. Meta-analysis of Phase II cooperative group trials in metastatic Stage IV melanoma to determine progression-free and overall survival benchmarks for future Phase II trials. *Journal of Clinical Oncology,* 2008;26:527-34.

[2] Ascierto P, Kirkwood J, Grob J, *et al*. The role of BRAF V600 mutation in melanoma. *Journal of translational medicine*, 2012; 10:85

[3] Abbreviations and definitions: RAS (**ra**t **s**arcoma): a small guanosine triphosphate enzyme (GTPase) found inside cells; RAF (rapidly accelerated fibrosarcoma): a protein kinase family implicated in cellular responses relevant to tumorigenesis, including cell proliferation, invasion, survival and angiogenesis. The RAF family is composed of 3 members, ARAF, BRAF and CRAF, each of which has a different function and is differentially regulated at various levels. ERK: Extracellular signal regulated kinase; MEK: Mitogen-activated ERK kinase. MEK is a protein kinase that is a part of the RAS-RAF signalling cascade that regulates expression of a large number of proteins involved in the control of cell proliferation, differentiation, and apoptosis. MAP: mitogen activated protein kinases. These are enzymes with serine/threonine kinase activity (such as ERK). MAPKs regulate various cellular processes, such as cell proliferation and cell differentiation, via downstream cellular regulatory targets in response to extracellular stimuli.

Figure 1. Structure of dabrafenib



The molecular formula of dabrafenib is $C_{23}H_{20}F_3N_5O_2S_2$ CH_4O_3S and molecular weight is 615.68 g/mol ($C_{23}H_{20}F_3N_5O_2S_2$ and 519.57 g/mol for the base). Dabrafenib is not closely related in structure to registered kinase inhibitors.

Dabrafenib mesilate is crystalline and its solubility is poorly documented but it is very slightly soluble in acid and essentially insoluble at higher pH. There is thus a possibility that bioavailability will be reduced in achlorhydric or hypochlorhydric patients.

The drug substance is micronised and particle size is controlled (see discussion of Study BRF113468 below).

Drug product

Immediate release, hard capsules containing 50 or 75 mg dabrafenib are proposed. They are distinguished by colour and markings. Capsules are formulated with dabrafenib mesilate but the label claims relates to the equivalent 50 mg or 75 mg of dabrafenib free base.

The capsule fill is the same for both strengths. It is formulated with conventional excipients. The capsule shells are made from hydroxypropyl methylcellulose (HPMC, also known as hypromellose). These are used instead of the more common hard gelatin capsule shells because of adverse stability effects arising from water from the gelatin. Bottle packs are proposed. These will have a child resistant closure.

GlaxoSmithKline has proposed that it is not necessary to routinely control related substances in batches of capsules at release. In keeping with advice from the Pharmaceutical Subcommittee (PSC, see below) this is not considered appropriate and will be resolved with the sponsor or made a condition of registration.

There is an *in vitro* dissolution test for capsules. Appropriate limits will be finalised prior to a decision made on this application. Controls on the water content of the filled capsules, which may affect stability, were also under negotiation.

Clinical trial formulations

Initially, 1 mg, 5 mg, 25 mg and 100 mg gelatin capsules were developed and then the 50 mg and 75 mg gelatin capsules were developed further. Hard gelatin capsule shells were replaced with HPMC capsule shells because of the better dissolution stability observed with hypromellose capsules (HPMC capsule shells have lower moisture content). Both gelatin and HPMC capsules have been used in clinical trials, as shown in Table 1:

Table 1. Dabrafenib formulations used in clinical trials

Capsules	Strength	Studies
Gelatin	1, 5, 25, and/or 100 mg	BRF112680 [First Time in Human (FTIH)] BRF113220 (Combination with trametinib; Cohorts A-C)
Gelatin	50 and/or 75 mg	BRF112680 (FTIH) BRF113468 (Particle Size, Cohort 1)[1] BRF113710 (Phase II) BRF113220 (Combination with trametinib; Cohorts A-C)
HPMC	50 and/or 75 mg	BRF113220 (Combination with trametinib; Cohort D)[2] BRF113468 (Food, Cohort 2) BRF113479 (Absolute Bioavailability) BRF113771 [Repeat Dose Pharmacokinetic (PK) and drug-drug interaction (DDI)] BRF113929 (Phase II, brain metastasis) BRF113683 (Phase III)

1. Particle size cohort used 75 mg gelatin capsules with micronized and non micronized dabrafenib mesylate
2. Cohort D is ongoing; results are not included in this submission.

The Phase III Study BRF113683 and the Phase II Study in brain metastases (BRF113929) used only HPMC capsules as proposed. The proposed commercial formulation is identical to the formulation used in the Phase III clinical Study (except for printing details).

Biopharmaceutics

Dabrafenib mesilate solubility is very low even in acid. Dabrafenib mesilate is a Class 2 (high permeability, low solubility) Biopharmaceutics Classification System drug, that is, bioavailability is liable to depend on capsule dissolution. Given the effect of pH on dabrafenib solubility there is a possibility that bioavailability will be reduced in achlorhydric or hypochlorhydric patients.

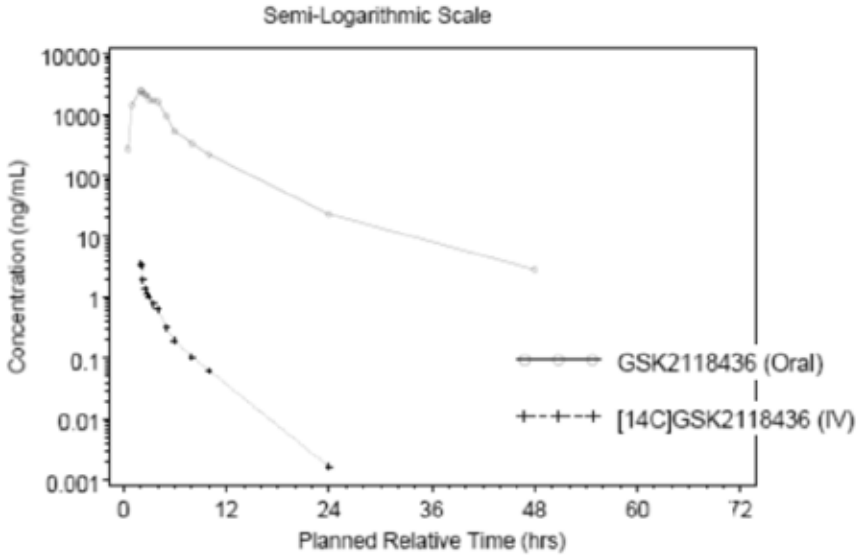
Individual pharmacokinetic profiles are conventional, with a time to achieve the maximum concentration (T_{max}) of about 2 hours.

Absolute bioavailability

Study BRF113479 measured the absolute bioavailability of dabrafenib 75 mg HPMC capsules by co-administration with an 50 µg intravenous (IV) dose of radiolabelled (^{14}C)-dabrafenib in patients. This was a study in just four patients with BRAF V600 mutation positive solid tumours.

After an overnight fast, patients received a single 150 mg oral dose (2 x 75 mg HPMC capsules) and remained fasting at least 4 h afterwards. A single IV dose was then infused over 15 min, starting 1.75 h after the oral dose (that is approximately at T_{max} for the oral drug). Plasma levels of 'cold' dabrafenib were measured conventionally and ^{14}C-dabrafenib concentrations were measured using chromatography and accelerator mass spectrometry. Mean plasma concentrations of dabrafenib and ^{14}C-dabrafenib are shown below:

Figure 2. Mean plasma concentrations of dabrafenib and ^{14}C-dabrafenib



GSK2118436B is the company code for dabrafenib mesilate; GSK2118436A is the code for dabrafenib base.

Oral absorption of the 150 mg dabrafenib doses was nearly complete. The measured individual bioavailabilities were 101.2, 105.9, 93.6 and 79.3% [least squares (LS) mean 94.5%; 90% confidence interval (CI) 81.3 - 109.7%]. It does appear, however, that IV exposure may be reduced by complexation (note the higher terminal elimination rate of the IV drug), which would inflate the bioavailability estimate.

Dabrafenib was administered as a 95 mg suspension in pharmacokinetics (PK) Study BRF113463, using ^{14}C-labelled drug. Administration of dabrafenib as a suspension resulted in faster absorption (T_{max} 1.0 hour), higher maximum concentration (C_{max}) but similar exposure when compared with that after administration of HPMC capsules.

Study BRF113468 was a study both of particle size (Cohort 1) and food effect (Cohort 2) on dabrafenib bioavailability; each cohort was conducted as a distinct 2-period crossover design.

Particle size effect

The study of particle size compared micronised and non-micronised dabrafenib doses (2 x 75 mg) filled into gelatin capsules, under fasting conditions in 14 patients. *In vitro* dissolution was very similar for both capsules (approximately 94% in 30 minutes). However, *in vivo* the non-micronised drug gave markedly higher C_{max} and area under the concentration-time curve (AUC), well outside bioavailability limits (90% CI 1.44 [1.13, 1.83] for AUC from time zero to infinity ($AUC_{0-\infty}$); 1.42 [1.06, 1.91] for C_{max}). The proposed capsules are made with micronised drug. The effect of particle size is likely to be minimal with dabrafenib in HPMC capsules, given the higher relative bioavailability observed with HPMC compared to gelatin capsules and the apparently almost complete oral absorption with HPMC capsules. All clinical safety and efficacy studies used capsules filled with micronised drug substance. Appropriate dissolution controls to ensure the consistency of future batches are currently being negotiated.

Food effect

Part of Study BRF113468 (Cohort 2) was a crossover comparison of the PK of micronised dabrafenib in HPMC capsules (2 x 75 mg) under fasting conditions or with a high-fat, high-calorie meal in 14 patients. The high-fat meal reduced the relative bioavailability (90% CI 0.69 [0.57, 0.85] for $AUC_{0-\infty}$). GlaxoSmithKline's recommendation is to administer

dabrafenib under fasting conditions, either 1 h before or 2 h after a meal, consistent with administration in Phase II and III studies.

Advisory committee considerations

The submission was considered at the 151st (2013/3) meeting of the Pharmaceutical Subcommittee (PSC). The PSC advice included the following:

1. The PSC endorsed all the questions raised by the TGA in relation to the pharmaceutic and biopharmaceutic aspects of the submission by GlaxoSmithKline Australia Pty Ltd to register capsules containing 50 mg and 75 mg of dabrafenib (as mesilate). In addition, the PSC agreed that the sponsor should be asked to:

· Include microbial limit in the drug product release specification.

· Undertake routine related substance testing at batch release at least until there was an overwhelming experience with the product.

2. The Committee agreed that water content and micronisation of the drug substance clearly had significant effects on the drug product.

Quality summary and conclusions

Some pharmaceutical aspects had yet to be finalised and it was anticipated that these would be satisfactorily resolved prior to a decision being made for this application. Otherwise, registration is recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical findings

Introduction

The general quality of the submitted nonclinical studies was reasonable. The range of studies was limited but consistent with the International Conference on Harmonisation (ICH) guidelines for anticancer drugs. Pivotal studies examining repeat-dose toxicity, genotoxicity and reproductive toxicity were conducted under good laboratory practice (GLP) conditions. While there was examination of different formulations in the early development of dabrafenib in order to optimise absorption, the majority of studies were conducted with a dabrafenib free base suspension formulation in aqueous 0.5% HPMC with 0.1% polyethylene sorbitan monooleate. The mesilate salt was subsequently found to lead to improved exposure compared to the free base suspension. The 13-week dog study was conducted with dabrafenib mesilate in gelatin capsule. A capsule formulation of the mesilate salt is the proposed clinical form. While the exposure ratios are not high in the animal studies, they are adequate to address the clinical relevance of the observed toxicities.

The following studies were not considered relevant to the safety evaluation of orally administered dabrafenib and are not included in this report:

· Two primary pharmacology studies (2011N111685_00 and 2012N132871_00) examined combination therapy with pazopanib and trametinib, respectively.

· A 4-week repeat dose toxicity study (2011N112335_00) examined the effect of combination treatment with trametinib.

Pharmacology

Mechanism of action

Dabrafenib mesilate is an inhibitor of RAF kinases, including wild-type BRAF kinase and BRAFV600E mutant kinase, with a mode of action consistent with adenosine triphosphate (ATP) competitive inhibition. BRAF is a serine/threonine kinase within the mitogen-activated protein kinase (MAPK) signal transduction pathway and is involved in the regulation of cell growth, proliferation and differentiation via the extracellular signal regulated kinase (ERK) cascade. This pathway is found in normal cells and in many human cancers, including melanomas, and can be constitutively activated by alterations in specific proteins including BRAF. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50-60% of melanomas. The most common BRAF mutation is V600E which increases BRAF activity 10-450 fold.

In vitro studies

In vitro studies demonstrated the ability of dabrafenib to inhibit cloned BRAF wild-type and BRAF V600E mutant enzymes from several species with 50% inhibitory concentration (IC_{50}) values of 3.2 and 0.65 nM, respectively. Other BRAF mutant enzymes BRAF V600K and BRAF V600D had similar IC_{50} values (0.5 and 1.84nM, respectively). The inhibition was not exclusive to BRAF enzymes, and 8 other human kinases (human BRK, LIMK1, NEK11, PKD2 and SIK1, ALK5, yeast CK1 and SIK2) had IC_{50} values < 100nM, including CRAF with an IC_{50} of 5.0 nM. The dissociation half-life (12-17 min) and ATP-dependence of the BRAF enzyme inhibition suggests a competitive mode of action. The inhibitory potency of dabrafenib is below the clinical plasma concentration (8.6 nM, free fraction, based on C_{max} and a plasma free fraction of 0.3%). Decreased phosphorylation of downstream substrates, MEK and ERK, was demonstrated in tumour cell lines carrying BRAF V600E mutations following dabrafenib treatment.

The three major dabrafenib metabolites also inhibited BRAF wild-type (WT) and BRAF V600E mutant enzymes. Hydroxy-dabrafenib (M7) and desmethyl-dabrafenib (M8) showed similar inhibition to dabrafenib (IC_{50} values7, 8, 9 nM, respectively) in an ERK phosphorylation assay in melanoma cells, while inhibition by carboxy-dabrafenib (M4) was lower (IC_{50} 156 nM). These dabrafenib metabolites were also selective RAF kinase inhibitors, with only 4/292 other kinases with IC_{50} values < 150 nM.

Table 2. Relative inhibitory activity (IC_{50} of metabolite/IC_{50} of parent) of hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib

	Dabrafenib (IC_{50} µM)	Hydroxy-dabrafenib	Carboxy-dabrafenib	Desmethyl-dabrafenib
BRAF V600E	0.65	3	26	2
BRAF V600K	0.50	3	13	1
BRAF V600D	1.86	2	16	1
Truncated cRAF (human)	2.51	6	20	1
WT BRAF (human)	2.24	6	46	1.5
WT BRAF (rat)	2.14	7	55	2

	Dabrafenib (IC_{50} µM)	Hydroxy-dabrafenib	Carboxy-dabrafenib	Desmethyl-dabrafenib
WT BRAF (dog)	2.0	6	55	2
WT BRAF (monkey)	1.91	6	50	2

Dabrafenib and metabolites, hydroxy-dabrafenib and desmethyl-dabrafenib, inhibited growth of melanoma cell line SK-MEL-28 (encoding BRAF V600E) (concentration required to reduce growth by 50% (gIC_{50}) < 23nM), compared with normal HN5 cells expressing wild type BRAF (gIC_{50} > 2µM). The growth inhibition was reversible by 3-4 days. Against a panel of 110 tumour lines, dabrafenib inhibited growth (gIC_{50} < 100 nM) of 73% of BRAF V600E cell lines.

Dabrafenib-resistant clones were isolated from melanoma cell lines A375 and YUSIT-1 and shown to have a deletion in MEK1 or a NRAS (a member of the RAS family of human proto-oncogenes that regulate and mediate cellular responses to growth signals) mutation, which reduced the phosphorylation of MEK but not ERK or S6P (a ribosomal protein). Combination treatment with trametinib overcame the observed resistance. The clinical significance of this result is currently being investigated by the sponsor.

In vivo studies

Dabrafenib was tested for its ability to inhibit phosphorylated ERK (pERK) formation and to inhibit tumour growth in CD-1 mice bearing human BRAF V600E-containing tumour xenografts, namely, A375P F11s melanoma cells, ES-2 ovarian cancer cells and Colo205 colon carcinoma cells. The levels of pERK in the A375P F11s melanoma tumours were reduced 50% after repeated exposure at 10 mg/kg/day (equivalent to < 5% of clinical exposure based on AUC). Reductions in pERK were also noted in Colo205 colon cancer xenografts and ES-2 ovarian cancer xenografts at 100 mg/kg/day. Inhibition of pERK was reversible following cessation of treatment. Significant inhibition of melanoma growth was noted after oral administration at 30 mg/kg/day (equivalent to < 20% of clinical exposure), which correlated with > 50% pERK inhibition. Similar tumour growth inhibition was achieved after IV administration at 3 mg/kg/day (equivalent to 7% of clinical exposure). Colorectal tumour xenografts showed similar tumour inhibition at similar oral dose levels. In both cases, there was tumour regrowth upon cessation of treatment. The melanoma xenograft responded to subsequent treatment, but there was a lack of sustained sensitivity to treatment. A correlation was noted between plasma interleukin-8 (IL-8) levels and the presence of A375P F11 xenografts in mice following dabrafenib treatment. The data suggests that IL-8 could be used clinically as a surrogate marker for dabrafenib activity.

Secondary pharmacodynamics

Dabrafenib showed no activity in a broad panel of biochemical assays for a range of proteins. Weak activity (inhibition or activation) at > 0.3 µM (> 3 0 times the steady state unbound plasma concentration) was observed for $\alpha 2_C$ adrenergic receptor (activation), and lymphocyte-specific protein tyrosine kinase (LCK) and Aurora B kinase (inhibition) only.

Safety pharmacology

In *in vitro* studies, dabrafenib inhibited human ether-a-go-go-related gene (hERG) channel current in human embryonic kidney cells at a 25% inhibitory concentration (IC_{25}) of

11.7μM (> 1000 times the steady state unbound plasma concentration) and showed no potential for cardiac arrhythmia. An IC_{50} could not be determined due to limited solubility of dabrafenib. Dabrafenib metabolites did not significantly inhibit hERG repolarisation (IC_{50} > 30μM) in a fluorescence polarisation assay. *In vitro* measurement of electrocardiogram (ECG) parameters in a rabbit left ventricular wedge preparation produced a reduction in QT interval[4] at 30 μM (> 3000 times the steady state unbound plasma concentration).

Dedicated *in vivo* safety pharmacology studies were conducted in rats and dogs to examine cardiovascular parameters. In rats, there were no effects on blood pressure or body temperature, but heart rate increased after a single dose of 5 mg/kg (by 4-9%), 20 mg/kg (by 3-14%) and 200 mg/kg (by 5-18%; equivalent to the clinical C_{max}). In dogs, heart rate increased and was accompanied by mild decreases in ECG PR wave and RR wave intervals after a single dose of 50 mg/kg (5 times the clinical C_{max}). There were no abnormal ECG waveforms or arrhythmias. The observed changes in rats and dogs were reversible. In a 4-week repeat dose study in dogs, there was no evidence of effects on heart rate or QTc intervals at 50 mg/kg/day (equivalent to the clinical C_{max}). Overall, these cardiovascular effects are not considered to be clinically significant.

There was no evidence of any central nervous system (CNS) or respiratory effects at 200 mg/kg in rats (equivalent to the clinical C_{max}). The potential for dabrafenib to lead to the development of fever was examined in mice over 29 days after fever occurred in some patients in clinical trials. Body temperature was unaffected by treatment at dose levels up to 1000 mg/kg/day (2 times the clinical C_{max}); nor was body temperature affected in rats at 200 mg/kg (2 times the clinical C_{max}). The results of animal studies do not indicate that increased body temperature is a clinically significant effect.

Pharmacodynamic drug interactions

Dabrafenib is reported to have synergistic effects when combined with trametinib or paxopanib, however these studies have not been evaluated.

Pharmacokinetics

Nonclinical PK studies were conducted in the mouse, rat, dog and monkey. Absorption following single dose oral administration was relatively rapid in all species (0.7-3 h), but dependent on solubility and dissolution in the formulation. Use of the mesilate salt significantly increased the exposure compared to the free base suspension. Bioavailability was similar for rats and dogs (77 and 82%, respectively) and lower for monkeys (46%). The plasma half-life was short in all species (0.3-3 h). Volume of distribution was low (0.6-1.4 times body water).

Hydroxy-, carboxy- and desmethyl-dabrafenib are three major metabolites in all species. Pharmacokinetic studies of hydroxy-dabrafenib were conducted in the rat and dog. Bioavailability was high and elimination half-life was relatively low (about 4 h in rats and 2 h in dogs). Desmethyl-dabrafenib was formed rapidly but plasma levels remained low since the elimination in rats was fast (half-life of 0.6 h).

In repeat dose studies in mice, rats and dogs, exposure was similar in males and females and increased less than dose-proportionally. In mice, exposure to hydroxy-dabrafenib was similar to dabrafenib, but exposure to carboxy-dabrafenib and desmethyl-dabrafenib was considerably higher. In rats, exposure to hydroxy-dabrafenib and carboxy-dabrafenib was higher than to unchanged drug and significantly higher than to desmethyl-dabrafenib. In

[4] 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 the QT interval corrected for heart rate.

dogs, exposure to hydroxy-dabrafenib was lower than to dabrafenib but considerably higher than to either carboxy-dabrafenib or desmethyl-dabrafenib. There was no evidence of accumulation in any species.

Ratio of major metabolites to dabrafenib after repeated dosing based on AUC (mean ratios of all doses and both genders).

Table 3. Exposure comparisons among species

Species (Duration)	Dose (mg/kg/day)	Hydroxy-dabrafenib	Carboxy-dabrafenib	Desmethyl-dabrafenib
Mouse (14 days)	100-1000	0.6	22.7	5.0
Rat (13 weeks)	20-400	3.2	2.3	0.06
Dog (13 weeks)	5-20	0.3	0.06	0.02
Human (6 weeks)*	150 mg twice daily (BID)	0.94	11.9	0.7

* Human data are from the sponsor's summary of clinical pharmacology.

Dabrafenib and its three major metabolites were highly bound to plasma protein in all species, including humans (dabrafenib: 98-> 99%; hydroxy-dabrafenib: 96-98%; desmethyl-dabrafenib: > 99%; carboxy-dabrafenib: 93% in mouse, 99% in rat and human, 95% in dog), and had minimal association with red blood cells. Following oral administration in rats, radiolabelled dabrafenib was distributed widely into tissues, with no evidence of penetration into brain or selective binding to melanin-containing tissues. Highest tissues concentration occurred at 4 h, with highest levels in liver. Tissue levels declined rapidly over the first three days and were below the level of detection by day 7.

The major pathways of metabolism of dabrafenib are oxidation to hydroxy-dabrafenib and subsequently to carboxy-dabrafenib, which is excreted mainly in the bile or further metabolised to desmethyl-dabrafenib. The latter is further metabolised to minor oxidative metabolites.

In vitro studies with microsomes from mouse, rat, dog, monkey and humans confirm cytochrome P450 (CYP) subtype 2C8 (CYP2C8) as the major enzyme responsible for formation of hydroxy-dabrafenib, which is further metabolised by CYP3A4. In hepatocytes from mouse, rat, dog, monkey, rabbit and human liver, qualitatively similar metabolic pathways are confirmed, with no evidence of any human-specific metabolites.

In *in vivo* studies, the three major metabolites were detected in mice, rats (intact and bile-duct cannulated), dog and humans. In rat and dog, the major component in faeces is unchanged dabrafenib. In bile duct-cannulated rat, the major component in bile is carboxy-dabrafenib. The faeces are the major excretion route (> 95% in rats and > 99% in dogs). Based on total excretion, the mean absorption in rats was at least 35.7% of administered dose.

On the basis of the submitted data, the PK of dabrafenib in animal species is similar to the PK in humans, with relatively rapid absorption, high plasma protein binding, rapid metabolism involving oxidation and decarboxylation to common metabolites, and rapid elimination via the bile and faeces.

Pharmacokinetic drug interactions

Dabrafenib is primarily metabolised to hydroxy-dabrafenib by CYP2C8 and 3A4, and hydroxy-dabrafenib to carboxy-dabrafenib and oxidation of desmethyl-dabrafenib by CYP3A4. Thus, CYP2C8 or 3A4 inhibitors may increase plasma concentrations of dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib. There were no animal studies on the potential effects of CYP450 inhibitors on the PK of dabrafenib. In clinical studies, co-administration of ketoconazole (a CYP3A4 inhibitor) increased exposure to dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib (from the sponsor's clinical overview).

Dabrafenib in an *in vitro* microsomal assay was a direct inhibitor of human liver CYP 1A2, 2C8, 2C9, 2C19 and 3A4 (IC_{50} 87, 8.2, 7.2, 22.4, 16/32 μM, respectively). The inhibition of CYP 3A4 by dabrafenib was also metabolism-dependent and inactivated CYP3A4 with a K_i of 38 μM. Hydroxy-dabrafenib also directly inhibited CYP1A2, 2C9 and 3A4 (IC_{50} 83, 29, 44 μM, respectively), but there was no metabolism-dependent inhibition. Carboxy-dabrafenib did not directly inhibit CYP enzymes. Desmethyl-dabrafenib directly inhibited CYP2B6, 2C8, 2C9, 2C19 and 3A4 (IC_{50} 78, 47, 6.3, 36, 20/17/28 μM, respectively), with metabolism-dependent inhibition of CYP3A4 (IC_{50} decreased by 1.7-2.3 fold). Although the IC_{50} values for dabrafenib, hydroxy-dabrafenib and/or desmethyl dabrafenib against 2C8, 2C9, 2C19 and 3A4 were similar to the combined total plasma C_{max} of the inhibitors, they were considerably below the combined free fraction plasma C_{max}. Furthermore, analysis by the sponsor using static mechanistic mathematical models including contributions by metabolites suggested no effects on exposure to CYP2C8, 2C9 and 2C19 substrates (rosiglitazone, warfarin and omeprazole, respectively) through the inhibition of these isoforms. Anticipated decreased exposure to midazolam (a CYP3A4 substrate) through CYP3A4 induction is consistent with the clinical results (see discussion below on CYP450 induction).

In human hepatocytes, dabrafenib induced the messenger ribonucleic acid (mRNA) levels of CYP2B6 and CYP3A4 with a ≥ 2 fold increase at 1.0 and 0.1 μM, respectively, and 30 fold at 30 μM. The induction of CYP3A4 *in vitro* is consistent with the moderate induction of CYP3A4 reported in a clinical study with midazolam as the CYP3A4 substrate. Dabrafenib did not induce CYP1A2. The induction of other CYP450 isoforms by dabrafenib was not studied.

With regard to transporters, dabrafenib and its metabolites did not inhibit P-glycoprotein (P-gp) in MDCK-MDR1 cells at 30 μM, but dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib were substrates for P-gp with high permeability. Dabrafenib was also a substrate for breast cancer resistant protein (BCRP) transporter in MDCK-Bcrp1 cells with a high intrinsic permeability, and dabrafenib and its metabolites were moderate or weak inhibitors of human BCRP-mediated transport (IC_{50} > 10 μM except 5.4 μM for desmethyl-dabrafenib). The P-gp and BCRP-mediated transport of dabrafenib was inhibited by LY335979 (a P-gp inhibitor) and Ko143 (a BCRP inhibitor), respectively (Mittapalli *et al*. 2013[5]). Reported in the same published study, dabrafenib at up to 25 μM did not inhibit the Bcrp1-mediated transport of prazosin (a BCRP substrate) or P-gp-mediated transport of vinblastine (a P-gp substrate) in cell lines expressing these transporters, although a higher concentration (50 μM) of dabrafenib showed inhibition of P-gp (but not Bcrp). Triple knockout *Mdr1a/b*$^{-/-}$*Bcrp1*$^{-/-}$ mice and wild-type mice receiving an oral dose of dabrafenib had comparable plasma dabrafenib concentrations, but the knockout animals showed greater brain distribution than the wild type animals. The lack of difference in plasma dabrafenib concentrations in *Mdr1a/b*$^{-/-}$*Bcrp1*$^{-/-}$ and wild-type mice and high permeability observed *in vitro* suggest that the absorption of dabrafenib is unlikely to be

[5] Mittapalli RK, Vaidhyanathan S, Dudek AZ, and Elmquist WF. Mechanisms limiting distribution of the threonine-protein kinase B-RaFV600E inhibitor dabrafenib to the brain: implications for the treatment of melanoma brain metastases. *J Pharmacol Exp Ther* 2013;344:655-664.

affected by P-gp inhibitors. Brain distribution may be increased by P-gp and/or BCRP inhibitors.

Table 4. Transporter inhibition (IC_{50}, µM) by dabrafenib and its metabolites

	OATP1B1	OATP1B3	OAT1	OAT3	BCRP	P-gp
Dabrafenib	1.4	4.7	6.9	3.4	52% at 10 µM; 44% at 30 µM*	>30
Hydroxy-Dabrafenib	4.3	23	29	7.3	82	>100
Carboxy-Dabrafenib	18	20	65% at 100 µM*	9	42% at 200 µM*	>80
Desmethyl-Dabrafenib	0.83	4.3	10	3.4	5.4	>100

* Data insufficient to calculate an IC_{50}. OATP: Organic anion transporting polypeptide

Dabrafenib and its metabolites were inhibitors of organic anion transporting polypeptide (OATP) OATP1B1 and OATP1B3 (hepatic uptake transporters), and OATP1 and OATP3 (renal excretion transporters). Given the high plasma protein binding of dabrafenib, the unbound plasma concentration is unlikely to be high enough for the potential inhibition of the cytochrome P450 enzymes or the potential inhibition of transporters to have clinical relevance.

Toxicology

Single dose toxicity

Specific single dose studies with dabrafenib were not conducted, but preliminary tolerability studies in rats and dogs are available. In rats, dabrafenib produced reduced body weight following an oral dose of 20-600 mg/kg, with no clinical signs of toxicity. There was no mortality in a 10-day repeat dose study at up to 1000 mg/kg/day in rats. In dogs, dabrafenib also produced reduced body weight following an oral dose of 30-600 mg/kg, together with abnormal faeces (soft, mucoid, loose/watery). The maximum non-lethal dose was 1000 mg/kg in rats (up to 26 times the clinical exposure to dabrafenib based on AUC) and 600 mg/kg in dogs (>100 times the clinical exposure to dabrafenib based on AUC). Dabrafenib has a low order of acute toxicity by the clinical (oral) route.

Repeat dose toxicity

Repeat dose studies up to 13 weeks were conducted in rats and dogs, and up to 14 days in mice, consistent with ICH S9 guidelines. All studies were conducted by the oral route with once daily dosing, except for the 13-week dog study which had BID dosing. The proposed clinical route of exposure is twice daily, based on an estimated terminal half-life of 8.4 h following oral administration (sponsor's summary of clinical pharmacology). All studies were conducted with dabrafenib free base, except for the 13-week dog study which was conducted with dabrafenib mesilate salt, the proposed clinical form.

Relative exposure (dabrafenib)

Exposure ratios have been calculated based on animal:human plasma $AUC_{0-24\ h}$ and C_{max} (mean of data from males (m) and females (f)).

Table 5. Relative exposure to dabrafenib in repeat-dose toxicity studies

Species	Study duration	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (µg·h/mL)	C_{max} (µg/mL)	Exposure ratio based on AUC#	Exposure ratio based on C_{max}#
Mouse (CD-1)	14 Days	100	8.04	1.76	0.9	1.2
		300	9.34	2.0	1.1	1.3
		1000	16.20	3.70	1.8	2.5
Rat (SpragueDawley)	4 weeks	5	2.66	0.91	0.3	0.6
		20	5.2	1.40	0.6	0.9
		200	20.45	2.71	2.4	1.8
	13 weeks	20	8.21	1.54	0.9	1.0
		200	19.8	3.88	2.3	2.6
		400	21.8	2.44	2.5	1.6
Dog (Beagle)	4 weeks	1	4.29	0.87	0.5	0.6
		5	12.25	2.67	1.4	1.8
		50	42.7	7.63	4.9	5.1
	13 weeks	5	21.1	2.30	3.3	1.5
		20	98.7	9.83	9.1	6.5
		60/100 (m/f)*	118	11.4	14	7.6

AUC_{0-24} (8.7µg.h/mL) based on actual geometric mean AUC_{0-12} value of 4.34 µg.h/mL achieved in subjects given 150mg BID on week 6 of phase III Study BRF113683. C_{max} (1.5µg/mL) is the mean C_{max} achieved in the same study (sponsor's summary of clinical pharmacology).
* male/female Day 1 values (dosing stopped on day 14/15 and animals killed on days 21/22 due to excessive toxicity).

Table 6. Relative exposure (dabrafenib metabolites)

Species /Duration	Dose# (mg/kg/day)	Hydroxy-dabrafenib		Carboxy-dabrafenib		Desmethyl-dabrafenib	
		C_{max}†	AUC†	C_{max}†	AUC†	C_{max}†	AUC†
Mouse (14 day)	1000	2.1	10.5	39.25	315	11.7	72.6
Rat (13 week)	400	4.05	54.5	2.04	35.3	0.05	0.88
Dog (13 week)	20	2.13	29.5	0.269	4.76	0.19	2.0
Human (6 weeks)*	150 mg BID	1.01	8.1	6.15	103	0.347	6.1
Animal/human exposure ratio							
Mouse (14 day)	1000	2.1	1.3	6.4	3.1	33.4	11.9
Rat (13 week)	400	5.6	6.7	0.33	0.34	0.17	0.14
Dog (13 week)	20	2.1	3.6	0.04	0.05	0.55	0.33

#Highest dose tolerated without significant mortality in toxicity studies. † Mean C_{max} (µg/mL) and AUC_{0-24h} (µg.h/mL) of male and female.
*AUC_{0-24} based on geometric mean AUC_{0-12} values of 4.07, 51.5 and 3.07µg/mL for hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, respectively, achieved in subjects given 150mg BID on week 6 of phase III Study BRF113683. C_{max} values are the geometric mean C_{max} achieved in the same study (Summary of Clinical Pharmacology).

Major toxicities

The nonclinical toxicity associated with dabrafenib included morbidity/mortality, cardiovascular effects, skin lesions, testicular toxicity and immunotoxicity potential. The lack of clear no observed adverse effect levels (NOAELs) in most of the long term studies with low animal:human exposure ratios and the observation of in more than one species raises the potential clinical relevance of these toxicities.

Increased morbidity in male (60 mg/kg/day) and female (100 mg/kg/day) dogs in the 13-week study lead to early termination of these animals. This may be related to the use of the mesilate salt and BID dosing in this study. With the exposure ratio > 9, this is considered to have low clinical relevance.

Cardiovascular effects included arterial degeneration in the right atrium and papillary muscle of the heart and hypertrophy and haemorrhage of atrioventricular valve of the heart in dogs. These effects only involved a small number of animals and were not seen in all studies. In rats, a slight increase in cardiac myopathy was noted in the 4-week study, but not in the 13-week study. The mechanism leading to the observed effects is unknown but dabrafenib may be a contributing factor and the effects should be considered as potentially clinically relevant.

Skin lesions were observed in both rats and dogs. In both rats (≥ 20 mg/kg/day) and dogs (≥ 5 mg/kg/day), there was acanthosis (epithelial hyperplasia)/hyperkeratosis of the skin, which underwent partial recovery during the recovery period. Similar skin lesions have been reported in animal toxicity studies and in patients with other kinase inhibitors (Carnahan *et al*., 2010[6]; Lacouture *et al*. 2008[7]; Wisler *et al*., 2011[8]) and may be related to the pharmacological activity of dabrafenib. The effects were observed at exposures comparable to the clinical exposure levels, and are therefore of clinical relevance. Epithelial hyperplasia was also evident in the forestomach of the rat at ≥ 20mg/kg/day, and although not directly anatomically relevant to humans, the result suggests that the observed proliferative effects are not limited to skin. Epithelial hyperplasia of the forestomach and other tissues, including oesophagus, urinary bladder and renal pelvis, has been reported with other RAF inhibitors (Carnahan *et al*., 2010; Wisler *et al*., 2011).

Testicular toxicity was observed in mice, rats and dogs following treatment with dabrafenib without significant reversal during the recovery periods in rats and dogs. Degeneration of testicular seminiferous tubule epithelium occurred in rats and dogs at all dose levels for 3 months. Effects were noted in both rats and dogs at exposures below the clinical exposure level. There is some evidence from literature reports that these testicular effects are likely to be pharmacologically-mediated (Berruti, 2000[9]; Wojnowski, 1998[10]). The observed effects with dabrafenib are considered to present a significant risk with respect to male fertility at clinically relevant exposure levels.

Literature reports suggest there is a potential for immunotoxicity related to RAF inhibitory activity (Hipp, 2008[11]; Zhao, 2008[12]). Thymic lymphoid depletion was observed in dogs at 20 mg/kg/day (exposure ratio of 9, based on AUC), decreased thymus weight in dogs at ≥ 5 mg/kg/day for 3 months (exposure ratio of 3) and in mice at ≥ 300 mg/kg/day for 2 weeks (similar to clinical exposure). Increases in white blood cells were noted in both dog and rat studies, possibly related to skin lesions and secondary infections. Blood lymphocyte counts were unaffected except for an increase in lymphocyte count in the 13-week rat study. The potential for immunotoxicity in humans is low.

Decreased red blood cells (RBC), haemoglobin (Hb), haematocrit (Hct) and recitulocyte counts were observed in the 13-week study in dogs at 60/100 mg/kg/day (male/female; exposure ratio 14. Only mild decreases in Hb and Hct were seen in male rats at 400 mg/kg/day (exposure ratio 2.5) in the 13-week study. The changes in peripheral white blood cells (WBC) and RBC masses in dogs were associated with a slight increase in myeloid cells and decrease in erythroid cells of the sternal bone marrow.

Exposure to dabrafenib metabolites in rats and dogs was higher than clinical exposure for hydroxy-dabrafenib but lower for carboxy-dabrafenib and desmethyl-dabrafenib. In mice, exposure to all three metabolites was higher than clinical exposure. The toxicity associated with dabrafenib and its metabolites is well characterised and appears to be common between species, with the skin and testicular toxicity possibly related to the

[6] Carnahan J, Beltran PJ, Babij C, Le Q, Rose MJ, Vonderfecht S *et al*. Selective and potent Raf inhibitors paradoxically stimulate normal cell proliferation and tumor growth. *Mol Cancer Ther* 2010;9:2399-410.
[7] Lacouture ME, Wu S, Robert C, *et al*. evolving strategies for the management of hand–foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. *The Oncologist,* 2008; 13:1001-11.
[8] Wisler JA, Afshari C, Fielden M, Zimmermann C, Taylor S, Carnahan J *et al*. Raf inhibition causes extensive multiple tissue hyperplasia and urinary bladder neoplasia inthe rat. *Toxicologic Pathology,* 2011;39:809-22.
[9] Berruti G. A novel Rap1/B-Raf/14-3-3 θ protein complex is formed in vivo during the morphogenetic differentiation of postmeiotic male germ cells. *Experimental Cell Research,* 2000;257:172-9.
[10] Wojnowski L, Berna R, Park CM, Handel MA, Hollander WF and Zimmer A. Reduced activity of BRAF protein kinase in *hop* and *hophpy* mouse mutants. *Mammalian Genome,* 1998;9:905-6.
[11] Hipp MM, Hilf N, Walter S, Werth D, Brauer KM, Radsak MP *et al.* Sorafenib, but not sunitinib, affects function of dendritic cells and induction of primary immune responses. *Blood,* 2008;111:5610-20.
[12] Zhao W, Gu YH, Song R, Qu BQ and Xu Q. Sorafenib inhibits activation of human peripheral blood T cells by targeting LCK phosphorylation. *Leukemia,* 2008;22:1226-33.

pharmacological activity, to which hydroxy-dabrafenib and desmethyl-dabrafenib contribute. New or additional toxicity specifically related to one or more metabolites is therefore unlikely. The low relative exposure values for carboxy-dabrafenib and desmethyl-dabrafenib in rats and dogs is not considered to raise any significant concerns in relation to the clinical use of dabrafenib, although it may reduce the overall safety margin for dabrafenib and increase the likelihood of adverse effects occurring under clinical conditions, because of the higher than expected exposure to the metabolites in humans.

Genotoxicity

The genotoxic potential of dabrafenib was adequately examined in *in vitro* studies in bacteria and mammalian cells and in an *in vivo* study in rats. In *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, and in *Escherichia coli* WP2 *uvrA*, there was no evidence of an increased frequency of mutations. In mouse lymphoma cells, there was no evidence of an increased frequency of mutations at the thymidine kinase (TK) locus. In the rat micronucleus test, there was no increase in the incidence of micronucleated polychromatic erythrocytes at 1000 mg/kg PO. The overall conclusion is that dabrafenib does not have genotoxicity potential.

Carcinogenicity

Carcinogenicity studies were not conducted. This is in accordance with ICH S9 guidelines as dabrafenib is intended to treat patients with advanced cancer.

Reproductive toxicity

Very limited assessment of reproductive toxicity was performed. This is consistent with ICH S9 guidelines as dabrafenib is intended to treat patients with advanced cancer. There were no studies on placental transfer or examination of potential excretion of dabrafenib into milk.

There were no specific fertility studies in male animals, however, there was clear evidence of testicular toxicity in mice, rats and dogs (discussed above), which indicates a potential human risk of impaired spermatogenesis with an associated effect on male fertility. Female fertility was examined in a combined study which also examined embryofetal development in rats. In accordance with ICH S9 guidelines, no embryofetal development study in a second species was performed, nor were dedicated studies on pre- and post-natal development.

Relative exposure

Exposure ratios have been calculated based on animal:human plasma $AUC_{0-24\,h}$ and C_{max}. The relative exposure in the embryofetal toxicity study ranged from < 0.5 to > 2 times the clinical exposure at steady state.

Table 7. Relative exposure in a fertility and embryofetal development study in rats

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)	C_{max} (µg/mL)	Exposure ratio based on AUC#	Exposure based on C_{max}#
Rat (S D)	Embryofetal development (Day 12, pre-mating)	5	2.04	0.677	0.2	0.5
		20	5.33	1.15	0.6	0.8
		300	16.9	2.38	1.9	1.6
	Embryofetal development (GD10)	5	2.62	0.765	0.3	0.5
		20	4.10	1.17	0.5	0.8
		300	22.6	2.17	2.6	1.4

AUC_{0-24} (8.7µg.h.mL) based on the geometric mean AUC_{0-12} value of 4.34 µg.h/mL achieved in subjects given 150 mg BID on week 6 of phase III Study BRF113683 (sponsor's summary of clinical pharmacology). C_{max} (1.5µg/mL) is the geometric mean C_{max} achieved in the same study. GD = gestation day.

In the female fertility/embryofetal development study in rats, there was evidence of maternal toxicity at pre-mating and during gestation at ≥ 20 mg/kg/day (reduced body weight gain) (equivalent to half the clinical exposure based on AUC). There was a decrease in the number of corpora lutea and implantations at 300 mg/kg/day (equivalent to 2.6 times the clinical exposure based on AUC), but no effect on oestrous cycle, mating or fertility. Fetal toxicity (body weight decrease) and developmental toxicity (delayed skeletal development, visceral variations) was evident at ≥ 20mg/kg/day (equivalent to half the clinical exposure). No visceral or skeletal malformations were observed at 20 mg/kg/day, but visceral malformations were observed at 300 mg/kg/day (2.6 times the clinical exposure based on AUC). The observed effects with dabrafenib are considered to present a significant risk with respect to female reproduction and embryofetal development at clinically relevant exposure levels.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[13] The sponsor recommends that dabrafenib should not be administered to pregnant women or nursing mothers, and also recommends that women of childbearing age should use effective methods of contraception.

The nonclinical data indicates that treatment with dabrafenib at the proposed levels of exposure during pregnancy leads to a high probability of an increase in visceral and skeletal variations in the fetus and the possibility of pre-implantation loss and visceral malformation. Pregnancy Category D is appropriate.

Local tolerance

The *in vitro* studies conducted did not demonstrate a potential for dabrafenib to be an eye or skin irritant or a skin sensitiser.

[13] 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.*

Impurities

The proposed specifications for impurities in the drug substance and product are below ICH qualification thresholds or have been adequately qualified.

Paediatric use

Dabrafenib is not proposed for paediatric use at this stage. However, a tolerability and dose-ranging study was conducted in neonate rats. In this preliminary study, dabrafenib was not well tolerated in young neonate rats (post natal day (PND) 7-35) at ≥ 50 mg/kg/day, but was better tolerated in older neonate rats (PND 22-35), consistent with higher exposures (based on AUC) in younger neonate rats than in older neonate rats. There was evidence of dehydration and reduced body weight gain at 10mg/kg/day (approximately equivalent to the clinical exposure). The sponsor is conducting further studies on juvenile animals.

Phototoxicity potential

Dabrafenib absorbs light between 290-700 nm and was shown to be phototoxic to Balb/c 3T3 mouse fibroblasts *in vitro*. Quantitative whole body autoradiography studies in rat with radiolabelled (^{14}C)-dabrafenib showed wide tissue distribution of dabrafenib, but no selective retention in skin. Skin lesions observed in repeat dose studies in rats and dogs occurred in a low ultraviolet (UV) exposure situation and were considered to be related to the pharmacological activity of dabrafenib. A low incidence of photosensitivity (2%) has been reported in clinical studies. Based on the available information, there is a low risk of photosensitisation following dabrafenib treatment.

Nonclinical summary and conclusions

- The data provided in Module 4 were adequate to analyse and assess the nonclinical pharmacological, PK and toxicological properties of dabrafenib in relation to its proposed clinical use. The data were in general accordance with the ICH guideline on nonclinical evaluation of anticancer pharmaceuticals (ICH S9). The majority of the nonclinical studies were conducted with dabrafenib free base or mesilate salt aqueous suspension. The mesilate salt was shown to have improved oral absorption. The proposed clinical form is a mesilate salt in a HPMC capsule. While the exposure ratios are not high in the animal studies, they are adequate to address the clinical relevance of the observed toxicities.
- The primary pharmacology studies confirm the activity of dabrafenib as an inhibitor of RAF kinases, including the BRAF wild-type enzyme and, in particular, BRAF^{V600E} mutant kinase found in a high percentage of melanomas. *In vitro* studies demonstrated the inhibition also extended to eight other human kinases. The three major dabrafenib metabolites (hydroxy-, desmethyl-, and to a lesser extent, carboxy-dabrafenib) also inhibited BRAF wild-type and BRAF^{V660E} mutant enzymes. Dabrafenib inhibited tumour growth in *in vivo* studies in a mouse model bearing a human melanoma xenograft or a human colorectal xenograft at exposure levels well below the clinical exposure. Tumour regrowth was seen upon cessation of treatment, and there was a lack of sustained sensitivity upon subsequent treatment.
- Dabrafenib showed either no activity or only weak activity in a panel of biochemical assays for a broad range of proteins. Safety pharmacology studies examined potential CNS, respiratory and cardiovascular effects. In *in vitro* studies, the effects on hERG potassium channel and QT interval were at concentrations far exceeding clinically relevant exposures. In *in vivo* studies in dogs, the mild increase in heart rate and decrease in PR and RR intervals after a single dose were not seen after repeat

exposure at 5 times clinical exposure based on C_{max}. There were no abnormal ECG waveforms or arrhythmias. Overall, cardiovascular effects were not considered to be clinically relevant. There was no evidence of respiratory or CNS effects at twice the clinical exposure. There was no effect on body temperature in mice or rats at twice the clinical exposure.

- The PK studies indicated that oral absorption is relatively rapid and bioavailability was high in rats and dogs (77 and 82%) but lower in monkeys (46%), and the half-life was short (0.3-3 h). Volume of distribution was low in all species. The 3 major human metabolites were formed in all animal species. In repeat dose studies, exposure was similar in males and females and increased less than dose proportionally. There was no evidence of accumulation. Dabrafenib and the three major metabolites were highly bound to plasma proteins in all species, including humans. Tissue distribution was rapid and wide, with maximum levels in liver, and rapid decline over 3 days. The major pathway of metabolism is oxidation to hydroxy-dabrafenib and subsequently to carboxy-dabrafenib. The major enzymes responsible are CYP2C8 and CYP3A4. Carboxy-dabrafenib is further decarboxylated to form desmethyl-debrafenib. In all species the major excretion route is via the bile, with unchanged dabrafenib the major component in the faeces.
- Regarding potential PK drug interactions, although there is *in vitro* evidence for CYP450 inhibition (CYP2C8, 2C9, 2C19, 3A4) at high concentrations, there is induction of CYP3A4 in human hepatocytes, consistent with the moderate induction of CYP3A4 reported in clinical studies. Since dabrafenib is predominantly metabolised by CYP2C8 and 3A4, drugs which inhibit or induce CYP2C8 or CYP3A4 may influence dabrafenib exposure.
- In the repeat dose studies, there was evidence of increased morbidity and mortality at high relative exposures (> 9), but this is considered to have low clinical significance. Cardiovascular adverse effects were observed in a small number of rats and dogs and not consistently observed in all studies, but the effects seen are considered potentially clinically relevant. Skin lesions (acanthosis/hyperkeratosis) in rats and dogs seen at clinical exposure levels may be related to the pharmacological activity of dabrafenib and are considered clinically relevant. Testicular toxicity (degeneration of testicular seminiferous tubule epithelium) was observed in mice, rats and dogs at exposures below the clinical exposure with no significant reversal during the recovery period. This is considered a clinically relevant risk with respect to male fertility. Decreased RBC, Hb, Hct and reticulocyte counts were observed in dogs at doses that necessitated early sacrifice. Exposure to the dabrafenib metabolites, carboxy-dabrafenib and desmethyl-dabrafenib in the animal studies was lower than clinical exposure; however, the metabolites contribute to the pharmacologically-mediated toxicity and are unlikely to lead to new toxicity. The overall safety margin for dabrafenib may be reduced due to the higher than expected exposure to the metabolites in humans.
- The genotoxicity data was adequate and produced negative results in *in vitro* and *in vivo* studies. No carcinogenicity studies were performed, consistent with the ICH guidelines for an anti-cancer drug for the treatment of advanced cancer.
- The limited reproductive toxicity studies are consistent with ICH guidelines for an anti-cancer drug. There were no studies on placental transfer or examination of potential transfer of dabrafenib into milk. There were no specific fertility studies in males, but clear evidence of testicular toxicity in repeat dose toxicity studies suggests dabrafenib may impair male fertility in humans. In the female fertility/embryofetal toxicity study, there was no effect on female fertility but fetal toxicity and developmental toxicity was evident at half the clinical exposure. The sponsor has proposed Pregnancy Category D, which is considered appropriate.

- Dabrafenib has been shown to be phototoxic in an *in vitro* study. While dabrafenib or its metabolites have a wide tissue distribution, there was no selective retention in skin. The risk of phototoxicity is considered to be low.

Nonclinical recommendation

- Based on the nonclinical data provided for dabrafenib mesilate and evaluated in this report, registration of dabrafenib mesilate is supported.
- Revisions are recommended to nonclinical statements in the draft PI.[14]
- Juvenile rat studies referred to in the updated risk management plan (RMP; see section on *Pharmacovigilance findings*, below) should be provided for evaluation in a separate submission.

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

Dabrafenib is proposed for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV) melanoma. The recommended dose is 150 mg twice daily by oral administration (corresponding to a total daily dose of 300 mg). The dose should be taken either at least 1 h before or at least 2 h after a meal, with approximately 12 h between doses. Treatment should continue until disease progression or the development of unacceptable toxicity.

Dabrafenib has been designated as an orphan drug (on 30 May 2012), with the indication *for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV) melanoma*.

The indication for dabrafenib sought in this submission is synonymous with the designated orphan indication.

Clinical rationale

The clinical rationale for dabrafenib as stated by the sponsor in the application letter is that unresectable or metastatic melanoma is refractory to most currently available anticancer agents, with a poor response to currently available systemic agents including chemotherapy and immunotherapy, and radiation and hormonal therapy having a limited, palliative role. The sponsor claims that although the treatment of advanced melanoma will improve with the availability of ipilimumab and vemurafenib, there is still high unmet medical need for alternative approaches to the treatment of advanced melanoma.

> **Evaluator comment**: It is acknowledged that prior to the registration in Australia of ipilimumab in July 2011 and vemurafenib in May 2012, there were limited effective treatments available for advanced melanoma. However these recent additions have provided alternative more efficacious treatments. It is noted that the current submission compares dabrafenib with the older treatments which were standard care at the time of drug development. However, an assessment also needs to be made of the benefit of dabrafenib with respect to these newer treatments.

[14] Details of these are beyond the scope of the AusPAR

Contents of the clinical dossier

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

- 6 clinical pharmacology studies (2 of which are interim reports), including 6 that provided pharmacokinetic data and 1 that provided pharmacodynamic data.
- 1 population pharmacokinetic analysis and 1 covariate PK analysis of dabrafenib metabolites.
- 1 exposure response analysis (PK/PD) study.
- 1 pivotal efficacy/safety study: BRF113683 (BREAK-3).
- 1 dose-finding study: BRF112680.
- 2 supportive efficacy/safety studies: BRF113710 (BREAK-2) and BRF113929 (BREAK-MB)
- 3 other studies with safety results: BRF113220 (combination with trametinib), BRF113928 (Phase II BRAF positive non-small cell lung cancer), and BRF114144 (rollover).

Also provided were the Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Guidance

A pre-submission meeting between TGA, the New Zealand regulatory agency Medsafe and the sponsor to discuss dabrafenib occurred on 12th April 2012. During this meeting, the pivotal and supporting studies for the use of dabrafenib were described with regards to their design and suitability as supporting data for the proposed submission. No outstanding issues were identified from the meeting minutes.

In this meeting, it was agreed that the proposed indication would be for a broad V600 mutation positive population, and that the use of PFS as the primary endpoint was acceptable and in line with the TGA-adopted EU *Guideline on the evaluation of human anticancer medicines in man*.

Paediatric data

The submission did not include paediatric data. However, details for a Paediatric Development Program for the treatment of adolescents with BRAF V600 mutant melanoma and paediatric patients with solid malignant BRAF V600 mutation-positive tumours were provided.

Good clinical practice

The Sponsor declared that all studies referred to in this application complied with the principles of Good Clinical Practice, and conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was reported to have occurred for all subjects, and the studies performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. No evidence was found by the evaluator to contradict this claim.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 8 shows the studies relating to each PK topic.

Table 8. Submitted pharmacokinetic studies.

PK topic	Subtopic		Study ID
PK in healthy adults	-		-
PK in subjects with solid tumours	General PK dose	- Single	BRF112680 BRF113479 ‡ BRF113463 BRF113771 ‡
		- Multi-dose	BRF112680 BRF113771 ‡
	Bioequivalence† dose	- Single	BRF113468 (particle size, capsule type) ‡
		- Multi-dose	-
	Food effect		BRF112680 BRF113468 ‡
PK in special populations	Target population § dose	- Single	BRF113479 BRF113463 BRF113771
		Multi-dose	BRF112680
	Hepatic impairment		-
	Renal impairment		-
	Neonates/infants/children/ adolescents		-
	Elderly		Population PK analysis
Genetic/gender -related PK	Males vs. females		Population PK analysis
PK interactions	Midazolam		BRF112680
	Ketoconazole		BRF113771

PK topic	Subtopic	Study ID
Population PK analyses	Healthy subjects	-
	Target population§	Population PK analysis Covariate metabolite analysis

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
‡ Dabrafenib formulated as HPMC capsules

Evaluator's overall summary and conclusions on pharmacokinetics

The PK analysis has been confounded somewhat due to the change in formulation of dabrafenib from gelatin to HPMC capsules part-way through the clinical trial process. Therefore, the studies presented contained a proportion that used either of the two formulation types. A significant issue is that there does not appear to have been any formal and direct clinical bioequivalence studies performed across the two formulations. The only information on bioequivalence contained within the submission was an exploratory analysis in Study BRF113468, and the population PK analysis. Moreover, these analyses found that the two formulations were not bioequivalent, with a single 150 mg dabrafenib dose in a HPMC capsule resulting in 1.8-fold higher exposure compared to administration in a gelatin capsule, and similar results at steady state.

It is acknowledged that the overall effect of the change in formulation from gelatin to HPMC capsules was an increase in bioavailability, therefore the expected effect would be an increase in clinical activity without significant impact on tolerability since a maximum tolerated dose (MTD) was not reached during the original dose-finding study. However, it is a limitation that the recommended dabrafenib dose of 150 mg BID determined in the dose finding study using gelatin capsules was continued as the recommended dose using HPMC capsules without any further dose-finding studies with this new formulation. In addition, there have been no bioequivalence studies performed on the two proposed dosage strengths of 50 mg and 75 mg HPMC capsules. Throughout the clinical evaluation report (CER; see Attachment 2 of this AusPAR), more emphasis has been placed on the results drawn from the studies using HPMC capsules, as is proposed for registration, where these were available.

From the results of the presented PK studies, it is concluded that dabrafenib is well absorbed when administered orally with a high bioavailability of 94.5%, a T_{max} of around 2 h, and a terminal half-life of between 4.8 to 8.4 h. There was no difference in exposure with BID or three times daily (TID) dosing, and thus BID dosing would seem appropriate. There was delayed absorption and bioavailability when dabrafenib was administered with food, and thus the recommendation to administer while fasted is warranted. Dabrafenib is highly plasma protein bound, and appears to cross blood brain barrier on repeat dosing and thus have a potential clinical effect on brain metastases.

Dabrafenib has been found to induce CYP enzymes and, via the induction of CYP3A4 (and possibly CYP2C8), it induces its own metabolism. Therefore there is no accumulation of dabrafenib on repeat dosing, but rather steady-state to single-dose ratios for C_{max} and AUC are of the order of 0.5 to 0..88 across the various studies. Similarly, the degree of increased exposure with increasing dabrafenib dose is diminished over time, although the extent of dose-proportionality remains uncertain as differences were observed between the different capsule formulations (gelatin or HPMC).

Ninety four percent of dabrafenib was found to be excreted in urine or faeces within 240 h of dosing. Elimination of dabrafenib is primarily by metabolism, with limited contribution from biliary and renal clearance. Therefore, the effect of enzyme induction is significant on total body clearance of dabrafenib. The population PK analysis calculated a non-inducible clearance (from all mechanisms) of 17.0 L/h and an inducible clearance that increased with time and reached a steady state of 17.3 L/h following administration of dabrafenib 150 mg BID (HPMC capsules). Therefore, the predicted total apparent oral clearance at steady state was 34.3 L/h reached after 14 days of dosing. Due the proposed long-term use of dabrafenib in the treatment of melanoma patients, it is arguably the PK at steady state after repeat dosing that is clinically relevant and should be stated within the PI.

Dabrafenib is sequentially metabolised to form the active metabolites hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib. In particular, hydroxy- and desmethyl-dabrafenib are thought to contribute to the clinical activity (and adverse event (AE) profile) of dabrafenib. The PK of hydroxy-dabrafenib parallels that of the dabrafenib, whereas carboxy- and desmethyl-dabrafenib exhibit longer half-lives.

High inter-individual variability was observed in the PK of dabrafenib. On population PK analysis, the only covariates found to significantly impact on the PK parameters were gender and body weight (using a full model approach with all covariate-parameter relationships entered simultaneously), neither of which was considered by the sponsor to be clinically relevant. However, the opinion of the evaluator is that body weight, for which the difference between subjects with low and high weight was found to be of the order of 32-52%, may be a relevant factor. There was no observable effect of age on the PK of dabrafenib.

The PK of dabrafenib has not been investigated in subjects with severe hepatic or renal impairment as such subjects were excluded from the clinical trials completed to date. However, based on the known metabolic and excretion pathway of dabrafenib with the majority being cleared by CYP enzymes, it is anticipated that hepatic impairment is likely to impact on the PK of dabrafenib and potentially increase its exposure. Therefore, caution is required in the administration of dabrafenib to subjects with hepatic impairment. Conversely, due to low renal excretion (22.7% of a radioactive oral dose), renal impairment is less likely to impact on dabrafenib PK. The results of studies in patients with hepatic and renal impairment currently being conducted will help to clarify these issues.

Due to the predominance of metabolism in the clearance of dabrafenib (over renal and biliary clearance), attention needs to be paid to mechanisms and interactions which may impact on metabolic pathways. Specifically, drugs or factors that lead to induction or inhibition of CYP enzymes (in particular CYP3A4 and CYP2C8) may impact on the PK of dabrafenib and its metabolites. This has been shown clinically with interactions seen between dabrafenib and midazolam and ketoconazole, while the results of interaction with warfarin and gemfibrozil are pending. However, other specific factors that may cause differences in enzyme function such as racial and genetic differences have not been investigated, and therefore dabrafenib should also be used with caution in ethnic groups other than Caucasians, and in those with genetic enzyme variations.

Pharmacodynamics

Studies providing pharmacodynamic data

Only two studies contributed pharmacodynamics (PD) data in this submission. Table 9 shows the studies relating to each pharmacodynamic topic.

Table 9. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on pERK inhibition	BRF112680
	Effect on FDG-PET* uptake	BRF112680
Secondary Pharmacology	-	
Gender other‡ genetic and Age-Related Differences in PD Response	Effect of gender	-
	Effect of age	-
PD Interactions	Midazolam	BRF112680
Population PD and PK-PD analyses	Healthy subjects	-
	Target population§	Exposure response analysis

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
‡ And adolescents if applicable.
* Fluorodeoxyglucose-positron emission tomography

None of the PD studies had deficiencies that excluded their results from consideration.

Evaluator's overall summary and conclusions on pharmacodynamics

Only a small amount of PD data was provided with this submission. This could be considered acceptable, as for this indication, it is arguably the clinical efficacy which is of greater clinical relevance than quantification of PD effects.

In Study BRF112680 dabrafenib was shown to inhibit the MAP kinase pathway, measured as dose-related decreases in pERK expression, of the order of 83.9%. Significant decreases in fluorodeoxyglucose-positron emission tomography (FDG-PET) uptake were also observed, with a median (95% CI) 50% effective dose (ED_{50}) of 214 mg (168 to 312 mg). The mean tumour size reduction was found to be generally related to the daily dose administered, and the estimated ED_{50} of 801 mg (95% CI: 571 to 1217 mg) was greater than the highest daily dose tested of 600 mg, suggesting that the change in tumour size is very close to being dose-linear. Adverse events (Grade 3 and 4) observed at higher dosage ranges included squamous cell carcinoma and pyrexia, however the MTD was not reached.

Secondary PD effects taken from preclinical studies anticipated effects on the cardiovascular system, proliferative skin effects, and testicular, reproductive and developmental toxicity. There is also a theoretical risk of immunotoxicity. These potential effects require ongoing monitoring in terms of AEs. See the section on *Safety*, below, for discussion of potential cardiovascular effects and ECG changes including QT prolongation.

The PK/PD exposure-response analysis found that at doses of dabrafenib 150 mg BID (HPMC capsules), PFS was similar in subjects whose exposure was above or below the median exposure (average concentration; Cavg) of 374 ng/mL, and this was likely because the response is at the top of the exposure-response curve. An exposure response

relationship was noted using objective response (OR) either at first assessment or confirmed response, with the effect reaching a plateau at an average dabrafenib exposure (Cavg) >300 ng/mL, although the model did not precisely fit the observed data. It is noted that the median exposure at the recommended dose is above this level. The exposure response analysis in terms of tumour size (TS) found a significant drug effect on the parameter describing progression, while subjects with higher exposure had longer duration of response than those with lower exposure as development of progression was delayed. In the exploratory AE analysis, there was some evidence that higher dabrafenib exposure was associated with higher fraction of subjects with pyrexia and palmar-plantar erythrodysaethesia (PPE).

Dosage selection for the pivotal studies

The dose of dabrafenib selected for use in the three main clinical efficacy and safety studies (BREAK-3, BREAK-2 and BREAK-MB) was 150 mg BID. This dose was chosen based on results from the Phase I dose-escalation Study BRF112680, where daily doses ranging from 12 to 600 mg were examined. The dose of 150 mg BID was selected based on:

1. the effect of dabrafenib on molecular biomarker targets (such as tumour pERK inhibition),
2. FDG metabolic uptake (measured by Day 15 FDG-PET),
3. disease assessment, which was measured by response per Response Evaluation Criteria in Solid Tumours (RECIST[15]) Version 1.1 criteria at first evaluation (that is, Weeks 8-9), and
4. overall safety profile.

Increasing the dosage from 150 mg BID to 200 mg BID was not shown to increase the exposure, result in increased inhibition of pERK, or increase the clinical activity in terms of response rate. The safety profile was consistent with that of dosages of 300 mg dabrafenib BID, although there were lower numbers of serious AEs (SAEs) compared to the 300 mg BID dose. A MTD of dabrafenib was not identified in this study.

> **Evaluator comment:** Based on the results of Study BRF112680, the selected recommended dose of 150 mg BID dabrafenib could be considered the minimum effective dose based on PK, PD, efficacy and safety parameters. It is noted that in this study, the small number of subjects dosed at 300 mg BID dabrafenib were found to have a greater clinical response, however the dose of 150 mg BID was selected due to the timeliness of the availability of the different cohort results, rather than for any specific PK, PD or safety reasons. Therefore, the potentially increased clinical activity observed at this higher 300 mg BID dosage level of dabrafenib may warrant further investigation as a treatment option to improve outcomes, however the effect on the safety profile would also need to be determined.
>
> It is also noted that in the dose-finding Study BRF112680, dabrafenib was formulated in gelatin capsules, which in Study BRF113468 were found to have a lower bioavailability than the proposed HPMC formulation. The recommended dose of dabrafenib was not altered with the change in formulation (150 mg BID), therefore greater efficacy and safety issues may occur at the proposed dosage and formulation than were observed in the studies using gelatin capsules, which should be considered in the analysis. However, no studies systematically

[15] RECIST is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.

investigated differences in PK, efficacy and safety of the two formulations at the same dosage.

Therefore, the selection of the recommended dosage of dabrafenib 150 mg BID in HPMC capsules is not based on ideal PK data, being based on a dose finding study using gelatin capsules which have different bioavailability, and the relative bioavailability of the two formulations has not been directly quantified. However, given the higher bioavailability of dabrafenib as HPMC capsules, and the greater efficacy observed at dosages of 300 mg BID using gelatin capsules in the dose finding study and tolerable safety profile with a MTD not reached, selection of the recommended dose could be accepted but there is a need to closely monitor for adverse effects.

Efficacy

Studies providing efficacy data

One pivotal study (BREAK-3), and two supportive studies (BREAK-2 and BREAK-MB) were submitted with this application in support of the proposed indication of use of dabrafenib for treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV melanoma).

Pivotal Study BREAK-3 was a multi-centre, two-arm, open-label, randomised, active-comparator, Phase III study. It aimed to assess the efficacy of oral dabrafenib compared to IV dacarbazine (abbreviated to DTIC) standard of care therapy in subjects with BRAF V600E mutation positive, treatment naïve, advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. The safety and tolerability of dabrafenib compared to dacarbazine was also assessed.

Supportive Study BRF113710 (BREAK-2) was a multi-centre, single-arm, Phase II, open-label study. The main purpose was to evaluate the efficacy of dabrafenib (gelatin capsules, 150mg BID) in adult subjects (aged ≥ 18 years) with BRAF V600E or V600K mutation positive metastatic (Stage IV) melanoma. Key inclusion and exclusion criteria were similar to that of the pivotal Study BRF113683 (BREAK-3), apart from the inclusion in this study of not only treatment-naïve subjects, but also those who had received prior treatment in the metastatic setting (such as chemotherapy, immunotherapy, prior targeted therapy) and also subjects with BRAF V600K mutations.

Supportive Study BRF113929 (BREAK-MB) was a global, multi-centre, open-label, single-arm, two-cohort, Phase II study designed to prospectively evaluate the activity of dabrafenib (150 mg BID, HPMC capsules) in subjects with histologically confirmed (Stage IV) BRAF-mutation-positive (V600E or V600K) melanoma metastatic to the brain.

Evaluator's conclusions on clinical efficacy of dabrafenib for treatment of patients with BRAF V600 mutation positive unresectable or metastatic (stage IV) melanoma

The evaluator's conclusions based on the data submitted are as follows:

BRAF V600E mutation positive advanced or metastatic melanoma (excluding brain metastases)

For patients with treatment naïve V600E positive metastatic melanoma, the BREAK-3 Study with 250 subjects (187 randomised to dabrafenib and 63 to dacarbazine) showed a statistically significant and clinically relevant improvement in the primary endpoint of investigator-assessed PFS compared to dacarbazine, of 5.1 months with dabrafenib compared to 2.7 months with dacarbazine, equating to an adjusted hazard ratio (HR) of 0.30 (95% CI: 0.18-0.51; $p < 0.0001$). This result was supported by independent review,

and also by the secondary endpoints of OS (87% at 6 months for dabrafenib compared to 79% for dacarbazine), OR rate (ORR; 53% for dabrafenib compared to 19% for dacarbazine), and duration of response (5.6 months for dabrafenib compared to 5 months for dacarbazine). Quality of Life (QoL) measures also indicated an advantage for dabrafenib over dacarbazine. These results were supported by Study BRF113710 (BREAK-2) in patients with previously treated metastatic BRAF V600E melanoma. The primary endpoint showed a favourable investigator-assessed ORR of 59% (41% on independent review), along with a PFS of 6.3 months and duration of response of 5.2 months. Therefore, the results of the BREAK-3 Study, supported by the BREAK-2 Study, indicate that the efficacy of dabrafenib is clinically superior to dacarbazine in the treatment of patients with advanced or metastatic (excluding brain metastases) BRAF V600E mutation positive melanoma.

BRAF V600E mutation positive metastatic melanoma to the brain

Patients with brain metastases were excluded from the pivotal BREAK-3 and supportive BREAK-2 Studies. As the frequency of CNS metastases in those who die from metastatic melanoma has been found to be 50-75%[16], a large proportion of the intended target population was, therefore, been excluded from the pivotal trial. The BREAK-MB Study assessed the effects of dabrafenib in 139 subjects with BRAF V600E mutation positive metastatic melanoma to the brain, however as a Phase II study, the absence of a comparator limits the interpretation of results.

The primary endpoint in the BREAK-MB Study of investigator-assessed overall intracranial response rate (OIRR) in V600E mutation positive subjects suggested a clinically beneficial effect of either 31% or 39% (depending on the previous use of local treatment), however the results with independent review were less convincing (18% or 20%). The investigator-assessed ORR in this group of patients (of 31% or 38% (23% or 28% with independent review) was less than in the BREAK-3 and BREAK-2 Studies, and this is not unexpected due to patients in the BREAK-MB Study having more advanced disease resulting in brain metastases. Similarly, results for median duration of response (20.1 or 22.1 weeks) and PFS (16.1 or 16.6 weeks) were shorter in this study. The median OS was 31.4 or 33.1 weeks.

The absence of a control population in the BREAK-MB Study was justified in the clinical study report (CSR) on the basis of there being no currently available active systemic therapy for use in melanoma patients with CNS involvement. However, it could be argued that there are currently available local therapies with demonstrated effectiveness, such as surgery and stereotactic radiosurgery (SRS; up to 40 weeks median survival reported[17]), and these would be appropriate comparators in a Phase III trial. No data was presented by the sponsor comparing the efficacy of dabrafenib with these local therapies. Therefore, pending more definitive evidence, although it would seem efficacious, it cannot be concluded that dabrafenib is superior to currently used local therapies in the management of BRAF V600E positive metastatic melanoma CNS lesions. It is recommended that more information be provided by the sponsor to specify the proposed use of dabrafenib in the setting of BRAF V600E positive melanoma brain metastases. Specific questions include whether dabrafenib should be used prior to, after, or instead of local management (surgery or SRS) that is deemed appropriate using current criteria. In addition, under what circumstances (such as degree of tumour burden) are the different treatments deemed appropriate? The evaluator noted that this conclusion is not entirely consistent with that of the sponsor.

[16] McWilliams RR, Rao RD, Buckner JC, Link MJ, Markovic S, Brown PD. Melanoma induced brain metastases. *Expert Rev Anticancer Ther* 2008;8:743-55

[17] Carlino MS, Fogarty GB, Long GV. Treatment of melanoma brain metastases. *Cancer J* 2012;18:208-12.

BRAF V600K mutation positive metastatic melanoma

Patients with BRAF V600K mutation positive metastatic melanoma were excluded from the pivotal BREAK-3 Study, but were assessed in the Phase II BREAK-2 and BREAK-MB Studies. Therefore, the results for this subgroup are limited by small numbers and the absence of an active comparator. Assessment of V600K mutation positive subjects was not a primary endpoint in either of the BREAK-2 or BREAK-MB Studies.

For 16 subjects in the BREAK-2 Study, the ORR for subjects with BRAF V600K metastatic melanoma excluding brain metastases was 13% which is more consistent with that seen in the dacarbazine arm in the BREAK-3 Study. Some improvements in PFS (4.5 months) and duration of response (5.3 months) were observed compared to historical studies.

For 33 subjects in the BREAK-MB Study, the investigator-assessed OIRR for patients with V600K positive metastatic melanoma to the brain was 7 or 22% depending on prior local treatment (0 or 11% with IR), while ORR was 0 or 28% (0 or 11% with independent review), median PFS was 8.1 or 15.9 weeks (7.9 or 15.3 weeks with independent review), and median OS was 16.3 or 21.9 weeks.

The results of both these studies do not meet the pre-defined criteria for clinical significance[18], and in any case with low numbers, lack of an active comparator, and as secondary endpoints, interpretation is limited. Therefore, the opinion of the evaluator is that the submitted evidence for the efficacy of dabrafenib in patients with BRAF V600K mutation positive metastatic melanoma is not convincing, and the clinical significance in this patient population remains undetermined. Particularly with respect to patients with BRAF V600K metastatic melanoma to the brain, there is no evidence of superiority of dabrafenib compared to appropriate local management (surgery or SRS). The claim in the BREAK-MB CSR that treatment with dabrafenib in V600K subjects with metastatic melanoma to the brain is clinically significant based on the PFS and OS being longer than observed with systemic chemotherapy is debatable in light of the limitations of the evidence.

However, due to the poor prognosis of metastatic melanoma and, until recently, the lack of an effective treatment, there may be a role for treatment of patients with BRAF V600K metastatic melanoma, provided the limitations in the evidence with regards to this patient subgroup are acknowledged and ongoing data is collected for further assessment.

Comparison of dabrafenib with the BRAF inhibitor vemurafenib and the monoclonal antibody ipilimumab

One major limitation of the data submitted in this application was the lack of comparison of dabrafenib with the now registered BRAF inhibitor vemurafenib, which was registered in Australia in May 2012. Although this agent was not registered at the time of design and implementation of the dabrafenib studies, it has now become standard of care for BRAF V600 mutation positive metastatic melanoma patients (superseding dacarbazine) according to the National Comprehensive Cancer Network (NCCN) Guidelines (Version 1.2013). Therefore, an assessment should also be made of the efficacy of dabrafenib compared to vemurafenib.

The pivotal study supporting the efficacy of vemurafenib was in 675 treatment naïve patients with predominantly BRAF V600E mutation-positive unresectable or metastatic melanoma, comparing treatment with either vemurafenib or dacarbazine.[19, 20] The co-

[18] Sponsor comment: This does not apply to BRF113929 (BREAK-MB). The intracranial and overall response rates were secondary endpoints for the V600K mutation positive subjects for which no pre-defined criteria for clinical significance was defined, either in the protocol or the Reporting and Analysis Plan (RAP).
[19] Chapman PB, Hauschild A, Robert C *et al*. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *New Engl J Med.* 2011;364(26):2507-2516

primary outcomes were OS and PFS. Those treated with vemurafenib had a median OS of 13.2 months (compared to 9.6 months with dacarbazine), and a median PFS of 5.3 months (compared to 1.6 months with dacarbazine). The dabrafenib PFS results from the BREAK-3 Study (5.1 months) compare favourably, however as the OS data for this study are not yet mature, it was not possible to compare OS results. Moreover, the allowance for treatment crossover on disease progression in the BREAK-3 Study is likely to confound the OS results. Therefore, based on the currently available pivotal study results, there is no obvious difference in efficacy between dabrafenib and vemurafenib, although no head-to-head comparison exists to determine the superiority of one treatment over the other.

Comparison of dabrafenib with ipilimumab is less relevant to the registration of dabrafenib due to being of a different class with a different mode of action. Ipilimumab has been registered for the second-line treatment of advanced or metastatic melanoma in Australia since June 2011, and similar to vemurafenib, is recommended as a first line treatment against advanced or metastatic melanoma by the NCCN Guidelines (Version 1.2013). Ipilimumab acts indirectly by enhancing a T lymphocyte (T-cell) mediated immune response against tumours. In the pivotal study supporting the efficacy of ipilimumab, the medial OS was 10 months in subjects given one course of ipilimumab compared to 6 months in the control group. As the data for OS in the BREAK-3 Study are not yet mature, no comparison can be made. It is noted that the clinical summary stated that the BREAK-2 Study found an OS of 13.1 months at 12 months follow-up, but no data was available in the submission to verify this figure. Again, no head-to-head data was provided to compare the efficacy of dabrafenib with ipilimumab. Ipilimumab has an advantage over dabrafenib and vemurafenib in that its efficacy is not limited to patients with BRAF V600 mutations. However, there are substantial safety concerns with its use which are discussed in the section on *Safety* below.

Data limitations

The exclusion from the pivotal BREAK-3 Study of subjects with brain metastases and BRAF V600K mutations precludes confident generalisation of the study results to these populations. Although these two factors were addressed in the supporting BREAK-2 and BREAK-MB Studies, the Phase II nature of these studies impacts on their generalisability. This has implications for assessing the likely efficacy of dabrafenib in the intended patient population of those with advanced or metastatic BRAF V600 mutation positive unresectable or metastatic melanoma, with CNS metastases and V600K mutations affecting up to 75% and 20% of this target population respectively.[21] Reduced efficacy of dabrafenib in these patient sub-groups may dilute the impact of treatment in the intended population, resulting in a reduced efficacy than was observed in the BREAK-3 trial.

Another limitation of the data includes the lack of non-White patients in the trial populations, meaning that the efficacy of dabrafenib in other racial groups remains unknown.

Differences in the formulation of dabrafenib in the BREAK-2 Study (gelatin capsules) compared to that used in the BREAK-3 and BREAK-MB Studies and proposed for registration (HPMC capsules) are likely to have reduced the amount of pharmacologically active dabrafenib used in the BREAK-2 Study, and therefore will not have affected the validity of the efficacy results (although this may have impacted on safety observations).

[20] Chapman PB, Hauschild A, Robert C *et al*. Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with *BRAFV600E*-mutated melanoma. 2012 ASCO Annual Meeting. *J Clin Oncol* 30, 2012 (suppl; abstract 8502).
[21] Jakob JA, Bassett RL, Ng CS *et al*. NRAS mutation status is an independent prognostic factor in metastatic melanoma. *Cancer* 2012;118:4014-4023 (published on line in 2011: doi: 10.1002/cncr.26724)

It is also noted that there are other forms of BRAF V600 mutations that occur infrequently (for example, V600D). No data was submitted examining the efficacy of dabrafenib in these subtypes, and therefore no evaluation assessment can be made.

Safety

Studies providing evaluable safety data

Integrated safety population

An Integrated Summary of Safety (ISS) was provided with the application. This integrated analysis combined the safety results from the studies: BRF113683 (BREAK-3); BRF11392 (BREAK-MB); BRF113710 (BREAK-2); BRF113220 (dabrafenib and trametinib); and BRF112680 (First-time-in-human (FTIH) Study). The safety results in the integrated dabrafenib safety population (N=578) were evaluated for consistency against the dabrafenib-treated subjects (n=187) in the pivotal BREAK-3 Study. Due to differences in assessment schedules across the 5 studies, integrated safety data were not summarised by time point. Integrated summaries of safety display baseline and worst-case on-therapy results only. In general, the baseline characteristics of the integrated safety population were similar to that of the dabrafenib arm of the BREAK-3 Study: mean and median age both 53.0 years, 61% male, and >95% White. Throughout the CER (Attachment 2 of this AusPAR), the results of the ISS are presented where relevant alongside the results of the pivotal Study BREAK-3.

In addition to the integrated safety population, the following individual studies provided evaluable safety data:

Efficacy studies

- the pivotal efficacy Study BRF113683 (BREAK-3)
- supportive efficacy/safety Study BRF113710 (BREAK-2)
- supportive efficacy/safety Study BRF113929 (BREAK-MB)

Other studies

- Study BRF113220 (an ongoing multi-centre, open-label, dose-escalation Phase I/II study, designed as a 4-part study to investigate the safety, PK, PD and clinical activity of dabrafenib in combination with trametinib in subjects with BRAF mutant metastatic melanoma.)
- Study BRF113928 (a Phase II study of dabrafenib 150 mg BID in subjects with advanced non-small cell lung cancer and BRAF mutations. The study is ongoing with 5 of a planned 40 subjects enrolled at the time of reporting).
- Study BRF114144 (a Phase I, multicenter, non-randomised, open-label rollover study to provide continued treatment with dabrafenib to subjects with BRAF mutation-positive tumours who have completed previous dabrafenib investigational studies and are still receiving benefit. As of the 30 March 2012 data cut-off, 98 subjects were enrolled, all of whom had been in early phase and clinical pharmacology studies.)
- Study BRF112680 (a dose-finding study, with multiple cohorts of subjects administered different doses of dabrafenib.)

Patient exposure

In the pivotal Study BRF113683 (BREAK-3), 187 subjects were allocated to dabrafenib in the randomised phase, with a mean and median daily dose of 284.9 mg and 300 mg,

respectively, and a median duration on study treatment of 4.9 months. The mean and median dose intensity of dacarbazine was 311.6 mg/m^2/week and 332.0 mg/m^2/week, respectively, with a median duration on study treatment of 2.8 months. In the crossover phase, 28 subjects were exposed to dabrafenib with a mean and median daily dose of 292.6 mg and 300 mg, respectively, and a median duration on crossover study treatment of 2.8 months.

In Study BRF113710 (BREAK-2), there were 92 subjects, with mean and median daily dose of dabrafenib being 282.4 mg and 300 mg, respectively, and a median duration on study treatment of 4.8 months.

In Study BRF113929 (BREAK-MB), there were 172 subjects in total. This consisted of 89 subjects in Cohort A, with mean and median daily dose of dabrafenib of 280.3 mg and 300 mg respectively and a median duration on study treatment of 3.9 months, and 83 subjects in Cohort B, with a mean and median daily dose of dabrafenib of 281.6 mg and 298.7 mg respectively and a median duration on study treatment of 4.0 months.

In the dabrafenib monotherapy arm of Study BRF113220, there were 53 subjects with a mean and median daily dose of dabrafenib of 295.95 mg and 299.12 mg respectively, and a median duration on study treatment of 3.81 months. No data was provided on individual duration of dabrafenib treatment in this study.

In Study BRF113928, 5 subjects were enrolled at the time of reporting. No details on duration of treatment were provided.

In the integrated safety population, exposure was similar to the dabrafenib arm in the BREAK-3 Study, with a mean and median daily dabrafenib dose of 284.8 mg and 300 mg respectively, and a median time on study treatment of 4.62 months.

> **Evaluator comment:** There is limited data on the safety of dabrafenib with long-term use, with only 5 subjects providing safety data at the proposed dose range for more than 12 months. Limited numbers of long-term follow up is acceptable in light of the generally poor prognosis of the target population, and therefore reduced likelihood of survival beyond 12 months.

Evaluator's overall summary and conclusions on clinical safety

Dabrafenib has distinct AE profile when compared with other conventional cytotoxic chemotherapy regimens. Overall 96% of subjects in the integrated safety population experienced an AE, and 26% of subjects reported a SAE. 24% subjects died in the integrated safety population, and disease under study reported as the primary cause of death in 97%.

Overall, dabrafenib was well tolerated and appeared to have a manageable safety profile. In the integrated safety population, only 2% of subjects discontinued treatment due to adverse effects, and 14% of subjects had a dose reduction due to adverse effects.

In particular, the following AEs were found to be clinically relevant to dabrafenib's use:

- **Premalignant and malignant skin lesions:** Dabrafenib has been found to increase the risk of premalignant and malignant skin lesions, with a rate of 9% in the integrated safety population. This is in keeping with the results from vemurafenib studies, and therefore is likely to be a class-effect of BRAF inhibitors. Cases of cutaneous squamous cell carcinoma (SCC) reported in the BREAK-3 Study were detected early with regular dermatologic screening, and the cumulative incidence in the integrated safety population appears to plateau. Therefore, early and frequent dermatologic monitoring is warranted with dabrafenib use. However, the long term effects of dabrafenib on the rate and severity/aggressiveness of cutaneous malignancies are not known in light of limited follow-up duration, and the continued monitoring and reporting of these

events would be of benefit. The current data does not suggest an association between use of dabrafenib and the development of other malignancies (other than SCC or keratoacanthoma), including no increased risk of new primary melanoma above what is expected in the melanoma patient population.

- **Pyrexia:** The study results suggest dabrafenib treatment is associated with pyrexia, with a frequency of 27% in the integrated safety population. The mechanism of pyrexia remains unknown, and 50% of cases occurred within 2 weeks of starting treatment. This pyrexia has the potential to be severe, with 18% of cases in the integrated safety population being considered SAEs, and this can have significant impacts on other organ systems and overall functioning. It is noted that pyrexia is not listed as an adverse effect of the currently registered BRAF inhibitor vemurafenib.
- **Cardiovascular adverse events:** Monitoring of cardiovascular AEs was performed based on AEs observed with other kinase inhibitors, and following the results of preclinical studies with dabrafenib. Dabrafenib was associated with a decrease in left ventricular ejection fraction (LVEF) from baseline in 54% of subjects in the BREAK-3 Study, similar to that for dacarbazine, however the magnitude of the decrease appeared to be slightly greater with dabrafenib. Cardiac valvular abnormalities were observed in preclinical studies of dabrafenib, and were observed in 2% of subjects in the BREAK-3 Study and considered possibly related to study treatment. Due to the rare occurrence of these events and the limited period of follow up to date, an association between dabrafenib use and the cardiovascular AEs of decreased LVEF and cardiac valvular abnormalities cannot be excluded, and further monitoring and follow up as part of the Risk Management Plan (RMP) are warranted. It is noted that these conclusions are at odds with those drawn by the sponsor as outlined in the clinical summaries.
- **QT prolongation:** There may be some association between dabrafenib use and QT prolongation, with 21% of subjects in the integrated safety population experiencing any increase in QT interval with Bazett's correction (QTcB) from baseline. In Study BRF112680, an exposure-QTc analysis found no statistically significant relationship between dabrafenib and QTc, however there was a positive relationship between all three dabrafenib metabolites and QTc, with the median change in population-corrected QT interval (QTcP) predicted to be ≤ 5.5 msec at the highest doses tested. Although this was assessed by the sponsor as indicating low risk of QT prolongation, due to the greater bioavailability of dabrafenib as HPMC capsules compared to the gelatin capsules used in this study, a clinically relevant effect of dabrafenib metabolites on QT prolongation cannot be excluded. As QT prolongation is also listed as an adverse effect of the BRAF inhibitor vemurafenib, for which exposure-dependent QT prolongation was observed in studies, a more thorough QT study may be warranted using the proposed dosage and formulation for registration. ECG monitoring should occur with dabrafenib use with appropriate precautionary measures taken in the event of its occurrence.
- **Palmar-plantar erythrodysesthesia:** This was observed in 20% of subjects in the dabrafenib arm of the BREAK-3 Study, and in 13% of the integrated safety population. Most cases were of low grade.
- **Cerebral haemorrhage in brain metastases:** Three deaths were attributed to the SAE of cerebral haemorrhage in the BREAK-MB Study. In at least one of these subjects, bleeding may have been precipitated by tumour shrinkage as a result of dabrafenib use. Therefore, bleeding into responding CNS lesions may be an AE of dabrafenib in the setting of brain metastases which needs to be monitored.

Other general conclusions drawn from the safety data include:

- The risk of an association between dabrafenib and hepatocellular injury appears to be low, but cannot definitively be excluded. Ongoing hepatic monitoring may be warranted with long-term use.
- Although not a frequent occurrence, an effect of dabrafenib on renal function cannot be excluded, and renal monitoring with long-term use may be warranted. In particular, the risk of renal failure may be exacerbated by the presence of drug-induced pyrexia with secondary renal insufficiency.
- There appears to be an association with dabrafenib and hyperglycaemia (observed in 48% of subjects in the integrated safety population), and hypophosphataemia (observed in 35%). Therefore, monitoring of laboratory markers may be warranted during dabrafenib therapy, and there may be specific implications for use in diabetic patients.
- Despite occurring less frequently than with dacarbazine, haematological abnormalities would still seem important associations with dabrafenib use. In the integrated safety population, anaemia was seen in 29% subjects, lymphocytopenia in 20% (with 6% Grade 3 and 5 subjects (< 1%) Grade 4), and neutropenia observed in 11%. The frequency may be increased when used with other therapies. Therefore, monitoring for haematological abnormalities may still warrant monitoring.

It is noted that arthralgia and rash were commonly reported as low grade AEs across all studies with a frequency of around 30%. This did not appear to have been investigated further within the submission as to possible mechanisms (such as possible autoimmune cause).

Comparison of dabrafenib's safety profile with that of the anti-melanoma agents vemurafenib and ipilimumab:

As discussed, the absence of head-to-head trails between dabrafenib and the now first-line agent vemurafenib and the second-line agent ipilimumab in the treatment of advanced or metastatic melanoma, mean that direct comparisons of their safety profiles cannot be made.

On examination of the PI for vemurafenib, there appear to be BRAF inhibitor class effects that are shared with dabrafenib, specifically an increase in cutaneous skin cancers, ophthalmic reactions and potentially QT prolongation. This latter finding strengthens the need for further studies into the effect of dabrafenib on the QT interval in light of study results suggesting an association. Liver laboratory abnormalities are also listed as an adverse effect of vemurafenib, and this may also be associated with dabrafenib use. It is noted that there appears to be a decreased incidence of hypersensitivity, dermatologic and photosensitivity reactions with dabrafenib compared to vemurafenib, however a higher incidence of pyrexia, PPE and possibly cardiac valvular abnormalities that need to be monitored. No information was provided in the vemurafenib PI regarding potential adverse effects in the setting of brain metastases.

On examination of the PI for ipilimumab, the main AEs listed are those associated with inflammatory adverse reactions resulting from increased or excessive immune activity. These include serious immune-mediated gastrointestinal events, hepatotoxicity, skin toxicity, neurological events, and endocrinopathy. Therefore, the AE profile of ipilimumab is considerably different to that of dabrafenib, in keeping with their differing mechanisms of action. Comparison of the relative severity of the AE profile of these two agents was not performed, given the absence of head-to-head data.

First round benefit-risk assessment

First round assessment of benefits

The benefits of dabrafenib in the proposed usage are:

- Clinically relevant improvement in PFS was found in the BREAK-3 Study for subjects with BRAF V600E mutation-positive advanced or metastatic melanoma, excluding brain metastases. Compared to standard therapy with dacarbazine, treatment with dabrafenib 150 mg BID (HPMC capsules) resulted in an adjusted HR for PFS of 0.30 (95% CI: 0.18-0.51; $p < 0.0001$). These results were supported by the secondary outcomes of BREAK-3 and also the BREAK-2 Study, and some improvement in QoL measures was also observed. These benefits can be considered highly significant in light of the traditional poor prognosis of patients with metastatic melanoma disease.
- Although it would seem efficacious, due to the absence of a Phase III trial, it cannot definitively be concluded that dabrafenib is superior to currently used local therapies (surgery or SRS) in the management of BRAF V600E positive metastatic melanoma CNS lesions (which includes up to 70% of patients with metastatic melanoma).
- Evidence for the efficacy of dabrafenib in patients with BRAF V600K mutation positive metastatic melanoma is not convincing, and the clinical significance in this patient population remains undetermined. Particularly with respect to patients with BRAF V600K metastatic melanoma to the brain, there is no evidence of superiority of dabrafenib compared to appropriate local management (surgery or SRS).

First round assessment of risks

Overall, the risks of dabrafenib in the proposed usage generally appear to be manageable. These include:

- There is an increased risk of premalignant and malignant skin lesions (9%), which are managed adequately by early detection with regular dermatologic screening. However, the long term effects of dabrafenib on the rate and severity/aggressiveness of cutaneous malignancies are unknown.
- Dabrafenib treatment is associated with an increased risk of pyrexia (27%) which commonly occurs within 2 weeks of starting treatment. Pyrexia has the potential to be severe (18% of cases), which can have subsequently impact on other organ systems, although generally does not require discontinuation of treatment.
- An association between dabrafenib use and LVEH, cardiac valvular abnormalities and QTc prolongation cannot be excluded.
- Low grade PPE is associated with dabrafenib use.
- There is the potential serious risk of cerebral bleeding into responding CNS lesions with brain metastases. This risk may be greater when dabrafenib is used in conjunction with other therapies.
- From the summary of worst-case chemistry grade changes from baseline grade in BREAK-3 (safety population) and across dabrafenib studies (ISS safety population) there appears to be an association between use of dabrafenib and hyperglycaemia (observed in 48%) and hypophosphotaemia (observed in 35%).
- Haematological abnormalities are associated with dabrafenib use, although at rates lower than other cytotoxic chemotherapeutic agents.

- An association between the use of dabrafenib and small increases in hepatocellular and renal insufficiency cannot be excluded. Risk of renal failure may be increased in the setting of pyrexia.
- The PK of dabrafenib in ethnic groups other than Caucasians has not been studied and remains unknown. As these groups may have differing enzyme activity, due to a large proportion of dabrafenib being cleared by metabolism, there is risk of overexposure.

First round assessment of benefit-risk balance

The benefit-risk balance of dabrafenib is unfavourable given the proposed usage, but would become favourable if the changes recommended in the section on *First round recommendation regarding authorisation*, below, are adopted.

This is because although the balance of risks to benefits is favourable in subjects with BRAF V600E (and most-likely V600K) mutation-positive advanced or metastatic melanoma excluding brain metastases, there issues relating to patients with brain metastases which need to be further addressed by the sponsor. In addition, there are aspects of the PI for which modifications are recommended.[22]

First round recommendation regarding authorisation

- It is recommended that dabrafenib be registered for the treatment of BRAF V600E mutation-positive advanced or metastatic melanoma, excluding brain metastases, pending satisfactory address of the clinical questions (see below).
- It is recommended that more guidance be provided for the use of dabrafenib in the setting of BRAF V600E positive melanoma brain metastases. Specifically guidance is needed as to whether dabrafenib should be given following local management (surgery or SRS) that is deemed appropriate using current criteria which may be more efficacious, or whether other local treatments should be excluded due to the potential increased risk of SAEs. Additional recommendations and justifications are required, which may be result in refining the proposed indication.
- Due to the poor prognosis of metastatic melanoma and, until recently, the lack of an effective treatment, there may be a role for treatment of patients with BRAF V600K metastatic melanoma, provided the limitations in the evidence with regards to this patient subgroup are acknowledged and ongoing data is collected for further assessment. It is recommended that dabrafenib treatment of BRAF V600K metastatic melanoma to the brain should be subject to additional guidance as above.
- The efficacy of dabrafenib for other BRAF V600 mutation types (including V600D, V600G and V600R) have not been investigated, and are therefore undetermined, and therefore it is recommended that they be excluded from the indication.
- The proposed dosage regimen and formulation of dabrafenib 150 mg BID in HPMC capsules is acceptable.
- Changes to the PK section of the PI are recommended.

  Additional precautions are recommended for inclusion in the PI, including information on the risk of cardiovascular abnormalities, QT prolongation, cerebral haemorrhage in

[22] Details of recommendations regarding product literature including the PI are beyond the scope of the AusPAR.

bran metastases, use in hepatic impairment, and risk of hepatic and renal impairment.[23]

Clinical questions

Pharmacokinetics

- Is further analysis available from Study BRF113771 to better characterise the dose-proportionality of dabrafenib in HPMC capsules?
- It was reported in the Clinical Pharmacology Summary part of the submission that the CL/F of dabrafenib after repeat dosing at 150 mg BID was measured at 35 L/h in Study BRF113683 (BREAK-3), although no reference to this could be found in the study CSR. Could the sponsor please provide the supporting data for this claim?
- Due to extensive metabolism of dabrafenib, is additional information available on the impact of drug interactions and genetic or ethnic variations in metabolism? Are updated results available for the drug interaction Study BRF113771?
- Are interim results available for the studies investigating the PK of dabrafenib in subjects with hepatic and renal impairment?

Efficacy

- Please provide data on the updated OS at 12 months follow-up in Study BRF113710 (BREAK-2).
- Similarly, are updated OS data available for Study BRF113683 (BREAK-3)?
- The data on the efficacy of dabrafenib in subjects with BRAF V600K mutations is equivocal, and without head-to-head trials, what argument can be made for dabrafenib's superiority over conventional management, particularly in light of the improved outcomes with currently available therapies vemurafenib and ipilimumab?
- What is the justification for including all BRAF V600 mutation types in the indication in the absence of data for mutation types other than V600E and V600K?
- Can more information be provided to justify and specify the proposed use of dabrafenib in the setting of BRAF V600 positive melanoma brain metastases? Specific questions include whether dabrafenib should be used prior to, after, or instead of local management (surgery or SRS) that is deemed appropriate using current criteria. In addition, under what circumstances (such as degree of tumour burden) are the different treatments are deemed appropriate? These details may need to be specified under *Indications* in the PI.
- Are there any studies (clinical or nonclinical) or analyses currently in progress to assess the efficacy and safety of dabrafenib compared to now currently available newer treatments for advanced or metastatic melanoma, including the BRAF inhibitor vemurafenib or the monoclonal antibody ipilimumab? If so, when will results be available? If not, what is the justification for omission of these comparisons in light of the current availability of these agents?

[23] The section describing the evaluator's assessment and recommendations on the PI and other product literature is not included in the Extract.

Safety

- Are additional precautions or monitoring required in the setting of brain metastases to mitigate the potential effect of bleeding into CNS lesions? Are recommendations needed as to the use of other local therapies in the treatment of patients with brain metastases?
- Given the limitations of the exposure-QT analysis in Study BRF112680 (discussed in the section on *Safety* above and in the CER Attachment 2 of this AusPAR), is a more thorough QT study in progress or planned using the proposed dosage and formulation (150 mg BID, HPMC capsules)? What is the justification if not, given that the effect on QT interval will not have thoroughly been investigated at the proposed dosage and formulation when dabrafenib metabolites have a known effect on QT prolongation? Furthermore, is more information available from the pivotal BREAK-3 Study on QT prolongation, including analysis of central tendency: actual increase (mean and median), and uncorrected values and Fridericia's correction?
- Please provide data from Study BRF113683 (BREAK-3) to support the claim of an incidence of phototoxicity of 3% in the dabrafenib arm, as stated in the conclusions of the CSR.

Other

- Please provide an update on progress on the commercial availability of a diagnostic test for detection of BRAF V600E and V600K mutation types.

Second round evaluation of clinical data submitted in response to questions

The sponsor's responses to the above questions were assessed by the Delegate and are discussed in the Delegate's Overview for this application (see section on *Overall conclusion and risk-benefit assessment* below).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (Dabrafenib EU-RMP version 00 (data lock point 19 December 2011) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing safety Concerns, shown at Table 10.

Table 10. Summary of Ongoing safety Concerns

Important identified risks	Cutaneous Squamous Cell Carcinoma Non-infectious febrile events Renal failure Hypersensitivity Pancreatitis Uveitis Palmar-plantar erythrodysesthesia syndrome (PPES)
Important potential risks	New primary melanoma Non-cutaneous malignancies Pregnancy Testicular toxicity
Important missing information	Paediatrics Non-white population Subjects with moderate to severe hepatic or renal impairment

Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specification, it is recommended that the above summary of ongoing safety concerns is acceptable.

Pharmacovigilance plan

The proposed pharmacovigilance activities are summarised in Table 11.

Table 11. Proposed pharmacovigilance activities

Safety concern	Planned action(s)
Important identified risks	
Cutaneous Squamous Cell Carcinoma	Routine pharmacovigilance
Serious non-infectious febrile events	Routine pharmacovigilance Targeted follow-up questionnaire Exploratory research for mechanism of action (pre-clinical, clinical) for serious non-infectious febrile events.
Renal Failure	Routine pharmacovigilance Targeted follow-up questionnaire
Hypersensitivity	Routine pharmacovigilance

Safety concern	Planned action(s)
Pancreatitis	Routine pharmacovigilance Targeted follow-up questionnaire
Uveitis	Routine pharmacovigilance
PPES	Routine pharmacovigilance
Important potential risks	
New primary melanoma	Routine pharmacovigilance Targeted follow-up questionnaire
Non-cutaneous malignancies	Routine pharmacovigilance Targeted follow-up questionnaire
Pregnancy	Routine pharmacovigilance
Testicular toxicity	Routine pharmacovigilance
Important missing information	
Paediatrics	Routine pharmacovigilance Planned Study BRF116013 in paediatric and adolescent subjects with advanced BRAF V600 mutation-positive solid tumours, including melanoma. Potential Study BRF116356 depending on results of BRF116013.
Non-white population	Routine pharmacovigilance Ongoing Study BRF116056 in Japanese subjects with BRAF V600 mutation positive solid tumours.
Patients with moderate to severe hepatic or renal impairment	Routine pharmacovigilance Planned Study BRA115947 - National Cancer Institute (NCI)-sponsored Phase I and PK study.

Targeted questionnaires are proposed as enhanced routine pharmacovigilance for important potential risks 'serious non-infectious febrile events, 'renal failure' and 'pancreatitis' and important potential risks 'new primary melanoma' and 'non-cutaneous malignancies'. The draft questionnaires have been provided as an appendix to the Australian-specific annex and are acceptable.

For the important identified risk 'serious non-infectious febrile events' the sponsor has proposed "exploratory research for mechanism of action for serious non-infectious febrile events". The sponsor will be requested to elaborate on the nature of this proposed activity.

The Australian-specific annex indicates that 7 studies listed in the EU-RMP are relevant to Australian patients as part of the pharmacovigilance plan. The protocols for these studies have been provided. The evaluator has no objection to these studies as part of the specified pharmacovigilance plan.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation (that is, product labelling) is sufficient to mitigate the risks associated with dabrafenib. In the Australian-specific annex "educational activities" are proposed as additional risk minimisation but details are limited.

The evaluator has no objection to the proposed use of product labelling as routine risk minimisation.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted dabrafenib EU-RMP (version 00, data lock point 10 December 2011) and Australian-specific annex is applicable without modification in Australia unless so qualified; and the draft PI and Consumer Medicine Information (CMI) documents should not be revised until the Delegates Overview has been received:

1. Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA consolidated request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.
2. For the important identified risk 'serious non-infectious febrile events' the sponsor has proposed "exploratory research for mechanism of action for serious non-infectious febrile events". The sponsor should elaborate on the nature of this proposed activity.
3. The sponsor should provide more information on the planned educational activities including whether these are targeted to healthcare professionals, patients or both.

Second round review: OPR assessment of sponsor responses

Response to recommendation 1.

Comments on the Safety Specifications of the RMP in the clinical evaluation report were:

The Safety Specification in the draft RMP is not entirely satisfactory and should be revised, having regard to the comments below.

It is the opinion of the evaluator that the following potential risks should also be included in the Safety Specification of the dabrafenib RMP, taking into account the comments outlined in the CER:

- Cardiovascular adverse effects including reduced LVEF, cardiac valvular abnormalities and QT prolongation.
- Potential increased risk of cerebral haemorrhage with brain metastases.
- Increased risk of SAEs with brain metastases when other local therapies are used.

- Haematological abnormalities
- Hyperglycaemia and hypophosphataemia
- Non-white subjects – potential differences in PK metabolism

Comments on the Safety Specifications of the RMP in the nonclinical evaluation report were:

> The sponsor has provided the EU RMP for dabrafenib together with an Australian Specific Annex. The results and conclusions drawn from the nonclinical program for dabrafenib detailed in the *Table on Safety Concerns from Nonclinical Studies* in the Safety Specifications section of the Risk Management Plan are in general concordance with those of the nonclinical evaluator.
>
> In the response to TGA questions, the sponsor described findings of juvenile rat toxicity studies in the updated RMP. The juvenile toxicity studies (except the dose range-finding study) have not been provided to TGA for review. Thus, the nonclinical evaluator cannot confirm adequacy of the statements.

OPR assessment of sponsor responses to the clinical and nonclinical comments on the safety specification

The issues of cardiovascular safety and lack of data in non-White subjects appears to have been addressed in an RMP update (see below) provided in response to the OPR recommendations. However the following risks suggested by the clinical evaluator do not appear to have been included in the revised RMP:

- Potential increased risk of cerebral haemorrhage with brain metastases.
- Increased risk of SAEs with brain metastases when other local therapies are used.
- Haematological abnormalities
- Hyperglycaemia and hypophosphataemia

It is noted that the sponsor has provided additional responses to the clinical evaluator's recommendations that will be reviewed by the Delegate. Should the Delegate find the responses unsatisfactory it is recommended that these risks are appropriately addressed in the RMP.

In addition, the sponsor has advised that the EU RMP has been updated to the new EU format. Changes were made as a result of a safety update and these are summarised in Table 12.

Response to recommendation 2

Requested information was provided and is acceptable.

Response to recommendation 3

The sponsor provided information on a planned educational program that would commence during preparations to launch the product in Australia. Although the exact details are yet to be determined, some information was provided on the proposed educational activities under consideration. The OPR evaluator considered the activities were reasonable. Once they are decided upon an overview of the education program should be included in an update to the ASA.

Updated RMP

In their response to the OPR recommendations, the sponsor provided an updated EU-RMP (version 1, dated 12 February 2013, data lock point 19 December 2011) + Australian-specific Annex (undated). Key changes from the version provided originally in the submission and evaluated at Round 1 are summarised below:

Table 12. Key changes in the updated RMP

Safety specification	Primary melanomas and non-cutaneous recurrent/secondary malignancies have been changed from potential to identified risks. The following potential risks have been added: Increased risk for Grade 3 or 4 AEs, SAEs or dose adjustment in elderly population (≥65 years) Off-label use in resectable/resected melanoma, non-melanoma tumours harbouring a BRAF V600-mutation, in combination with other anti-cancer agents, or when non-validated tests are used Paediatric effects Drug-drug interactions The following important missing information have been added: Use in patients with Class II, III, or IV heart failure (NYHA functional classification system) Safety in patients with severe renal impairment Safety in patients with moderate to severe hepatic impairment Use in Non-White population Developmental toxicity and risks in lactation Use in patients with reduced cardiac function Potential for QT prolongation Risks in patients with ECOG[24] 2-4 Ability to detect adverse reactions which are rare
Pharmacovigilance activities	A QT study is ongoing to evaluate QT effects
Risk minimisation activities	Pancreatitis has been included under the *Precautions* section of the draft PI.

Notwithstanding the clinical evaluator's recommendations regarding the Safety Specifications (see above) the OPR evaluator had no objection to the above changes and recommended to the Delegate that the updated version is implemented.

[24] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used: 0 - Fully active, able to carry on all pre-disease performance without restriction; 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5 – Dead

OPR recommendation

- Implement dabrafenib EU-RMP (version 1, dated 12 February 2013, data lock point 19 December 2011) with Australian-specific Annex (undated) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

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

Introduction

The sponsor has applied to register dabrafenib mesilate, 50 mg and 75 mg capsules, for the indication:

> *Tafinlar is indicated for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV) melanoma.*

The proposed dose regimen is 150 mg BID. Each dose should be taken ≥1 h before or 2 h after a meal, with approximately 12 h between doses. Treatment should continue until disease progression or unacceptable toxicity.

Targets and mechanism of action

Dabrafenib mesilate is a synthetic small molecule (molecular weight 616 g/mol) inhibitor of BRAF and some other kinases. It has little structural similarity to registered kinase inhibitors (such as vemurafenib).

BRAF is part of the RAS/RAF/MEK/ERK (MAPK) pathway.[25] Derangements of the ERK1/2 MAPK cascade have been implicated in many cancers, particularly melanoma.

Dabrafenib inhibits wild-type and mutant BRAF as well as CRAF. IC_{50} values were similar for BRAF V600E and BRAF V600K. A low IC_{50} does not translate to pathway inhibition; *"ATP-competitive kinase inhibitors can have opposing functions as inhibitors or activators of signalling pathways, depending on the cellular context"* (and genotype).[26]

Eight other kinases were inhibited (IC_{50} < 100 nM) in a nonclinical screen.[27] There was little activity against a broad panel of other proteins.

Melanoma

If there is regional lymph node involvement (but no distant metastasis) Stage III is assigned. If there is distant spread, Stage IV is assigned. 10-13% of melanoma patients present with regional disease and 2-5% present with distant metastatic disease. In the NCCN guidelines (ME-10), distant metastatic disease is characterised on the basis of appropriate investigations as "limited (resectable)" or "disseminated (unresectable)".

In 45-60% of metastatic melanomas (but a slightly lower fraction of primary melanomas), BRAF is mutated, resulting in constitutive activation of the pathway. Long *et al.*[28] characterise BRAF mutant metastatic melanoma in 197 Australian patients. Median

[25] Qi and Elion. MAP kinase pathways. *J Cell Science* 2005; 118 (16):3569-3572
[26] Hatzivassiliou G *et al*. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature* 2010;464 (7287):431-435.
[27] These were: BRK; LIMK1; NEK11; PKD2; SIK1; ALK5; CK1; SIK2
[28] Long GV *et al*. Prognostic and clinicopathological associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol* 2011;29:1239-1246.

survival in patients newly diagnosed with distant metastases and not treated with BRAF inhibitors was reported as 5.7 months for those with BRAF mutations and 8.5 months for those without, although the analysis was biased by criteria used to decide whether BRAF inhibition should be used.

Of BRAF mutations in melanoma, 70-90% are V600E and 10-30% are V600K. V600R mutations may account for 3-7%. It is claimed that in older patients or those with evidence of chronic sun damage at the site of the primary cutaneous melanoma, V600K may be more prominent than in younger patients or those without chronic sun damage[29] (frequency would still be < 30% of BRAF mutations).

Melanoma treatment has advanced with availability of ipilimumab (an anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody that enhances T-cell mediated immune responses) and vemurafenib (a BRAF inhibitor).

- Ipilimumab is indicated as monotherapy in patients with unresectable or metastatic melanoma who have failed or are intolerant to prior therapy.
- Vemurafenib is indicated in patients with unresectable stage IIIC or stage IV metastatic melanoma positive for BRAF V600 mutation.

Use of vemurafenib is discouraged in wild-type BRAF melanoma. Preclinical models show that BRAF inhibitors can enhance the MAPK pathway in tumour cells with wild-type BRAF and upstream RAS mutations.[30] 20% of metastatic melanomas may have NRAS mutations; tumours with NRAS mutations and BRAF mutations are usually mutually exclusive (Jakob *et al.,* 2012[31]).

Sorafenib also inhibits BRAF V600E kinases but is not indicated in melanoma.

Agents currently approved for treatment of advanced melanoma in Australia include dacarbazine, fomustine and temozolomide.

TGA guidelines

The TGA has adopted the EMA's *Guideline on the Evaluation of Anticancer Medicinal Products in Man* and appendices.

Overseas status

The EU application was under review as of 19 June 2013. The FDA approved dabrafenib on 29 May 2013, with the following indication: *Tafinlar is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.*

The FDA-approved indication limits usage to those patients with V600E-mutant tumours.

Quality

The Module 3 (chemistry, quality, pharmaceutics and bioavailability) evaluation drew attention to several topics:

[29] Klein O *et al*. BRAF inhibitor activity in V600R metastatic melanoma. *Eur J Cancer* 2013;49:1073-1079
[30] National Cancer Institute. General information about melanoma. <http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/HealthProfessional> page9
[31] Jakob JA, Bassett RL Jr, Ng CS *et al*. NRAS mutation status is an independent prognostic factor in metastatic melanoma. *Cancer*. 2012; 118: 4014-4023.

- Dabrafenib mesilate solubility is poorly documented, but it is very slightly soluble in acid and essentially insoluble at higher pH. There is thus a possibility that bioavailability will be reduced in achlorhydric or hypochlorhydric patients.

This issue is addressed in the most recently proposed PI.

- GlaxoSmithKline has proposed that it is not necessary to routinely control related substances in batches of capsules at release. In keeping with PSC advice this is not considered appropriate and will be resolved with the sponsor or made a condition of registration.
- The sponsor is also negotiating with Module 3 evaluators regarding inclusion of a microbial limit in the drug product release specification.

While noting the need to finalise some pharmaceutical aspects (as per above), registration was recommended with regard to chemistry, quality control and bioavailability aspects.

Nonclinical

The nonclinical evaluator supported registration.

The evaluator identified testicular toxicity as a potentially relevant clinical issue; there was no significant reversal during the recovery period. Fetal and developmental toxicity were also identified; the evaluator supported the sponsor's proposal of Pregnancy Category D.

Clinical

Overview of studies

Table 13. Overview of key studies

Study name	Regulatory significance	Description / comment
BRF113683 ("BREAK-3")[32]	Pivotal	Two arm, open label, Phase III. Randomisation (3:1) to oral dabrafenib 150 mg BID (n=187) versus IV dacarbazine (n=63). HPMC formulation. Treatment-naïve, BRAF V600E, unresectable Stage III or metastatic (Stage IV) melanoma. Exclusion of patient with brain metastases.
BRF113710 ("BREAK-2")	Supportive	Single-arm, open label, Phase II. 150 mg BID. 92 patients studied. Gelatin formulation. Treatment naïve or experienced, BRAF V600 (E or K) Stage IV melanoma. Exclusion of patients with brain metastases.
BRF113929 ("BREAK-MB")	Supportive	Single-arm, open label, Phase II. 150 mg BID. HPMC. BRAF V600 (E or K) Stage IV melanoma with brain metastases. Two cohorts: prior local therapy for

[32] Hauschild A *et al*. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012:380;358-365

Study name	Regulatory significance	Description / comment
		brain metastases (n=89) and no prior local therapy (n=83).
BRF112680[33]	Dose-finding; PK data	First-time-in-human. Open-label. Cohorts dosed from 12 mg once daily (OD) to 300 mg BID; individuals could escalate dose after 9 weeks. Part 2 used 150 mg BID and 50 mg BID dosing. Gelatin formulation. BRAF-mutation-positive solid tumours (n=184), including n=156 with melanoma.
BRF113771	PK data	Relevant outcomes given dose (150 mg) and formulation (HPLC).

There were six clinical pharmacology studies (including BRF112680 and BRF113771), but one (BRF13220; PK of dabrafenib in combination with trametinib[34]) was not considered relevant by the clinical evaluator.

There was a population PK analysis, an analysis of dabrafenib metabolites and an exposure/response analysis.

There were three other studies with clinical safety data (BRF113220 in combination with trametinib; BRF113928 in non small cell lung cancer (NSCLC); rollover Study BRF114144).

Formulation

An HPLC formulation is proposed for marketing; this was used in BREAK-3 and BREAK-MB. BREAK-2 used a gelatin formulation. There was no formal study of bioequivalence of gelatin and HPLC capsules; AUC was approximately 1.8-fold higher in patients given the HPMC capsule than in patients given the gelatin capsule. Based on population PK results, the difference may be smaller with repeat dosing. The gelatin capsule shells were replaced with HPMC because of the latter's better dissolution stability (a decrease in dissolution over time was seen with gelatin capsules).

Pharmacokinetics

Some characterisation of PK was via a population PK analysis. The pivotal and supportive efficacy studies above contributed data to the population PK analysis via sparse sampling in subsets; sampling was more comprehensive in BRF112680 (gelatin).

Population PK analysis excluded data from BRF113771. BRF112680 (gelatin; data in population PK analysis) showed a less than dose-proportional increase in AUC. In BRF113771 (HPLC; data not in population PK analysis) increasing dose resulted in a more proportionate increase in AUC.

Key PK features are:

- High bioavailability (94.5%[35]) suggests low first-pass metabolism (Study BRF113479). Administration with food slows and reduces absorption (BRF112680 [gelatin

[33] Falchook GS *et al*. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet* 2012;379:1893-901
[34] Flaherty KT *et al*. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *NEJM* 2012;367:1694-1703
[35] The Module 3 evaluator suggested this was perhaps an overestimate due to reduced exposure with IV administration after complexation

formulation], BRF113468 [HPLC formulation]. The PI recommends taking the drug, which is administered BID, fasted.

- With repeat dosing, AUC and half life decline relative to single dose PK, due to autoinduction of CYP3A4. Induction of CYP3A4 enzymes was confirmed in a study using midazolam as a probe substrate. Steady state dabrafenib levels were predicted to occur within 14 days, as was steady state for the induction of CYP3A4.
- Dabrafenib is extensively metabolised and has active metabolites. It is metabolised by CYP3A4 and CYP2C8 to hydroxy-dabrafenib. This is metabolised by CYP3A4 to carboxy-dabrafenib. This is decarboxylated to desmethyl-dabrafenib, by a non-CYP enzyme -mediated pathway. Clearance was conceptualised as via non-inducible and inducible (enzyme-mediated) mechanisms (population PK study). Renal excretion is minimal.
- There are no data on use in severe hepatic impairment. Population PK analysis included n=65 (10.9%) with mild impairment and only n=3 with moderate impairment. The analysis found that mild impairment did not influence PK; it did not address moderate impairment. A dedicated study is being conducted by the NCI (BRA115947; final report due 2015).
- There are no data on use in severe renal impairment. Population PK analysis included n=233 (39.2%) with mild impairment and n=30 (5%) with moderate impairment. Analysis found that mild to moderate impairment (to glomerular filtration rate (GFR) 30 mL/min/1.73 m^2) did not influence PK. A study in severe impairment is being conducted (BRA115947).
- Clearance was lower in females in the population PK analysis; dabrafenib trough concentration (C_{trough}) in particular was 26% higher than in males, although AUC was only 9% higher.
- Weight influenced PK in the population PK analysis; the effect was not considered relevant by the sponsor using a reference weight of 80 kg since "even at body weight of 40 kg, the difference in exposure in a typical individual would average 26%".

The potential for clinically relevant drug interactions was characterised, to an extent:

- Effects of some drugs on dabrafenib were characterised in Study BRF113771. Ketoconazole (a potent CYP3A4 inhibitor) may increase dabrafenib AUC by 71% and C_{max} by 33%. Effects were also observed on dabrafenib metabolites. Gemfibrozil (a CYP2C8 inhibitor) may increase dabrafenib AUC by 47% (but not C_{max}).
- Dabrafenib is a P-gp substrate, and a BCRP substrate.
- Dabrafenib induces CYP3A4 and CYP2C9, and possibly other enzymes. Dabrafenib may reduce warfarin AUC by about one third (C_{max} may rise slightly); warfarin is a CYP2C9 substrate. Likewise, dabrafenib reduces the AUC of midazolam (a CYP3A4 substrate).

Efficacy

Dose selection

The reasoning behind the choice of dose in the pivotal study was not entirely clear.

- Dose-finding relied on BRF112680 (gelatin formulation). A 150 mg BID dose was chosen for further investigation, prior to results of the 300 mg BID cohort becoming available.
- The 300 mg BID cohort achieved higher OR rates (70%) than the 150 mg BID cohort (44%), although toxicity was higher too.

- The 150 mg BID dose was extrapolated to HPMC capsules, despite the gelatin formulation having lower bioavailability.

In terms of efficacy, there is evidence that most patients treated at 150 mg BID in the pivotal study were already at the top of the exposure-response curve.

BREAK-3 (BRF113683)

This was an open-label, randomised, Phase III study of patients with BRAF V600E mutation positive, treatment naïve, advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. The study was designed to show superiority of dabrafenib over dacarbazine. Four Australian centres enrolled 16 of 250 subjects. The study was initiated on 2 February 2011; the data cut-off was 19 December 2011 and results here are from that cut-off unless otherwise specified. The sponsor provided some updated outcomes based on June 2012 and December 2012 cut-offs.

Inclusions and exclusions are noted in the CER (Attachment 2 of this AusPAR). Patients had good Eastern Cooperative Oncology Group performance status (ECOG 0-1). The study excluded patients with active brain metastases and patients with cardiac abnormalities (such as low LVEF or New York Heart Association (NYHA) Class II-IV heart failure; QTc ≥ 480 ms; recent arrhythmias; recent acute coronary syndromes or angioplasty/stenting; valve abnormalities). Prior treatment with IL-2, surgery and/or radiotherapy was allowed.

After screening 733 subjects, a total of 250 subjects were randomised (3:1) to receive:

- Oral dabrafenib 150 mg BID (HPMC capsules) daily, fasted (1 hour before or 2 hours after a meal)
- IV dacarbazine 1000 mg/m^2 every 3 weeks

187 subjects received dabrafenib and 63 received dacarbazine. After disease progression, 28/63 dacarbazine arm patients crossed over to receive dabrafenib (using the December 2012 cut-off, this had risen to 36/63).

Subjects in the dabrafenib arm were slightly older. Almost all subjects had Stage IV disease (94-96%); most had multiple metastatic sites. About a quarter of subjects had already received interferon.

Progression-free survival

The primary endpoint was PFS determined by the investigator. A summary of the results is shown in Table 14 and Figure 3.

Table 14. Efficacy results for BREAK-3 (pivotal study in metastatic melanoma; ITT population)

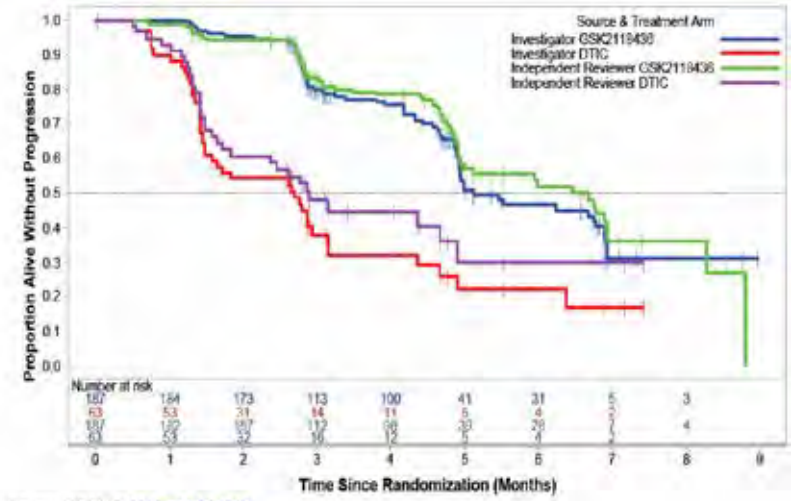
Endpoints/ Assessment	Dabrafenib N=187	DTIC N=63
Progression-free survival		
INV-assessed, median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR (95% CI)	0.30 (0.18, 0.51) p<0.0001	
IRC-assessed, median, months (95% CI)	6.7 (5.0, 6.9)	2.9 (1.7, 4.9)
HR (95% CI)	0.35 (0.20, 0.61)	
Overall survival		
% at 6 months[a] (95% CI)	87 (79.2, 91.9)	79 (59.7, 89.5)
HR (95% CI)	0.61 (0.25, 1.48)	
Overall response[b]		
INV-assessed[c], % (95% CI)	53 (45.5, 60.3)	19 (10.2, 30.9)
IRC-assessed[c], % (95% CI)	50 (42.4, 57.1)	6 (1.8, 15.5)
Overall response duration		
INV-assessed[c]	N=99	N=12
Median, months (95% CI)	5.6 (4.8, NR)	NR (5.0, NR)
IRC-assessed[c]	N=93	N=4
Median, months (95% CI)	5.5 (5.0, 6.7)	NR (NR, NR)

Source: BRF113683 CSR Section 6.2.1 and BRF113683 Table 15, Table 16, Table 17, Table 18 and Table 19, BRF113683 Table 7.4003 and Table 7.4005

Abbreviations: CI: confidence interval; DTIC: dacarbazine; HR: hazard ratio; INV: investigator-assessed; IRC: independent review committee; NR-not reached

a. Estimated from Kaplan-Meier estimates at 6 months; overall survival data are not yet mature and median overall survival has not been reached for either arm
b. Defined as complete response+partial response.
c. Confirmed response.

Figure 3. Efficacy results for BREAK-3 (pivotal study in metastatic melanoma; ITT population)



Source: BRF113683 Figure 17.1010

Abbreviations: DTIC: dacarbazine; GSK2118436: dabrafenib

The HR for PFS was 0.30 in favour of dabrafenib (95% CI 0.18-0.51), with median PFS 5.1 months for the dabrafenib arm versus 2.7 months for the dacarbazine arm. Blinded review supported investigator assessment of PFS. Results were robust to sensitivity analyses.

There was no suggestion of particularly worse dabrafenib efficacy relative to dacarbazine in any tested subgroup.

An exposure-response analysis found that lactate dehydrogenase (LDH) level and BRAF V600 mutation type were significant covariates in PFS and OS analyses.

An updated analysis (June 2012 cut-off, that is, 6 months further follow-up) was provided in the evaluation phase. The updated analysis shows median PFS for dabrafenib of 6.9 months, and for dacarbazine still 2.7 months; the HR is 0.37 (95% CI 0.24-0.58).

Overall survival

Overall survival data were immature at the data cut-off, that is, median OS had not been reached in either arm. OS was 87% at 6 months in the dabrafenib arm, and 79% in the dacarbazine arm (including cross-over subjects, obscuring any actual difference), with a HR not statistically significantly different from 1, at 0.61 (95% CI, 0.25-1.48).

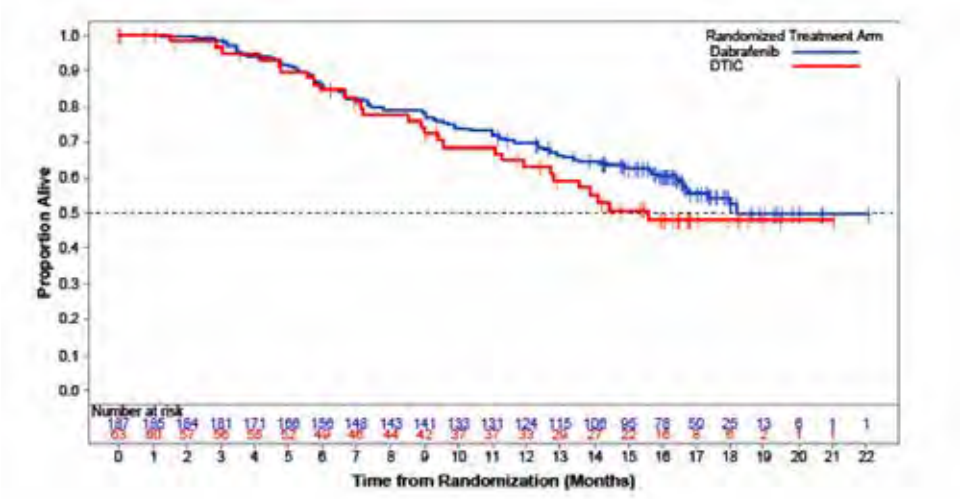
Overall survival may be influence by subsequent treatments (see above for cross-over to dabrafenib in the dacarbazine arm). As of the initial data cut-off, 23% of the dacarbazine arm and 15% of the dabrafenib arm had received follow-up anti-cancer therapy other than dabrafenib. Updated survival results were presented during the evaluation phase (Table 15 and Figure 4).

Table 15. Updated survival data for BREAK-3. Survival analysis results from the primary and post-hoc analyses (ITT)

Cut-off dates	Treatment	Number of deaths (%)	Median	Hazard Ratio (95% CI)	Number of cross-over subjects (%)
December 19, 2011	DTIC	9 (14%)	NR [NR, NR]	0.61 (0.25, 1.48) (a)	28 (44%)
	dabrafenib	21 (11%)	NR [NR, NR]		
June 25, 2012	DTIC	21 (33%)	NR[NR, NR]	0.75 (0.44, 1.29) (a)	35 (56%)
	dabrafenib	55 (29%)	NR [11.3,NR]		
December 18, 2012	DTIC	28 (44%)	15.6 [12.7, NR]	0.76 (0.48, 1.21) (a)	36 (57%)
	dabrafenib	78 (42%)	18.2 [15.6, NR]		

(a) Subjects were not censored at the time of cross-over

Figure 4. Updated survival data for BREAK-3. Kaplan-Meier curves based on 18 December 2012 data (ITT)



Response rate and durability

Objective response rate (ORR) was a secondary endpoint. It clearly favoured dabrafenib (Table 14). An update (June 2012 cut-off) showed similar results, but median duration of response was updated to 8.0 months for dabrafenib and 7.6 months for dacarbazine.

Quality of life

Quality of life was measured using several questionnaires. There was a suggestion of improved QoL in the dabrafenib arm.

BREAK-2 (BRF113710)

This uncontrolled Phase II study of adults with BRAF V600E or V600K mutant, Stage IV melanoma used the 150 mg BID dose regimen but with the gelatin capsule formulation (lower bioavailability). 211 subjects were screened and 92 metastatic melanoma subjects were enrolled; both treatment-naive and previously treated patients were enrolled (but those with active CNS disease were excluded). The study does provide some data about use in patients with V600K mutations (n=16). Key results are tabulated in Table 16; ORR was the primary endpoint.

Table 16. Key efficacy data from the supportive Study BREAK-2 (All treated subjects)

Endpoints/ Assessment	BRAF V600E (Primary) N=76	BRAF V600K N=16
Overall response		
INV-assessed[a], % (95% CI) **IRC-assessed**[a], % (95% CI)	59 (48.2, 70.3) 41 (29.7, 51.8)	13 (0, 28.7) 25 (3.8, 46.2)
Response duration		
INV-assessed Median, months (95% CI)	N=45 5.2 (3.9, NR)	N=2 5.3 (3.7, 6.8)
IRC-assessed Median, months (95% CI)	N=31 6.2 (5.1, NR)	N=4 5.0 (3.4, NR)
Progression-free survival		
INV-assessed, median, months (95% CI)	6.3 (4.6, 7.7)	4.5 (2.6, 6.2)
IRC-assessed, median, months (95% CI)	6.1 (4.6, NR)	4.5 (2.6, 6.2)
Overall survival		
Primary analysis at 6 months follow-up, median, months (CI)	9.5 (9.5, NR)	7.9 (5.5, NR)
Updated analyses at 12 months follow-up[b], median, months (CI)	13.1 (10.4, NR)	12.9 (6.9, 17.1)

Source: BRF113710 CSR Table 13, Table 14, Table 15; BRF113710 Table 7.106, Table 7.107, Table 7.108, Table 7.109 Table 7.110, Table 7.112, Table 7.113, Table 7.114, Table 7.115; Table 7.16, Table 7.17, Table 7.18, Table 7.19

Abbreviations: CI: confidence interval; INV: investigator-assessed; IRC: independent review committee; NR-not reached

a. Confirmed response.
b. Updated analyses at 30 April 2012 data cut-off.

Investigator-assessed ORR and PFS results in patients with V600E mutations were better than in BREAK-3 (despite the formulation difference and despite 74/92 subjects in BREAK-2 receiving prior treatment).

Results in patients with V600K mutations were worse than in those with V600E mutations (for example, investigator-assessed ORR, 13% versus 59%; investigator-assessed median PFS 4.5 months versus 6.3 months), but few V600K patients were assessed.

BREAK-MB (BRF113929)

This uncontrolled but relatively large Phase II study used the HPMC capsule. It allowed study of efficacy in patients with brain metastases, and allowed study of the HPMC formulation in V600K mutation positive patients (with brain metastases). The primary endpoint was overall intracranial response rate in V600E positive patients. Results are shown in Table 17, broken down by V600E versus V600K and whether patients had received prior local therapy for brain metastases or not.

Table 17. Key efficacy data from the key Study BREAK-MB (All treated subjects)

	BRAF V600E (Primary)		BRAF V600K	
Endpoints/ Assessment	**Cohort A N=74**	**Cohort B N=65**	**Cohort A N=15**	**Cohort B N=18**
Overall intracranial response rate, % (95% CI)				
INV-assessed[a]	39 (28.0, 51.2)	31 (19.9, 43.4)	7 (0.2, 31.9)	22 (6.4, 47.6)
IRC-assessed[a]	20 (11.8, 31.2)	18 (9.9, 30.0)	0 (0, 21.8)	11 (1.4, 34.7)
Overall intracranial response duration, median, months (95% CI)				
INV-assessed	N=29 4.6 (2.8, NR)	N=20 6.5 (4.6, 6.5)	N=1 2.9	N=4 3.8 (NR, NR)
IRC-assessed	N=15 4.7 (4.5, 6.5)	N=12 4.6 (4.2, 4.6)	NA	N=2 NR
Overall response, % (95% CI)				
INV-assessed[a]	38 (26.8, 49.9)	31 (19.9, 43.4)	0 (0, 21.8)	28 (9.7, 53.5)
IRC-assessed[a]	28 (18.5, 40.1)	23 (13.5, 35.2)	0 (0, 21.8)	11 (1.4, 34.7)
Overall response duration, median, months (95% CI)				
INV-assessed	N=28 5.1 (3.7, NR)	N=20 4.6 (4.6, 6.5)	NA	N=5 3.1 (2.8, NR)
IRC-assessed	N=21 4.6 (4.3, NR)	N=15 4.6 (2.8, NR)	NA	N=2 NR
Progression-free survival, median, months (95% CI)				
INV-assessed	3.7 (3.6, 5.0)	3.8 (3.6, 5.5)	1.9 (0.7, 3.7)	3.6 (1.8, 5.2)
IRC-assessed	3.6 (2.6, 5.2)	3.7 (3.5, 3.8)	1.8 (0.7, 1.9)	3.5 (1.9, 5.6)
Overall survival				
Median, months (95% CI)	7.6 (5.9, NR)	7.2 (5.9, NR)	3.7 (1.6, 5.2)	5.0 (3.5, NR)

Source: BRF113929 CSR Table 11 to Table 12 and Table 20 to Table 21; BRF113929 Table 7.2005, Table 7.2006, Table 7.3005, Table 7.3006, Table 7.6005, Table 7.6006, Table 7.7003, Table 7.7004, Table 7.8013, Table 7.8014, Table 7.8015, Table 7.8016, Table 7.9009, Table 7.9010

Abbreviations: CI: confidence interval; INV: investigator-assessed; IRC: independent review committee; NA: not applicable; NR: not reached

a. Confirmed response.

Cohort A: subjects with no prior local therapy for brain metastasis.

Cohort B: subjects who received prior local therapy for brain metastasis.

PFS was distinctly lower in this study, most notably in the small number of V600K patients with no prior local therapy. Outcomes based on independent review were less favourable than those based on investigator assessment; a third party's position aligned with the investigator in 68% of cases.

There was concomitant use of corticosteroids in 36% (Cohort A, no prior local therapy for brain metastases) and in 49% (Cohort B, failed prior therapy). The clinical evaluator noted that dexamethasone, which is commonly used, is a CYP3A4 substrate, and that dabrafenib is also metabolised by CYP3A4.

The evaluator commented that it is not possible based on BREAK-MB to assess efficacy of dabrafenib in CNS metastases relative to techniques such as stereotactic radiosurgery. Evidently these techniques would supplement therapy for extracranial disease.

Overall, BREAK-MB provided evidence of activity in CNS disease, and also confirmed a lower response in V600K tumours.

In Study 112680, 9/10 subjects with asymptomatic, untreated brain metastases had a decrease in brain lesion size, and 4/10 achieved complete resolution of all brain lesions; it may be that subjects in BREAK-MB had more advanced CNS lesions, that were less likely to resolve completely.

Safety

The integrated safety population was N=578, including n=178 from BREAK-3. Patients in BREAK-2 and BREAK-MB were included, as were patients in BRF112680 and BRF113220 (dabrafenib + trametinib, but with a dabrafenib monotherapy arm). Exposure is described in the CER (see Attachment 2 of this AusPAR); Table 18 describes exposure by duration on therapy (n=161 subjects received the proposed dose for ≥6 months).

Table 18. Exposure to dabrafenib in clinical studies according to dose and duration: proposed dose range = proposed maximum dose = 150 mg BID.

Study type/Indication	Proposed dose range = Proposed maximum dose			
	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any duration
Clinical pharmacology				
BRF112680	53*	30*	5*	70*
Stage III & IV melanoma, treatment naive				
Active-controlled BREAK-3	154	49	0	187
Subtotal Indication 1				
Stage III & IV melanoma, dabrafenib crossover from dacarbazine or previous other treatment				
Uncontrolled BREAK-3 crossover	13	2	0	28
Uncontrolled BREAK-2	69*	40*	0	92*
Uncontrolled BRF113220	n/a	n/a	n/a	53*
Subtotal Indication 2				
Melanoma CNS metastases				
Uncontrolled BREAK-MB	116	40	0	172
Subtotal Indication 2				
Other cancer indications				
Uncontrolled BRF113928	n/a	n/a	n/a	5
Uncontrolled Rollover BRF114144	n/a	n/a	n/a	98*
Subtotal Indication 2				
TOTAL	405	161	5	705

* Gelatine capsules: Note different drug formulations in different studies and impact on development of AEs.

A summary of AEs in BREAK-3 is shown in Table 19.

Table 19. Summary of Adverse Events (AEs) in BREAK-3

	dabrafenib	dacarbazine
Grade 3, 4 or 5 AEs	34%	44%
Serious AEs	23%	22%
Related Serious AEs	15%	3%
Discontinuation due to AEs	3%	3%

Deaths

In BREAK-3, 11% of dabrafenib recipients and 15% of dacarbazine recipients died, almost all due to metastatic melanoma. In the supportive studies, higher proportions of subjects had died by data cut-offs, but almost all deaths were attributed to disease progression.

Common AEs

In BREAK-3, common AEs in the dabrafenib arm were hyperkeratosis (37%), headache (32%), pyrexia (28%), arthralgia (27%), skin papilloma (24%), alopecia (22%) and PPE syndrome (20%). The profile was distinct from that of dacarbazine.

More frequent severe AEs in the dabrafenib arm were pyrexia (3%), SCC (3%), back pain (3%), hypophosphataemia (2%) and PPE syndrome (2%). Decreased white and red cells and platelets were common severe AEs for dacarbazine.

Notable AEs

Nervous system events

In BREAK-MB, 10 subjects had CNS haemorrhage. The evaluator raises concerns about haemorrhage into responding lesions (a case study is described in the CER (Attachment 2 of this AusPAR); another case was reported by Klein *et al.*[36] as 'unrelated' to dabrafenib). This may be an issue if alternative treatments do not pose such a risk. The sponsor states there is a historical rate for spontaneous haemorrhage of melanoma brain metastases of 14-35% for other treatments.

Premalignant and malignant skin lesions, and other malignancies

These have been encountered with vemurafenib. In BREAK-3, 9/187 patients developed SCC, all treated and resolving without dose modification. No dacarbazine patients developed SCC. Actinic keratoses and keratoacanthomas were also observed in the dabrafenib arm but not in the dacarbazine arm.

It has been reported that BRAF inhibitors increase ERK phosphorylation in cell lines with wild-type BRAF that harbour upstream pathway activation (such as oncogenic RAS) ("paradoxical MAP kinase pathway activation"[37]). The implication is that if a cell harbours a RAS mutant (or any other upstream pathway activating mutation, for example, in epidermal growth factor receptor; EGFR), dabrafenib exposure may drive proliferation of the cell, and accelerate tumour formation.

Three subjects were reported to have new primary melanomas, 5 to have basal cell carcinomas (BCCs) and 1 to have mycosis fungoides, all in the dabrafenib arm. A new

[36] Klein O *et al*. BRAF inhibitor activity in V600R metastatic melanoma. *Eur J Cancer* 2013;49:1073-1079
[37] Su F *et al*. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. *NEJM* 2012;366: 207-215. It has been reported that "inhibitor binding activates wild-type RAF isoforms by inducing dimerization, membrane localization and interaction with RAS-GTP" (Hatzivassiliou *et al* 2010).

primary melanoma is discovered in 6% of subjects in the year following diagnosis of melanoma, so it is possible that these occurrences are the result of study in a sun-exposed population predisposed to melanoma. A role for dabrafenib has not been excluded. The sponsor should check new melanomas in ongoing clinical trials for oncogenic RAS status, if possible. Oncogenic RAS is also seen in some BCCs.

Acute myeloid leukaemia(AML): In BREAK-2, a subject discontinued dabrafenib after developing AML. RAS-mutant leukaemia was reported after treatment with vemurafenib.[38] RAS status was not tested in the AML subject in BREAK-2.

Cardiac

Abnormal ejection fraction. Left ventricular ejection fraction was below the lower limit of normal in 4/187 dabrafenib subjects and 0/59 dacarbazine subjects; but otherwise differences across arms in this regard were minimal. In BREAK-3, there was a slight decrease in diastolic blood pressure (BP) and a decrease in systolic BP of 4-10 mmHg, with magnitude increasing over time.

Valvulopathy. There was a modest signal in dogs of hypertrophied atrioventricular valves. In clinical studies, two valvular changes were possibly related to dabrafenib, including one case of moderate thickening of the aortic valve. Also, tricuspid valve disease in a dabrafenib patient led to discontinuation.

QT prolongation. Analysis of BRF112680 linked 'exposure to dabrafenib metabolites' and QT prolongation, but magnitude of effect was not large. Actual QT prolongation was similar in frequency and extent across arms in BREAK-3. There was no pre-clinical signal of QT prolongation. The sponsor has initiated Study BRF113773 to assess cardiac repolarisation in subjects with BRAF mutant tumours (report due late 2014).

Pyrexia

Pyrexia was a prominent AE. Six of 187 patients had grade 3 pyrexia (readings reached 40.2°C), and 5/187 had pyrexia lasting > 10 days. Most events resolved. Pyrexia was a common cause of dose interruption (about 10% of patients) and dose reduction (about 5% of patients). In exposure-response analysis, higher exposure was associated with a higher rate of pyrexia.

The sponsor has addressed mechanism of action for serious non-infectious febrile events seen with dabrafenib. The sponsor notes that multiple mechanisms may explain fever in the given setting, including occult infection, tumour necrosis, auto-inflammation and presence of CNS metastases. The sponsor is actively exploring three hypotheses:

- Direct modulation of CNS thermoregulation via prostaglandin E2 (PGE2)
- Activation of systemic inflammation via toll-like receptors (the sponsor notes structural similarities between dabrafenib and imiquimod)
- Underlying generalised systemic inflammatory response

Arthralgia and related AEs

Arthralgia is prominent with dabrafenib use. Pyrexia, rash/erythema and uveitis/iritis are also seen.

It has been suggested that hydralazine may induce autoimmunity (that is, a lupus-like syndrome) by inhibiting ERK pathway signalling.[39] ERK is downstream of RAF. However,

[38] Callahan MK *et al*. Progression of RAS-mutant leukemia during RAF inhibitor treatment. *NEMJ* 2012;367:2316-2321.
[39] Deng C *et al*. Hydralazine may induce autoimmunity by inhibiting extracellular signal-related kinase pathway signalling. *Arthritis and Rheumatism* 2003;48: 746-756. The hypothesis is that normal ERK signalling up-regulates DNMT1, whereas inhibition of ERK signalling decreases DNMT1 and leads to DNA hypomethylation, with concomitant gene expression changes favouring autoimmunity.

the sponsor provided analyses indicating that in subjects with autoimmune disease, flares of disease were not a major concern; also, such subjects were not more likely to develop events such as pyrexia, rash and uveitis. The only caveat is that the subset considered to have autoimmune disease was probably highly diluted by subjects with non-autoimmune thyroid disease and Type 2 diabetes. There were no convincing cases of drug-induced lupus; but autoimmune serology was not checked.

There were 5/578 subjects in the integrated safety database reporting uveitis or iritis; 4 cases were possibly related. 5 subjects reported phototoxicity.

Other

Hypophosphataemia has been observed with other tyrosine kinase inhibitors (for example, imatinib, nilotinib, dasatinib, sunitinib[40]). It led to dose reduction in 2% of dabrafenib patients in BREAK-MB. Severe hypophosphataemia in itself can cause muscle weakness, or an acute syndrome of weakness, bone pain, rhabdomyolysis and altered mental state. If low phosphate is due to inhibition of bone turnover, chronic hypophosphataemia could be associated with skeletal abnormalities.

Other significant laboratory abnormalities are discussed in the CER (see Attachment 2 of this AusPAR). For example, high and low serum glucose levels were both more common in the dabrafenib arm than the dacarbazine arm in BREAK-3. Grade 3 or higher hyperglycaemia was seen in 34 dabrafenib subjects; 33 had baseline impaired glucose tolerance.

Subjects ≥ 65 yrs of age

Subjects ≥ 65 yrs of age had a higher incidence of SAEs compared with those aged < 65 years (41% versus 22%), and more often needed dose reduction or interruption. In the population PK analysis, age was not seen as an influence on PK parameters, although older subjects had a greater exposure to some metabolites.

Safety update

The sponsor provided an updated integrated safety report (n=586 patients treated; latest cut-off date, 25 June 2012). Median duration of treatment had increased by about 1 month to 5.5 months in this update; 46% had been treated for ≥6 months and 15% had been treated for ≥12 months. The update did not change the safety profile established above.

An additional 3 subjects had a fatal AE, bringing the total to 8. One of the three new cases was a fatal acute coronary syndrome, considered related to dabrafenib by the investigator.

In the update there were 65 subjects with SCC, Bowen's disease or keratoacanthoma.

There were an additional 3 subjects with renal failure, bringing the total to 7/586. In three cases, renal failure was associated with pyrexia and / or dehydration. One case was fatal.

Clinical evaluator's recommendation

The clinical evaluator recommends registration with a modified indication (restriction to V600E mutations; exclusion of patients with brain metastases).

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA's OPR. The RMP evaluator recommends the following condition of registration:

[40] Giles FJ *et al*. Class effects of tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. *Leukemia* 2009;23:1698-1707. A hypothesis is advanced there is inhibition of bone turnover, perhaps linked to inhibition of platelet derived growth fact receptor (PDGFR)-alpha.

- Implement dabrafenib EU-RMP (version 1, dated 12 February 2013, data lock point 19 December 2011) with Australian-specific Annex (undated) and any future updates.

Risk-benefit analysis

Delegate considerations

Efficacy: aspects of the pivotal study

The primary efficacy endpoint was not OS but PFS, which the Delegate considered acceptable given crossover was appropriate. The primary endpoint was based on investigator assessment; there was concordance with independent review. Dose of dacarbazine in BREAK-3 was 1000 mg/m^2 every 3 weeks (q3wk), which varies from that recommended in dacarbazine PIs. However, it is consistent with guidance from EviQ[41] so can be considered an established dosage regimen. Overall, results from BREAK-3 appear valid.

Efficacy: active CNS disease

Active CNS disease is common in metastatic melanoma patients42 so benefit-risk in this subset is important to define. Distribution of dabrafenib into the CNS was discussed by the clinical evaluator.

The Phase III Study BREAK-3 excluded patients with CNS involvement.

BREAK-MB showed dabrafenib has activity in CNS disease but the study was uncontrolled and the investigator and independent review results were discordant. The clinical evaluator considers that the data do not demonstrate superiority of dabrafenib over currently used local therapies.

The sponsor considers that BREAK-MB provided sufficient evidence to include patients with brain metastases in dabrafenib's indication; the sponsor notes that a study of dabrafenib with stereotactic radiosurgery is underway (NCT01721603[43]).

The Delegate considered that it is reasonable to include patients with brain metastases in the indication, on the basis that patients in this subgroup have a generally poor prognosis and that dabrafenib at least has some clinical evidence to support utility in this context.

Efficacy: V600E, V600K and others

N=49 patients with V600K mutations were included in BREAK-2 and BREAK-MB, both uncontrolled studies. The clinical evaluator was not convinced of the clinical significance of dabrafenib's efficacy in V600K mutant tumours, but acknowledged that there was a generally poor prognosis with metastatic melanoma.

The sponsor has argued that while V600K tumours have a lower response rate, patients may benefit ("*as evidenced by disease stabilisation and an overall survival similar to subjects with V600E tumours*"). While nonclinical data would suggest similar activity in V600E and V600K tumours, this was not borne out in clinical studies. The sponsor notes that *"subjects with V600K melanoma tend to be older and exhibit a higher degree of cumulative sun-induced damage"* (in BREAK-2, median age of V600K patients was 64.5 years, while median age of V600E patients was 52 years).

[41] A service provided by the cancer institute of NSW: <https://www.eviq.org.au/>
[42] Jakob JA *et al*. NRAS mutation status is an independent prognostic factor in metastatic melanoma. *Cancer* 2012;118: 4014-4023. Jakob *et al.* reported that risk of CNS involvement at diagnosis of Stage IV disease was 24% in BRAF mutant tumour patients versus 12% in patients WT for both BRAF and NRAS.
[43] A Phase 2 Prospective Trial of Dabrafenib With Stereotactic Radiosurgery in BRAFV600E Melanoma Brain Metastases, available at <http://clinicaltrials.gov/ct2/show/NCT01721603?term=NCT01721603&rank=1>

The sponsor notes that median OS was similar in BREAK-2 for V600E (13.1 months) and V600K (12.9 months) patients, and these medians compared favourably with historical values. In BREAK-MB, median OS in V600E was 31-33 weeks, and in V600K 16-22 weeks, but the sponsor contended that the V600K outcomes were better than might be expected historically.

Mutations other than V600E and V600K are rare. Little weight can be placed on sensitivity to dabrafenib in nonclinical assays of melanoma cell lines, given that sensitivity to V600K was similar to V600E, yet clinical outcomes appear worse with V600K. Some data have emerged from compassionate use in V600R. Klein and others reported experience in seven patients with V600R treated with dabrafenib[44]; 4/5 evaluable patients had a partial response.

The Delegate supported approval of the more open V600 indication, on the basis that outcomes for patients with V600K, V600R (and other mutation type) metastatic melanoma are poor and that at least dabrafenib activity in such tumours is supported by some level of clinical evidence.

Efficacy: tumour mutation assays

A 'Precaution' in the proposed dabrafenib PI states: Before taking dabrafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test.

Also, the *Dosage and Administration section states: Confirmation of BRAF V600 mutation using an approved / validated test is required for selection of patients appropriate for Tafinlar therapy*.

The sponsor used an 'investigational use only' assay in the Phase II and III studies; this was an allele-specific polymerase chain reaction (PCR) performed on deoxyribonucleic acid (DNA) extracted from formalin-fixed paraffin-embedded (FFPE) tumour tissue. The assay was designed to distinguish V600E and V600K mutations.

The sponsor notes that currently, various methods such as reverse transcriptase (RT) PCR are used to detect V600 mutation. The sponsor notes that currently, various methods are used to detect V600 mutation.

The sponsor also notes: *"As laboratory developed (Class 3 in-house in vitro diagnostic; IVD) assays are not required to be entered on the Australian Register of Therapeutic Goods (ARTG) until 2014, provided that the laboratory has National Association of Testing Authorities (NATA) accreditation, the number and type of V600 testing methods is difficult to quantify at present."*

The sponsor also notes that there is a variety of V600 testing methods available.

Efficacy: resistance

A significant issue with dabrafenib is acquired resistance to inhibition (for example, median PFS was 5.1 months); reactivation of the MAPK pathway is often found upon clinical relapse.

Efficacy: comparison with vemurafenib

Vemurafenib is a registered medicine and indicated in V600 mutation positive metastatic melanoma; it is now standard of care (where there is a BRAF mutation).

No pivotal or supportive studies compared dabrafenib with vemurafenib. The vemurafenib pivotal study is outlined in the vemurafenib PI. Cross-study comparison is difficult but here is aided by a similar target population and by use of the same comparator, dacarbazine. Median PFS was similar for dacarbazine arms (1.6 months in the

[44] Klein O *et al*. BRAF inhibitor activity in V600R metastatic melanoma. *Eur J Cancer* 2013;49:1073-1079. In this selected cohort, patients with V600K again had a lower response rate (2/10 for BRAF inhibitors).

vemurafenib pivotal study; 2.7 months for BREAK-3); median PFS was 5.3 months for vemurafenib, 5.1 months for dabrafenib). This does not suggest that outcomes with dabrafenib will be significantly lower than those with vemurafenib. Only a head-to-head study can resolve this issue.

Efficacy: comparison with ipilimumab

Ipilimumab is registered for second-line use in advanced or metastatic melanoma, though some guidelines suggest first-line use. Comparison of pivotal studies is more difficult in this case because of different patient populations and the absence of a dacarbazine comparator arm.

Safety: concomitant use with ipilimumab

Concomitant use of vemurafenib and ipilimumab results in significant hepatic derangement.[45] There is some basis to speculate that the same may occur with concomitant use of dabrafenib and ipilimumab, since ipilimumab may well cause an autoimmune hepatitis and it is possible that dabrafenib may exacerbate this autoimmune pathology (see comments above). Therefore the dabrafenib PI should include a precaution to this effect, until data prove the *Precaution* unnecessary.

Safety: use after ipilimumab

It has also been reported that of 13 patients treated with ipilimumab who were subsequently given vemurafenib, 4 developed a severe rash unresponsive to glucocorticoids. Treatment was stopped for up to 11 days to allow resolution of the rash, and in all 4 patients a lower dose of vemurafenib was then used successfully.[46] It is possible that this is a class effect and that a similar picture will emerge if dabrafenib is used after ipilimumab.

Indication

The sponsor has proposed:

> *Tafinlar is indicated for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV) melanoma.*

The clinical evaluator has noted less promising outcomes in V600K mutant tumours, and has also drawn attention to the absence of appropriate comparators for V600K and also for use in CNS disease.

The vemurafenib indication in Australia includes "V600" mutant tumours.

The Delegate considered it was appropriate to allow use in patients with V600 mutations other than V600E, as long as there is information in the PI explaining that experience in such patients is limited and suggests relatively less benefit.

The sponsor's proposed indication includes those patients with Stage III disease whose nodal involvement cannot be managed with lymph node dissection. Only 1 patient in BREAK-3's dabrafenib arm had Stage IIIA-B disease; only 6 patients had Stage IIIC disease. There is little experience with unresectable advanced disease.

The sponsor's indication would also include patients with lower stage melanoma in whom surgical excision is unfeasible, for example, due to comorbidity or cosmetically sensitive tumour location. These subjects were not studied. There was no comparison with any topical treatments, intralesional treatments, regional chemotherapy or radiation.

On balance, the Delegate considered the indication should be modified to:

[45] Ribas A *et al.* Letter: hepatotoxicity with combination of vemurafenib and ipilimumab. *NEJM* 2013;368:1365-1366
[46] Harding JJ *et al*. Letter: vemurafenib sensitivity skin reaction after ipilimumab. *NEJM* 2012;366: 866-868

Tafinlar is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage IIIC or metastatic (Stage IV) melanoma

Proposed actions

The Delegate proposed to approve the application, with a slightly modified indication:

Tafinlar is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage IIIC or metastatic (Stage IV) melanoma

The Delegate also proposed several revisions to the product literature including the PI. Details of these are beyond the scope of the AusPAR.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request the committee address the following specific questions:

- Is it reasonable to include patients with V600 mutations other than V600E in the indication?
- Is it reasonable to include patients with CNS disease in the indication?

Response from sponsor

Executive summary

- The TGA Delegate recommends registration with the following indication:

  Tafinlar is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage IIIC or metastatic (Stage IV) melanoma
- Primary efficacy endpoint of PFS in pivotal BREAK-3 Study clearly demonstrated superiority of dabrafenib over dacarbazine, and
- PFS is an acceptable endpoint (compared to OS) to the TGA Delegate given the ethical considerations for trial design incorporating crossover on disease progression.
- Clinical efficacy has been demonstrated for dabrafenib in patients with various V600 mutations (BREAK-3, BREAK-MB, BREAK-2)
- Dabrafenib has shown clinical activity in patients with different V600 mutation positive metastatic melanoma with CNS disease (BREAK-MB)
- The safety profile of dabrafenib is comparable, if not more tolerable than other current treatment for patients with metastatic melanoma. A robust risk management plan together with appropriate PI addresses necessary safety information for the physician
- Dabrafenib has received a positive opinion from the EMA's CHMP on June 27 2013 for the following indication: Tafinlar (dabrafenib) in monotherapy is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
- Dabrafenib was approved by the FDA on May 29, 2013 for the following indication: *Tafinlar is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.*

Clinical efficacy has been demonstrated

The primary evidence to support the clinical efficacy of dabrafenib is provided by the pivotal randomised Phase III Study (BREAK-3), the Phase II Study in patients with brain metastases (BREAK-MB) and the supportive Phase II Study (BREAK-2). These studies have

collectively demonstrated clinical efficacy for dabrafenib in the treatment of patients with advanced metastatic melanoma with V600 mutations.

The chosen primary endpoint (PFS) for BREAK-3 was acceptable to regulatory agencies (FDA, EMA, TGA), as the trial design allowed for treatment cross over for patients on progression, based on ethical grounds. At the time of trial design and initiation, dacarbazine was the standard of care treatment. The results from BREAK-3 show superiority of dabrafenib over dacarbazine for metastatic melanoma patients with V600E mutation; which has been acknowledged by both the clinical evaluator and TGA Delegate.

The outcomes of the Phase II, BREAK-2 Study substantiated the results for patients with the V600E mutation and provided clinical evidence for the efficacy of dabrafenib in patients with the V600K mutation. The efficacy results, while not as robust as that seen in patients with V600E mutations show that patients with BRAF V600K mutations may still benefit from dabrafenib as evidenced by disease stabilisation and an OS similar to patients with V600E tumours. The efficacy in V600K (and other V600 mutation) patients is further discussed below in response to the TGA Delegate's Question 1 to the ACPM.

The Phase II, BREAK-MB Study was conducted to investigate efficacy of dabrafenib in patients with brain metastases, a subset of the patient population typically excluded from clinical trials (these patients were excluded from BREAK-3 and BREAK-2). To the sponsor's knowledge, this is the first study reporting data on this patient population with a BRAF inhibitor. The TGA Delegate has stated that: *"Overall, BREAK-MB provided evidence of activity in CNS disease"*. The clinical study also confirmed activity in patients with the V600K mutation, although at a lower level in line with the results from the BREAK-2 Study.

In summary, dabrafenib demonstrated clinical benefit in all 3 trials, regardless of site of metastases or prognosis. This was observed in all subgroups, including subjects with either BRAF V600E or BRAF V600K mutations, and subjects with brain metastases, stage M1c disease, or an elevated LDH level, all of which are associated with poor prognosis. Specifically, the data of subjects with brain metastases from Study BREAK-MB provide robust evidence of clinical benefit in an area of high unmet medical need.

Safety profile is comparable, if not more tolerable than current therapies

The safety of dabrafenib at the proposed dose of 150 mg BID has been well characterised in subjects with metastatic or unresectable melanoma in the integrated safety population. The side effects that were observed are both clinically manageable and amenable to risk reduction through routine pharmacovigilance, patient education, and labelling. Long-term dosing (> 6 months) can be achieved without the need for frequent dose modification, corresponding to the expected clinical use. Missing or limited information for other populations are addressed in the sponsor's RMP.

The following conclusions can be drawn from the safety data:

- The most common AEs were manageable conditions and were primarily Grade 1 or Grade 2 in severity.
- There were low numbers of grade 3 or higher AEs. The most frequent AEs occurring at Grade 3 or higher included SCC, hypophosphatemia, and lymphopenia.
- Pyrexia and cutaneous SCC were the only SAEs occurring in ≥ 2% of subjects, and clinical management of these events did not require treatment discontinuation. Pyrexia was the only AE that resulted in dabrafenib dose reduction in > 1% of subjects. Cutaneous SCC and keratoacanthoma were reported in 9% of subjects. This is an expected toxicity of BRAF inhibition attributed to therapy-induced tumorigenesis in RAS-primed cells. Pyrexia and cutaneous SCC were closely monitored in study protocols and are addressed in the RMP as important identified risks. Non-cutaneous SCC has not been reported in dabrafenib monotherapy clinical trials.

- Other AEs of special interest identified for close monitoring in study protocols and addressed in the RMP included but were not limited to: treatment-emergent malignancies, renal failure, PPE and uveitis. Additionally, new primary melanoma, hypersensitivity and pancreatitis were identified as important identified risks for the RMP.
- Events of decreased LVEF, valvular abnormalities and neutropenia were identified in small numbers of subjects in the integrated safety population and were not clinically significant. Non-specific cardiac toxicity has been added to the RMP as a potential risk for dabrafenib.
- No clinically significant trends in vital signs or clinical laboratory evaluations were evident. No hepatic or hematologic safety signals were identified.
- Significant case reports of hypersensitivity and pancreatitis were identified outside of the integrated safety population; these events are included in the proposed RMP.
- Overall, the incidence of AEs and AEs related to study treatment were similar in subjects with active brain metastases as compared with those without.

Based on the results of BREAK-3, dabrafenib exhibited a distinct safety profile from dacarbazine with significantly less myelosuppression or severe gastrointestinal (GI) toxicity. In addition, severe immune-mediated toxicities, such as those seen with T-cell activators (such as ipilimumab) were not observed. An experienced medical oncologist at the Sydney Cancer Centre states in reference to ipilimumab treatment for advanced melanoma: *"While some patients experience little in the way of side effects, in those that do experience immune related adverse events the ramifications can be severe. Vemurafenib, the closest comparator to dabrafenib in terms of efficacy, is not associated with fevers, however is associated with photosensitivity in 40-50% of patients across the clinical trials. In an Australian context, the rates of photosensitivity may in fact be much higher. The development of rash and arthralgia are also more prominent with vemurafenib (41% and 56% respectively in the Phase II trials) in comparison to dabrafenib (22% and 16% in the Phase II trials). Elevated liver function tests (LFTs) are seen in around a quarter of vemurafenib patients and may necessitate dose reduction and loss of efficacy. This side effect is much less commonly seen with dabrafenib.*

In summary, dabrafenib monotherapy compares favourably with other available melanoma treatments in terms of safety."

Specific questions raised by TGA delegate for ACPM's advice

Delegate's question 1: Is it reasonable to include patients with V600 mutations other than V600E in the indication?

The clinical evaluator recommended that the indication should be restricted to patients with BRAF V600E and V600K, however, the TGA Delegate *"supported approval of the more open V600 indication, on the basis that outcomes for patients with V600K, V600R (etc) metastatic melanoma are poor and that at least dabrafenib activity in such tumours is supported by some level of clinical evidence."*

The sponsor agrees with the Delegate while acknowledging the lower overall response rate in the V600K population relative to the V600E; however while the response rate is lower, patients with V600K tumours may still benefit from dabrafenib as evidenced by disease stabilisation and an overall survival similar to subjects with V600E tumours. This view is substantiated by two prominent Australian medical oncologists: *"It is reasonable to include V600 mutations. It would be unethical to restrict the indication to V600E."*

"In the light of these data, and reports of efficacy in rarer subtypes such as V600R, I would recommend a broad indication that is inclusive of all V600."

The sponsor believes that it is not clear whether the lower response rate in V600K patients is due to lack of response to treatment or the apparent poorer prognosis of patients with the V600K mutation. The sponsor is concerned that if the indication is limited to V600E and V600K mutation positive patients only, that patients with other V600 mutations, would only have dacarbazine as an alternative treatment option to vemurafenib, rather than benefiting from dabrafenib.

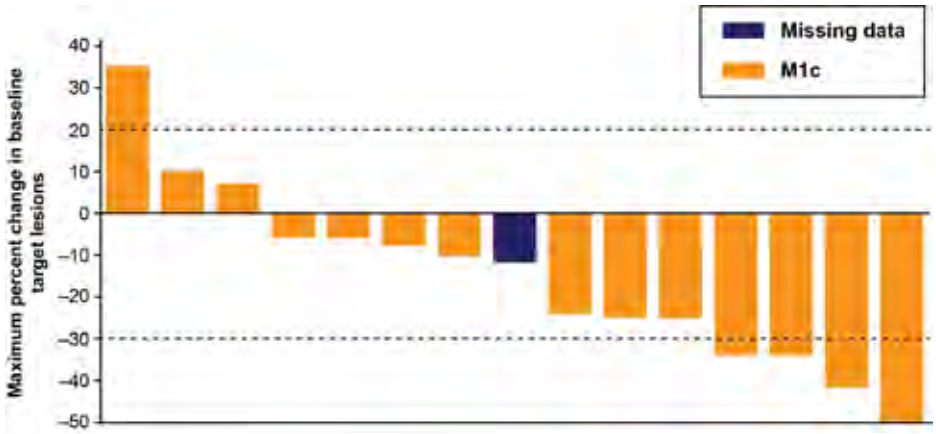
The BRAF gene is the most commonly mutated component of the MAPK pathway in metastatic melanoma, of which the most prevalent mutation is V600E, followed by V600K. A number of other substitutions also occur, including V600R, V600D, V600G and V600M; however their anticipated frequency is much lower. Large studies recently conducted in Australia, Texas, and Florida show that in these regions, the V600K (valine to lysine) genotype is more prevalent than previously reported, and may comprise 20% or more of BRAF mutant melanomas (Menzies *et al*., 2012[47]). Similarly, the frequency of V600K mutation in patients enrolled on BREAK-2 and BREAK-MB (17 to 19%) was consistent with data from the FTIH Study BRF112680 as well as from recently published reports about mutation incidence (Long *et al.*, 2011[48]; Jakob *et al*., 2012[49]).

Given the low frequency of V600 mutations other than E, studying patients with these mutations prospectively in a randomised clinical trial setting to obtain meaningful estimates of time to event endpoints such as PFS would have not been feasible. Forty-nine subjects with BRAF V600K mutation positive melanoma have been studied across the dabrafenib monotherapy program, plus an additional 9 subjects who received dabrafenib monotherapy on the combination Study BRF113220. This is the largest prospectively selected sample of patients whose tumour harbours the V600K activating mutation sub-type allowing characterisation of response rate, duration of response and other efficacy parameters in a relatively infrequent mutation subtype. Response rates (RR) in the V600K population have ranged from 0% in the local treatment naive cohort on BREAK-MB to 33% on the monotherapy arm of BRF113220. The totality of evidence, with respect to RR, duration of response, PFS and OS after BRAF inhibition argues for clinical benefit in the V600K population and compares favourably to chemotherapy.

In Study BREAK-2, the response rate as assessed by the investigator was lower in subjects with V600K mutation positive melanoma (13%; 95% CI: 0. 28.7%) compared with V600E (59%; 95% CI, 48.2–70.3). In addition to the 2 subjects with the V600K mutation with a confirmed response, 7 (44%) V600K mutation positive subjects had stable disease (SD) for a minimum of 12 weeks and most subjects experienced some degree of tumour shrinkage as illustrated by the waterfall plot provided in Figure 5. This is double the historical PFS estimate for dacarbazine of approximately 6 weeks.

[47] Menzies AM, Haydu LE, Visintin L *et al*. Distinguishing clinicopathologic features of patients with V600E and V600K BRAF-mutant metastatic melanoma. *Clin Cancer Res* 2012;18(12):3242-9.
[48] Long GV, Menzies AM, Nagrial AM *et al*. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol* 2011;29:1239-46.
[49] Jakob JA, Bassett RL Jr, Ng CS, *et al*. NRAS mutation status is an independent prognostic factor in metastatic melanoma. *Cancer* 2012;118:4014-23.

Figure 5. Tumour shrinkage responses in patients treated with dabrafenib (V600K; investigator assessment)



In Study BREAK-MB, ORRs for V600K subjects were 0% in Cohort A and 28% (5 overall responders) in Cohort B, compared to 38% (28 overall responders) and 31% (20 overall responders), respectively, in V600E mutation positive subjects. The rate of overall SD was higher in Cohort A (47%) than in Cohort B (22%), but again is clinically relevant in both. The majority of subjects in both cohorts experienced some degree of tumour shrinkage. The median duration of overall response in Cohort B is 13.6 weeks. The median OS in subjects with V600K positive melanoma was lower than in V600E mutation positive subjects (Cohort A: V600K 16.3 weeks versus V600E 33.1; Cohort B: V600K 21.9 weeks versus V600E 31.4 weeks).However, given the historical range of median overall survival (2.8 to 4 months), the median OS in both cohorts is comparable or favourable to standard of care figures.

In addition, recent publications reporting data from a compassionate use program with dabrafenib and vemurafenib in Australia provided evidence of benefit in subjects with V600R mutations who received dabrafenib (Klein *et al*., 2013[50], Klein *et al*., 2013a[51]). Of 6 assessable patients with V600R melanoma treated with dabrafenib, 5 achieved a response.

An oncologist's opinion states: *"In the light of these data, and reports of efficacy in rarer subtypes such as V600R, I would recommend a broad indication that is inclusive of all V600."*

Recent evidence suggests there are clinical differences between V600E and V600K melanoma which could contribute to this difference in activity. Notably, subjects with V600K melanoma tend to be older than those with V600E. In BREAK-MB, the median age of subjects with V600K was 64.5 years versus 52 years for subjects with V600E and all subjects with V600K mutation whose M (metastases) status was known had M1c disease, the poorest prognosis metastatic melanoma subgroup. In a population analysis conducted by Menzies, it was also found that the V600K population was significantly older at first diagnosis of first distant metastasis (median 61 years for V600K versus 53 years for V600E, P=0.031) (Menzies *et al*., 2012[52]). V600K patients exhibit a higher degree of cumulative sun-induced damage than V600E patients, with V600K patients having high scores (2-3), while V600E patients having low scores of 0 to 1 (P=0.002). Recent studies have lead the authors to suggest that V600K patients have a poorer prognosis than V600E patients and therefore a poorer response to any BRAF inhibitor in V600K patient may not reflect a difference in targeting of the drug to the mutation. Rather, this may reflect the fact

[50] Klein OA, Clements A, Menzies AB *et al*. BRAF inhibitor activity in V600R metastatic melanoma. *Eur J Cancer* 2013;49:1073– 1079.
[51] Klein OA, Clements A, Menzies AB *et al*. BRAF inhibitor activity in V600R metastatic melanoma - Response. *Eur J Cancer* 2013a;49:1797– 1798.
[52] Menzies AM, Haydu LE, Visintin L *et al*. Distinguishing clinicopathologic features of patients with V600E and V600K BRAF-mutant metastatic melanoma. *Clin Cancer Res* 2012;18(12):3242-9.

that V600K patients differ epidemiologically from their V600E counterparts (Jewell *et al*., 2012[53], Menzies *et al*, 2012).

It is important to note that the BRAF mutation validated tests developed so far would not necessarily enable prescribers to differentiate different sub-types of mutations as sensitivity and specificity vary depending of the type of assays used; Specifically, retrospective testing of samples from patients enrolled in the main pivotal study of vemurafenib, BRIM-3 with the Cobas 4800 BRAF V600 test confirmed that the test detected also less common BRAF V600 mutations, despite being highly sensitive and specific to V600E (Klein *et al.*, 2013). Further the bMx THxID BRAF validated assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5% V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue), however retrospective bi-directional Sanger sequencing analyses have shown that the test also detects the less common BRAF V600D mutation and V600E/K601E mutation with lower sensitivity.

As outlined in the *Clinical Trial* section of the vemurafenib PI, in the Phase III study (BRIM-3), a total of only 19 patients out of 220 (8.6%) whose tumours were analysed retrospectively by sequencing were reported to have BRAF V600K mutation-positive melanoma. The incidence of V600K in the BRIM-3 Study is approximately half that noted in dabrafenib clinical trials and reported in the literature. Whether the activity seen in these few patients is reflective of the overall V600K population is therefore unclear. The *Clinical Trial* section of the vemurafenib PI also states that *although limited by the low number of patients, compared to V600E patients' efficacy analyses among these patients with V600K-positive tumours suggested treatment benefit of vemurafenib in terms of OS, PFS and the confirmed best overall response*. Despite vemurafenib having a limited number of patients with a V600K mutation, which may not be reflective of the overall V600K population, the vemurafenib indication was not restricted to V600E; therefore, it is important that the Tafinlar indication be assessed in a similar context. An Australian oncologist, when discussing the registration data for vemurafenib based on the test used for V600 mutation identification, remarks: *"This test does not detect V600K mutations with high sensitivity, and thus the data for vemurafenib efficacy in the V600K population are relatively lacking"*.

Delegate's question 2: Is it reasonable to include patients with CNS disease in the indication

The TGA Delegate considers *"that it is reasonable to include patients with brain metastases in the indication, on the basis that patients in this subgroup have a generally poor prognosis and that dabrafenib at least has some clinical evidence to support utility in this context."*

Melanoma brain metastases are common, confer a poor prognosis and are difficult to treat, particularly given the lack of effective systemic treatments (Long *et al*., 2012[54]). Twenty percent of patients have brain metastases at diagnosis and nearly 50% develop them during the course of the disease. Median OS in patients with brain metastases is approximately 17-22 weeks from diagnosis. While oligometastatic disease may be managed with stereotactic radiation, whole brain radiation is much less successful. Chemotherapeutic agents have demonstrated little benefit as a standard of care. The need for effective treatments to control systemic melanoma concurrently and to prolong overall survival of patients with melanoma metastatic to the brain remains an unmet medical need as these patients are generally excluded from clinical trials. The goal of treatment in these patients is reduction of tumour size, and by extension, potential resolution of clinical

[53] Jewell R, Chambers P, Harland, M *et al*. Clinicopathologic Features of V600E and V600K Melanoma-Letter. *Clin Cancer Res* 2012;18(24):6792.
[54] Long, GV, Trefzer U, Davies M. *et al*. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAKMB): a multicentre, open-label, phase 2 trial. *The Lancet Oncology* 2012;13:1087-1095.

manifestations of underlying disease. Evidence from cohort B in particular suggests that prior local treatment, which is commonly given to minimise symptoms of poorly located lesions, does not preclude subsequent benefit from BRAF inhibition. Based on this body of evidence, the sponsor strongly advocates that these patients should not be excluded from the intended patient population in the PI as further discussed below.

Historically, systemic therapy options for patients with melanoma brain metastases have demonstrated limited efficacy. Indeed, this sub-population has received limited attention in terms of clinical research, given that most studies exclude brain metastases in the eligibility criteria due to the poor prognosis and difficulty of treatment. BREAK-MB is the largest prospective study ever undertaken in melanoma brain metastases and included 172 patients with V600E/K BRAF mutant metastatic melanoma with asymptomatic brain metastases. The majority of subjects in both cohorts had more than 1 intracranial target lesion (V600E: 71%; V600K: 67%). In addition the majority of subjects also had non-target intracranial disease. This study enrolled patients with and without previous local therapy to brain metastases and allowed intracranial lesions with a largest diameter between 0.5 cm-4 cm. Baseline sum of lesion diameters ranged from 0.5 cm up to 13.6 cm, with median sum of the diameters being 2.3 cm. As such the majority of patients had significant burden of disease in the brain at the start of the trial. Dabrafenib was active (OIRR: 39% for cohort A and 31% for cohort B) and OS was similar in both cohorts. Patients in both cohorts could have had prior symptoms, thus ongoing stable or decreasing doses of corticosteroids were allowed.

In BREAK-MB, dabrafenib was active in patients irrespective of whether or not they had had previous local treatment for brain metastases. Therefore, dabrafenib could be considered as initial treatment or after progression following local brain treatment (stereotactic or surgical). The intracranial disease control rate of > 80% and median survivals > 31 weeks observed in patients with V600E BRAF tumours argue for consideration of dabrafenib as first-line therapy for patients with V600E/KBRAF melanoma and brain metastases, and in those who failed local brain-directed treatment (Long *et al*., 2012). In patients with brain metastases, while the survival of V600K patients with intracranial disease may be inferior to that of V600E individuals, and the small numbers again lead to overlap of 95% CIs the drug is clearly active in both cohorts A and B when overall disease control (ODC; complete response (CR) + partial response (PR) + stable disease (SD)) is considered. Specifically, the ODC in cohort A was 47%, and for cohort B, 50%.

In a recent paper, Klein *et al*.[55] reported further analyses of their treatment of patients with V600R mutations and brain metastases. Three out of 9 patients with V600R metastases had brain metastases. All 3 were treated with dabrafenib. Of the three patients, one patient had a partial response, one patient had minor reduction in the size of metastases and had disease stabilisation for 6 months and the third patient had had a reduction in lesion size and stable disease for 10 months. In these patients, activity of dabrafenib was seen regardless of whether the patient received prior radiotherapy or not.

The majority of patients with brain metastases present with extracranial disease. Determining the best course of treatment in these patients will require an individualised approach, factoring in mutation status, presence of extracranial metastases, the pace of disease, number and site of brain metastases and presence of symptoms. The totality of evidence from the BREAK-MB Study suggests that dabrafenib may be reasonable, both as initial therapy for patients with melanoma brain metastases to be followed by local brain treatment (stereotactic or surgical) upon progression, or as therapy in those who have failed local brain treatment.

[55] Klein OA, Clements A, Menzies AB *et al*. BRAF inhibitor activity in V600R metastatic melanoma - Response. *Eur J Cancer* 2013a;49:1797– 1798.

An oncologist addresses the TGA Delegate's question with the following clinical opinion: *"It is reasonable to include patients with CNS disease in the indication. Separate to this specific indication, it would be unethical to exclude patients with CNS disease from accessing dabrafenib. Patients with melanoma brain metastases carry an extremely poor prognosis (median OS 16-20 weeks). Although dabrafenib was not tested in patients with active brain metastases in a phase 3 study (there is no ethical design of a phase 3 trial that could demonstrate a survival benefit), there is sufficient evidence of a strong clinical benefit in patients with active brain metastases from the phase 1 and 2 (BREAK-MB) study. Unlike many other anti-cancer treatments, the activity of dabrafenib is so clear on radiology that we did not need to resort to other methods of brain evaluation in these studies, other than RECIST. In addition, all areas and organs with metastases can be treated quickly and efficiently at once using dabrafenib, and we are able to add other brain-directed local treatments as needed later."*

Safety concerns about the use of dabrafenib with ipilimumab

Additive skin toxicity has been reported with the combination of vemurafenib and ipilimumab (Harding *et al.*, 2012[56]) along with additive hepatotoxicity (Ribas *et al.*, 2013[57]). Several factors suggest that the safety concerns raised by the vemurafenib/ipilimumab experience may not be as much of a concern for dabrafenib:

- Unlike vemurafenib, severe dermatological reactions (such as Stevens-Johnson syndrome or toxic epidermal necrolysis) have not been observed with dabrafenib. The incidence and severity of photosensitivity is also lower [2% overall; none ≥ Grade 3 for dabrafenib versus 37% overall; 4% ≥ Grade 3 for vemurafenib (Zelboraf AusPAR)]. Grade 3 or higher liver abnormalities were unusual with dabrafenib (≤ 1% of subjects for alkaline phosphatase, alanine transaminase (ALT), or aspartate transaminase (AST)). By contrast, liver function abnormalities were seen in 24% of vemurafenib-treated subjects and 12% were ≥ Grade 3 (Zelboraf AusPAR). The starting dose of vemurafenib (960 mg) in the ipilimumab combination regimen was the monotherapy MTD. An MTD has not been established for dabrafenib. The most common toxicities for dabrafenib (fever and hyperproliferative skin disorders) are non-overlapping with ipilimumab.
- To date, 3 subjects have been treated with the dabrafenib/ipilimumab doublet on Study BRF115984. All have received the 4 planned infusions of ipilimumab at the labelled dose of 3 mg/kg along with dabrafenib 150 mg BID for 2 weeks prior to ipilimumab and ongoing. All 3 subjects are now in the post-ipilimumab part of the study and continuing on dabrafenib 150 mg BID. To date there has been a lack of AEs involving skin toxicities or hepatotoxicity. Dose-limiting toxicity has not been observed in any of these subjects through the first few weeks of treatment in contrast to the reported experience with vemurafenib plus ipilimumab where early hepatotoxicity was routinely observed (Ribas *et al*., 2013). All subjects are continuing on treatment as of 27 June 2013.

Taken altogether, the sponsor does not believe it necessary to add precautions regarding the use of dabrafenib concomitantly, or after, ipilimumab.

Benefit-risk assessment: conclusion

The clinical activity of dabrafenib compared to dacarbazine, as seen by the large effect on PFS and the high response rate in BREAK-3 are highly consistent with that seen with vemurafenib in a nearly identical patient population. Furthermore, dabrafenib has

[56] Harding JJ, Pulitzer M, Chapman P. Vemurafenib Sensitivity Skin Reaction after Ipilimumab. *NEJM* 2012;366:866
[57] Ribas A, Hodi FS, Calhan L *et al*. Hepatotoxicity with Combination of Vemurafenib and Ipilimumab. *NEJM* 2013;368: 1365

demonstrated strong evidence of activity in subjects with melanoma brain metastases in the BREAK-MB Study, an area of high unmet medical need. This addresses a need in a patient population typically excluded from clinical trials due to poor prognosis and concerns that systemic therapies will be less active due to the inability of many drugs to cross the blood-brain barrier. Although the data in subjects with BRAF V600K mutations are not as compelling as for BRAF V600E, the evidence of activity supports dabrafenib as a treatment option for BRAF V600K mutation positive melanoma, given the limited treatment options available for V600K patients.

These benefits must be weighed against possible dabrafenib-induced risks.

An oncologist summarises the risks with the following: *"Dabrafenib monotherapy is an extremely well tolerated anti-cancer medicine. Dabrafenib improves patients' quality of life has a rapid mode of action and few side effects. In contrast to vemurafenib, there is no photosensitivity, minimal risk of liver toxicity, fewer cutaneous side effects and less arthralgia. Dabrafenib may cause fever, however severe recurrent fever is rare. Fever in dabrafenib monotherapy is usually a single event, managed easily with a short treatment interruption."*

The sponsor has addressed possible risks to patients in the *Precautions* section of the PI. The combination of communication, monitoring and guidance to manage risks as described in the RMP is believed to be sufficient to minimise the risk and to identify any change in the risk profile for dabrafenib related to these events.

The sponsor concurs with the TGA Delegate that the favourable benefit:risk assessment demonstrated in these studies supports dabrafenib for registration with the following indication:

> *Tafinlar is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage IIIC or metastatic (Stage IV) melanoma*

Advisory committee considerations

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

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Tafinlar capsules containing 50 mg and 75 mg of dabrafenib (as mesilate) to have an overall positive benefit–risk profile for the following proposed indication;

> *Tafinlar is indicated for the treatment of patients with confirmed BRAF V600 mutation positive unresectable or metastatic melanoma*

The ACPM advised that despite patients with CNS metastases being excluded from the pivotal trial, possibly due to the higher expected rate of AEs, this was unwarranted and these patients should be included in the treatment population.

The ACPM expressed some concern as to the development and availability of suitable assays to accurately diagnose and differentiate the various V600 mutations.

Proposed conditions of registration:

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

Proposed PI and CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Tafinlar capsules containing dabrafenib mesilate 50 mg and 75 mg, indicated for:

> *Tafinlar is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma*

Specific conditions of registration applying to these goods

- The dabrafenib EU-RMP (version 3, dated 17 June 2013, data lock point 19 December 2011) and Australian-specific annex (undated) and any other 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

Therapeutic Goods Administration

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