AUSTRALIAN PRODUCT INFORMATION
Zelboraf® (vemurafenib)

1. NAME OF THE MEDICINE
Vemurafenib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 240 mg vemurafenib (as a co-precipitate of vemurafenib and hypromellose acetate succinate)

For the full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM
Film coated tablets

Oval, biconvex, pinkish white to orange white tablets with "VEM" engraved on one side

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Zelboraf is indicated for the treatment of unresectable stage IIIC or stage IV metastatic melanoma positive for a BRAF V600 mutation.

4.2 DOSE AND METHOD OF ADMINISTRATION
Dose

Before taking Zelboraf, patients must have BRAF V600 mutation-positive tumour status confirmed by a TGA approved assay performed by a NATA accredited laboratory.

The recommended dose of Zelboraf is 960 mg (four 240 mg tablets) twice daily (equivalent to a total daily dose of 1920 mg). The first dose should be taken in the morning and the second dose should be taken in the evening approximately 12 hours later. Both doses of Zelboraf should be taken either at least 1 hour before or at least 2 hours after a meal.

Zelboraf tablets should be swallowed whole with a glass of water.

Zelboraf tablets should not be chewed or crushed.

It is recommended that treatment with Zelboraf continue until disease progression or the development of unacceptable toxicity (see Tables 1 and 2).

Missed Doses

If a planned dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice-daily regimen. Both doses should not be taken at the same time.

Vomiting

In case of vomiting after Zelboraf administration, the patient should not take an additional dose of the medicine but the treatment should be continued as usual.

Dose Modifications

Management of symptomatic adverse events or prolongation of QTc may require dose reduction, temporary interruption or treatment discontinuation of Zelboraf (see 4.4 Special Warnings and Precautions for Use). Dose modifications or interruptions are not recommended for cutaneous squamous cell carcinoma (cuSCC). Dose reductions resulting in a dose below 480 mg twice daily are not recommended.

Dose modifications should be made according to Tables 1 and 2.

Table 1: Dose Modifications

Recommended Zelboraf Dose Modification		
Toxicity Grade (CTC-AE)*	**Zelboraf dose changes during current treatment period**	**Dose modification at resumption of treatment**
Grade 1 or tolerable Grade 2	No change	N/A
Intolerable Grade 2 or Grade 3		
1st Appearance^	Interrupt until resolved: grade 0 – 1	Reduce dose by 240 mg twice daily
2nd Appearance^	Interrupt until resolved: grade 0 – 1	Reduce dose by 240 mg twice daily
3rd Appearance^	Discontinue permanently	N/A
Grade 4		
1st Appearance^	Discontinue permanently or interrupt until resolved: grade 0 – 1	Reduce dose to 480 mg twice daily
2nd Appearance^	Discontinue permanently	N/A

*The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)
^ Any AE where treatment interruption and dose reduction are clinically indicated and undertaken

Table 2: Dose Modification Schedule Based on Prolongation of the QT Interval

Dose modification schedule based on prolongation of the QT interval - QTc value	**Recommended dose modification**
QTc > 500 ms at baseline	Treatment not recommended.
QTc increase meets values of both > 500 ms and > 60 ms change from pre-treatment values	Discontinue permanently.
1st occurrence of QTc > 500 ms during treatment and change from pre-treatment value remains ≤ 60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures under *PRECAUTIONS, QT Prolongation*. Reduce both the morning and evening dose by 240mg daily (total daily dose reduction 480 mg).
2nd occurrence of QTc > 500 ms during treatment and change from pre-treatment value remains ≤ 60ms	Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures under *PRECAUTIONS, QT Prolongation*. Reduce both the morning and evening dose by 240 mg daily (total daily dose reduction 480 mg) (or discontinue permanently if the dose has already been lowered to 480 mg twice-daily).
3rd occurrence of QTc > 500 ms during treatment and change from pre-treatment value remains ≤ 60ms	Discontinue permanently.

Special populations

Paediatrics

The safety and efficacy of Zelboraf in patients under the age of 18 years have not been established. Zelboraf is not approved for use in patients under the age of 18 years (see section 5.2 Pharmacokinetic Properties, Pharmacokinetics in Special Populations).

Elderly

In clinical trials, all patients received the same starting dose of Zelboraf independent of age. No dose adjustment is required in elderly patients aged 65 years and older (see section 4.4 Special Warnings and Precautions for Use).

Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties). The potential need for dose adjustment in patients with severe hepatic impairment cannot be determined due to insufficient data. Cases of liver injury, including severe liver injury, have been reported with Zelboraf ((see section 4.4 Special Warnings and Precautions for Use, Liver Injury for important information on monitoring and management).

Renal Impairment

No adjustment to the starting dose is required in patients with mild or moderate renal impairment (see sections 4.4 Special Warnings and Precautions for Use, Use in Renal Impairment and 5.2 Pharmacokinetic Properties). The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data.

4.3 CONTRAINDICATIONS

Zelboraf is contraindicated in patients with hypersensitivity to vemurafenib or to any of its excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Before taking Zelboraf, patients must have BRAF V600 mutation-positive tumour status confirmed by a TGA approved assay performed by a NATA accredited laboratory.

The efficacy and safety of Zelboraf in patients with tumours expressing BRAF V600 non-E mutations have not been convincingly established (see section 5.1 Pharmacodynamic Properties, Clinical Trials).

Malignancies

Cutaneous Squamous Cell Carcinoma (cuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with Zelboraf (see section 4.8 Adverse Effects (Undesirable Effects)). CuSCC usually occurred early in the course of treatment. Potential risk factors associated with cuSCC in Zelboraf clinical trials included age (≥ 65 years old), prior skin cancer, and chronic sun exposure. Cases of cuSCC were typically managed with simple excision, and patients were able to continue treatment without dose adjustment.

It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and be monitored routinely while on therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per local standard of care. Monitoring should continue for up to 6 months following discontinuation of Zelboraf or until initiation of another anti-neoplastic therapy.

Patients should be instructed to inform their physicians upon the occurrence of any skin changes, including rash and photosensitivity.

Non-Cutaneous Squamous Cell Carcinoma (non-cuSCC)

In clinical studies rare cases of squamous cell carcinoma of the head and neck (tongue and tonsils) have been reported. Patients should undergo a head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation prior to initiation of treatment and every 3 months during treatment. Pelvic (for women) and anal examinations are recommended before and at the end of treatment or when considered clinically indicated. As per routine disease management, chest CT scans performed prior to initiation of treatment and every 6 months during treatment should be reviewed for non-cuSCC. Following discontinuation of Zelboraf, monitoring for non-cuSCC should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be evaluated as clinically indicated.

New Primary Malignant Melanoma

New primary malignant melanomas have been reported in clinical trials. Cases were managed with resection and patients continued on treatment without dose adjustment. Monitoring for skin lesions should occur as outlined above for cutaneous squamous cell carcinoma.

Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylaxis have been reported in association with Zelboraf and upon re-initiation of treatment (see sections 4.3 Contraindications and 4.8 Adverse Effects (Undesirable Effects)). Severe hypersensitivity reactions included generalised rash and erythema or hypotension. In patients who experience a severe hypersensitivity reaction, Zelboraf treatment should be permanently discontinued.

Dermatologic Reactions
Severe dermatologic reactions have been reported in patients receiving Zelboraf, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in the pivotal clinical trial. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with Zelboraf (see 4.8 Adverse Effects (Undesirable Effects), Post-marketing Experience). In patients who experience a severe dermatologic reaction, Zelboraf treatment should be permanently discontinued.

Photosensitivity
Mild to severe photosensitivity was reported in patients who were treated with Zelboraf in clinical trials (see 4.8 Adverse Effects (Undesirable Effects)). All patients should be advised to avoid sun exposure while taking Zelboraf. While taking Zelboraf, patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sun screen and lip balm (SPF ≥ 30+) when outdoors to help protect against sunburn.

For photosensitivity, grade 2 (intolerable) or greater adverse events, dose modifications are recommended (see section 4.2 Dose and Method of Administration).

Dupuytren's contracture and plantar fascial fibromatosis
Dupuytren's contracture and plantar fascial fibromatosis have been reported with Zelboraf. The majority of cases were mild to moderate, but severe, disabling cases of Dupuytren's contracture have also been reported (see section 4.8 Adverse Effects (Undesirable Effects); Post-marketing Experience).

Events should be managed with dose reduction, treatment interruption, or with treatment discontinuation (see section 4.2 Dose and Method of Administration, Dose Modifications).

Ophthalmologic Reactions
Serious ophthalmologic reactions including uveitis have been reported in patients treated with Zelboraf. Treatment with steroid and mydriatic ophthalmic drops may be required to manage uveitis. Additionally, blurry vision, iritis, photophobia and retinal vein occlusion have been reported. Patients should be monitored routinely for ophthalmologic reactions, and be advised to urgently seek medical attention in the event of acute onset eye pain and/or change in visual acuity.

QT Prolongation
Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase II QT sub-study in previously treated patients with metastatic melanoma (see 4.8 Adverse Effects (Undesirable Effects)). QT prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de Pointes. Treatment with Zelboraf is not recommended in patients with uncorrectable electrolyte abnormalities, long QT syndrome, or who are taking medicinal products known to prolong the QT interval.

ECG and electrolytes should be monitored before treatment with Zelboraf and after dose modification. Further monitoring should occur monthly during the first 3 months of treatment followed by every 3 months thereafter or more often as clinically indicated. Initiation of treatment with Zelboraf is not recommended in patients with QTc > 500 ms. If, during treatment, the QTc exceeds 500 ms (CTCAE ≥ grade 3), Zelboraf treatment should be temporarily interrupted, electrolyte abnormalities should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should not occur until the QTc decreases below 500 ms and should be re-initiated at a lower dose, as described in section 4.2 Dose and Method of Administration, Dose Modifications. Permanent discontinuation of Zelboraf treatment is recommended if, after correction of associated risk factors, the QTc increase meets values of both > 500 ms and > 60 ms change from pre-treatment values.

Pancreatitis

Pancreatitis has been reported in Zelboraf-treated subjects, generally occurring within two weeks after initiation of Zelboraf treatment. Unexplained abdominal pain should be promptly investigated, including appropriate diagnostic tests for pancreatitis. Patients should be closely monitored when re-starting Zelboraf after an episode of pancreatitis.

Liver Injury

Liver injury, including cases of severe liver injury, has been reported with Zelboraf (see 4.8 Adverse Effects (Undesirable Effects)*;* Post-Marketing Experience).

Liver laboratory abnormalities may occur with Zelboraf (see 4.8 Adverse Effects (Undesirable Effects), Clinical Trials). Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be measured before initiation of treatment and monitored monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption, or with treatment discontinuation (see section 4.2 Dose and Method of Administration, Dose Modifications).

Concurrent Administration with ipilimumab

In a Phase I trial, asymptomatic grade 3 increases in transaminases and bilirubin were reported with concurrent administration of ipilimumab (3 mg/kg) and Zelboraf (960 mg twice daily or 720 mg twice daily). Based on these data, the concurrent administration of ipilimumab and Zelboraf is not recommended outside of a clinical trial.

Use in Renal Impairment

Limited data are available in patients with renal impairment. A risk for increased exposure in patients with severe renal impairment cannot be excluded (see sections 4.2 Dose and Method of Administration and 5.2 Pharmacokinetic Properties).

Other Malignancies

Based on its mechanism of action, Zelboraf may cause progression of cancers associated with RAS mutations (see 4.8 Adverse Effects (Undesirable Effects), Post-Marketing Experience). Zelboraf should be used with caution in patients with a prior or concurrent cancer associated with RAS mutation.

Use in Hepatic Impairment

Limited data are available in patients with hepatic impairment. As vemurafenib is cleared by the liver, patients with severe hepatic impairment may have increased exposure (see sections

4.2 Dose and Method of Administration and 5.2 Pharmacokinetic Properties). Cases of liver injury, including severe liver injury, have been reported with Zelboraf (see section 4.4 Special Warnings and Precautions for Use; Liver Injury for important information on monitoring and management).

Paediatric Use
The safety and efficacy of Zelboraf in paediatric patients below 18 years of age have not been established.

Use in the Elderly
Ninety-four (94) of 336 patients (28%) with unresectable or metastatic melanoma treated with Zelboraf in the phase III study were ≥ 65 years old. Elderly patients (≥ 65 years old) may be more likely to experience adverse events, including cuSCC, decreased appetite, and cardiac disorders. The effects of Zelboraf on overall survival, progression-free survival and best overall response rate were similar in the elderly and younger patients (see section 5.2 Pharmacokinetic Properties).

Effects on laboratory tests
Creatinine
Creatinine increases, mostly cases of mild (> 1-1.5 x ULN) to moderate (> 1.5 – 3 x ULN) and mostly reversible in nature, have been reported (see section 4.8 Adverse Effects (Undesirable Effects)).

Serum creatinine should be measured before initiation of treatment and periodically monitored during treatment as clinically indicated. For recommended dose modifications, see section 4.2 Dose and Method of Administration, Dose Modifications.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Effects of Vemurafenib on Other Medicinal Products
CYP1A2 inhibition was observed when a single dose of caffeine (CYP1A2 substrate) was co-administered after repeat dosing with vemurafenib for 15 days. This resulted in a 2.6-fold increase (geometric mean ratio) (maximum 5-fold) in caffeine plasma exposure after vemurafenib treatment. In another clinical trial, vemurafenib increased AUC_{last} and AUC_{inf} of a single 2mg dose of tizanidine (CYP1A2 substrate) approximately 4.2 and 4.7 fold, respectively.Vemurafenib may increase the plasma exposure of substances predominantly metabolised by CYP1A2 and dose adjustments should be considered for CYP1A2 substrates with narrow therapeutic indices (such as theophylline, tizanidine, neuroleptics, including clozapine, olanzapine, carbamazepine and phenytoin, tricycle antidepressants, methadone, cyclosporine and warfarin) if co-administration cannot be avoided.

When a single dose of dextromethorphan (CYP2D6 substrate) was co-administered after repeat dosing with vemurafenib for 15 days, the plasma AUC of dextromethorphan and its metabolite dextrorphan increased by 47% (geometric mean ratio). The reason for this is unknown but does not appear related to CYP2D6 inhibition.

CYP3A4 induction was observed when a single dose of midazolam (CYP3A4 substrate) was co-administered after repeat dosing with vemurafenib for 15 days. This resulted a 39% decrease (geometric mean ratio) (maximum 80%) in midazolam plasma exposure after vemurafenib treatment. Vemurafenib may decrease the plasma exposure of substances predominantly

metabolised by CYP3A4 and dose adjustments should be considered for CYP3A4 substrates with narrow therapeutic indices. The efficacy of contraceptives metabolised by CYP3A4 may be decreased.

When a single dose of warfarin (CYP2C9 substrate) was co-administered after repeat dosing with vemurafenib for 15 days, some patients exhibited increased warfarin exposure (18% for S-warfarin by geometric mean ratio). Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.

Vemurafenib moderately inhibited CYP2C8 *in vitro*. The *in vivo* relevance of this finding is unknown, but a risk for a clinically relevant effect on concomitantly administered CYP2C8 substrates cannot be excluded. Concomitant administration of CYP2C8 substrates with a narrow therapeutic window should be made with caution since vemurafenib may increase their concentrations.

Due to the long half-life of vemurafenib, the full modulatory effect of vemurafenib on a concomitant medicine might not be seen for 8 days. After ceasing vemurafenib, a washout of 8 days may be needed to avoid an interaction with a subsequent treatment.

Effects of Other Medicinal Products on Vemurafenib

Vemurafenib is a substrate of CYP3A4 and, therefore, concomitant administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Coadministration of rifampin, a strong CYP3A4 inducer, significantly decreased the plasma exposure of vemurafenib (AUC) by approximately 40% following a single 960 mg dose of vemurafenib (see section 5.2 Pharmacokinetic Properties, Metabolism). Coadministration of itraconazole, a strong CYP3A4 inhibitor, increased steady state vemurafenib AUC by approximately 40%. Caution should be used when vemurafenib is co-administered with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) and inducers (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital, rifapentine, St John's Wort [hypericin]). Dose reduction of vemurafenib may be considered during co-administration with a strong CYP3A4 inhibitor, if clinically indicated (see section 4.2 Dose and Method of Administration, Dose Modifications).

Interaction of Vemurafenib with Drug Transport Systems

In vitro studies have demonstrated that vemurafenib is an inhibitor of the efflux transporter P-glycoprotein (P-gp). Clinical drug interaction study GO28394 using a P-gp substrate drug (digoxin) demonstrated that multiple oral doses of vemurafenib (960 mg twice daily) increased the exposure of a single oral dose of digoxin, with an approximately 1.8 and 1.5 fold increase in digoxin AUC_{last} and C_{max}, respectively. Caution should be exercised when dosing vemurafenib concurrently with P-gp substrates. Dose reduction of the concomitant P-gp substrate drug may be considered, if clinically indicated.

Vemurafenib is a weak P-gp substrate *in vitro* and its pharmacokinetics may be affected by medicines that inhibit or influence P-gp (e.g. verapamil, clarithromycin, ciclosporin, ritonavir, dronedarone, amiodarone, itraconazole, ranolazine). Concomitant administration of potent inducers of P-gp and vemurafenib should be avoided since the efficacy of vemurafenib may be reduced.

In vitro studies have demonstrated that vemurafenib is both a substrate and an inhibitor of breast cancer resistance protein (BCRP). The effects of vemurafenib on drugs that are substrates of BCRP, and the effects of P-gp or BCRP inducers and inhibitors on vemurafenib exposure are unknown but vemurafenib may increase the exposure of co-administered drugs that are substrates for BCRP.

In vitro, at clinically-relevant concentrations, vemurafenib was an inhibitor of the bile salt export pump (BSEP).

In vitro, vemurafenib was not a substrate for OATP1B1 or OATP1B3. It is unknown if vemurafenib is a substrate to other transport proteins.

Potentiation of Radiation Toxicity
Cases of radiation recall and radiation sensitisation have been reported in patients treated with radiation either prior, during or subsequent to Zelboraf treatment (see 4.8 Adverse Effects (Undesirable Effects)), Post-Marketing Experience). In the majority of cases, patients received radiotherapy regimens greater than or equal to 2 Gy/day (hypofractionated regimens).

Zelboraf should be used with caution when given concomitantly or sequentially with radiation treatment. Most cases were cutaneous in nature but some cases involving visceral organs had fatal outcomes.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility
No fertility studies have been conducted with Zelboraf. No histopathological findings were noted in male and female reproductive organs at subclinical systemic exposures in repeat-dose toxicology studies.

Use in Pregnancy - Category D
Women of childbearing potential and men should use effective contraception while receiving Zelboraf and for at least 6 months after discontinuation of Zelboraf.

Zelboraf is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

No clinical studies of Zelboraf in pregnant women have been performed, however placental transfer of vemurafenib to a fetus has been reported. Based on its mechanism of action, vemurafenib could cause fetal harm when administered to a pregnant woman. The teratogenic potential of vemurafenib has not been adequately evaluated in animal studies, although no unequivocal treatment-related increases in the incidences of malformations were observed in the fetuses of rats at doses up to 250 mg/kg/day (approximately 1.4 times the human clinical exposure based on AUC) and rabbits at doses up to 450 mg/kg/day (approximately 0.5 times the human clinical exposure based on AUC).

Use in Lactation
It is not known whether Zelboraf is excreted in human breast milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or

discontinue Zelboraf therapy after considering the benefits of breast-feeding for the child and the benefits of therapy for the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of Zelboraf on the ability to drive and use machines have been performed.

However, on the basis of reported adverse effects, Zelboraf may have a minor influence on the ability to drive and use machines. Fatigue, dizziness and eye problems may occur during treatment with Zelboraf (see sections 4.4. Special Warnings and Precautions for Use and section 4.8 Adverse Effects (Undesirable Effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

Summary of the safety profile

An estimated total of 6,300 patients have received Zelboraf in the clinical development program.

Adverse drug reactions (ADRs) were identified from two clinical trials, a phase III randomised, active-controlled study in treatment-naïve patients (*n* = 336) with BRAF V600 mutation-positive unresectable or metastatic melanoma (NO25026) and a phase II study (NP22657) in patients with BRAF V600 mutation-positive metastatic melanoma whom had failed at least one prior systemic therapy (*n* = 132).

In the phase III open-label study (NO25026), patients randomised to the Zelboraf arm received a twice-daily oral starting dose of 960 mg, and patients randomised to the active control arm received dacarbazine 1000 mg/m^2 administered intravenously every 3 weeks. At the time of analysis, the median duration of Zelboraf treatment was 6.6 months compared to 0.8 months for dacarbazine. The phase II study (NP22657) was an open-label, uncontrolled, single-arm study in which patients received Zelboraf 960 mg twice daily. The median treatment duration in this study was 5.7 months.

The most common ADRs of any grade (≥ 30% in either study) were arthralgia, fatigue, rash, photosensitivity reaction, alopecia, nausea, diarrhoea, headache, pruritus, vomiting, skin papilloma and hyperkeratosis. The most common (≥ 5%) grade 3 ADRs were cuSCC, keratoacanthoma, rash, arthralgia and gamma-glutamyltransferase (GGT) increased. The incidence of grade 4 adverse reactions was ≤ 4% in both studies.

The incidence of adverse events resulting in permanent discontinuation of study medication in NO25026 was 7%. In NP22657, the incidence of adverse events resulting in permanent discontinuation of study medication was 3%.

Table 3 below summarises the ADRs occurring in patients with melanoma and the frequency categories given are the highest incidence seen in any of the major clinical trials. ADRs are listed by MedDRA system organ class. The corresponding frequency category for each ADR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 3 Summary of adverse reactions* occurring in patients with unresectable or metastatic melanoma treated with Zelboraf in clinical trials

ADRs	Treatment-Naive Patients		Patients who Failed at least One Prior Systemic Therapy		Frequency category
	n = 336		n = 132		
	All Grades (%)	Grade 3 (%)	All Grades (%)	Grade 3 (%)	
Skin and subcutaneous tissue disorders					
Rash	43	9	55	8	Very Common
Photosensitivity reaction	40	4	54	4	Very Common
Alopecia	48	<1	40	-	Very Common
Pruritus	26	1	33	2	Very Common
Hyperkeratosis	29	2	31	-	Very Common
Rash maculo-papular	10	3	21	6	Very Common
Actinic keratosis	13	-	20	-	Very Common
Dry skin	24	-	21	-	Very Common
Erythema	18	-	11	-	Very Common
Palmar-plantar erythrodysaesthesia syndrome	10	<1	11	2	Very Common
Keratosis pilaris	10	<1	10	-	Very Common
Rash papular	5	<1	2	-	Common
Panniculitis	<1	-	2	-	Common
Erythema nodosum	2	<1	3	-	Common
Stevens-Johnson syndrome	<1	<1	-	-	Uncommon
Toxic epidermal necrolysis	<1	<1	-	-	Uncommon
Musculoskeletal and connective tissue disorders					
Arthralgia	56	6	70	9	Very Common
Myalgia	15	1	27	2	Very Common
Pain in extremity	23	<1	11	-	Very Common
Musculoskeletal pain	13	<1	12	-	Very Common
Back pain	16	<1	13	<1	Very Common
Arthritis	4	<1	11	2	Very Common
Dupuytren's contracture	<1	<1	<1	-	Uncommon
General disorders and administration site conditions					
Fatigue	47	3	60	4	Very Common
Edema peripheral	15	<1	27	-	Very Common
Pyrexia	22	<1	20	2	Very Common
Asthenia	15	<1	2	-	Very Common
Gastrointestinal disorders					
Nausea	39	2	45	3	Very Common
Diarrhea	37	2	32	<1	Very Common
Vomiting	22	2	33	2	Very Common
Constipation	16	<1	18	-	Very Common
Nervous system disorders					
Headache	34	2	31	<1	Very Common
Dysgeusia	16	-	11	-	Very Common
Neuropathy peripheral	4	-	11	<1	Very Common
Dizziness	12	<1	10	-	Very Common
VIIth nerve paralysis	<1	-	3	<1	Common
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)					
Skin papilloma	29	<1	33	-	Very Common

Squamous cell carcinoma of skin [#]	20	20	26	26	Very Common
Keratoacanthoma	11	11	5	5	Very Common
Seborrhoeic keratosis	14	<1	15	-	Very Common
Basal cell carcinoma	3	3	8	8	Common
Cardiac disorders					
Electrocardiogram QT interval prolonged	4	-	3	-	Common
Eye disorders					
Retinal vein occlusion	-	-	<1	<1	Uncommon
Uveitis	3	<1	5	-	Common
Iridocyclitis	<1	-	2	-	Common
Hepatobiliary disorders					
GGT increased [§§]	7	4	17	7	Very Common
Metabolism and nutrition disorders					
Decreased appetite	23	1	23	-	Very Common
Weight decreased	10	1	11	<1	Very Common
Respiratory, thoracic and mediastinal disorders					
Cough	15	-	17	-	Very Common
Vascular disorders					
Vasculitis	1	<1	2	-	Common
Injury, poisoning and procedural complications					
Sunburn	17	<1	17	-	Very Common
Infections and Infestations					
Folliculitis	8	<1	11	<1	Very Common

* Adverse drug reactions, reported using MedDRA and graded using NCI-CTCAE v4.0 (NCI common toxicity criteria) for assessment of toxicity.

[#] All cases of cutaneous squamous cell carcinoma were to be reported as Grade 3 per instructions to study investigators and no dose modification or interruption was required.

[§§] Grade 4 GGT increased reported in patients with unresectable or metastatic melanoma (< 1% in Treatment-Naïve patients and 4% in patients who failed at least one prior systemic therapy).

Gender

The grade 3 adverse events reported more frequently in females than males were rash, arthralgia and photosensitivity (see section 5.2 Pharmacokinetic Properties, Gender).

Description of selected ADRs from clinical trials

Cutaneous squamous cell carcinoma (cuSCC) (see section 4.4 Special Warnings and Precautions for Use)

In patients with unresectable or metastatic melanoma the incidence of cuSCC in Zelboraf-treated patients across studies was approximately 20%. The majority of excised lesions reviewed by an independent central dermatopathology laboratory were classified as SCC-keratoacanthoma subtype or with mixed-keratoacanthoma features (52%), both of which are a more benign, less invasive type of cuSCC. Most lesions classified as "other" (43%) were benign skin lesions (e.g. verruca vulgaris, actinic keratosis, benign keratosis, cyst/benign cyst). CuSCC usually occurred early in the course of treatment. Among patients who developed cuSCC, the median time to onset ranged from 7.1 to 8.1 weeks. Of the patients who experienced cuSCC, approximately 33% experienced > 1 occurrence with median time between occurrences of 6 weeks. Cases of cuSCC were typically managed with simple excision, and patients generally continued on treatment without dose modification.

Hypersensitivity Reactions (see section 4.4 Special Warnings and Precautions for Use)
A case of hypersensitivity reaction with rash, fever, rigors and hypotension 8 days after starting Zelboraf 960 mg twice daily was reported in a clinical trial. Similar symptoms were observed upon re-initiation of treatment with a single dose of 240 mg Zelboraf. The patient discontinued Zelboraf permanently and recovered without sequelae.

QT Prolongation (see section 4.4 Special Warnings and Precautions for Use)
Analysis of centralised ECG data from an open-label uncontrolled phase II QT sub-study in 132 patients treated with Zelboraf 960 mg twice daily showed a mean increase from baseline in QTc from Day 1 (3.3 ms; upper 95% CI: 5 ms) to Day 15 (12.8 ms; upper 95% CI: 14.9 ms). An exposure-dependent QTc prolongation was observed in this study and the mean QTc effect remained stable between 12 and 15 ms beyond the first month of treatment, with the largest mean QTc prolongation (15.1 ms; upper 95% CI: 17.7 ms) observed within the first 6 months of treatment (n = 90 patients). Two patients (1.5%) developed treatment-emergent absolute QTc values > 500 ms (CTCAE Grade 3), and only one patient (0.8%) exhibited a QTc change from baseline of > 60 ms.

Modeling and simulation of QT prolongation resulted in the following estimates: for the 960 mg twice-daily dose, the percentage of patients with QTcP (population correction formula) prolongation exceeding 60 ms was predicted to be 0.05%. This percentage was predicted to increase to 0.2%, for obese patients with BMI of 45 kg/m^2. The percentage of patients with a change from baseline in QTcP greater than 60 ms was predicted to be 0.043% for males and 0.046% for females. The percentage of patients with QTcP values above 500 ms was predicted to be 0.05% for males and 1.1% for females.

Laboratory Abnormalities
Liver laboratory abnormalities in the phase III clinical study are summarised in Table 4 below as the proportion of patients who experienced a shift from baseline to grade 3 or 4.

Table 4: Change from Baseline to Grade 3/4 Liver Enzyme Abnormalities*

	Change From Baseline to Grade 3/4	
	Zelboraf (%)	**Dacarbazine (%)**
GGT	11.5	8.6
AST	0.9	0.4
ALT	2.8	1.9
Alkaline phosphatase	2.9	0.4
Bilirubin	1.9	-

*For ALT, alkaline phosphatase and bilirubin there were no patients with a change to grade 4 in either treatment arm.

Creatinine changes from baseline in the Phase III clinical study are summarised in table 5 below.

Table 5: Creatinine change from baseline

	Vemurafenib (%)	Dacarbazine (%)
Change >= 1 grade from baseline (all grade)	27.9	6.1
Change >= 1 grade from baseline to grade 3 or higher	1.2	1.1
● To grade 3	0.3	0.4
● To grade 4	0.9	0.8

Post-Marketing Experience

The following ADRs have been identified from post-marketing experience with Zelboraf (Table 6) based on spontaneous case reports and literature cases. ADRs are listed according to system organ classes in MedDRA and any corresponding frequency category estimation for each ADR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 6: Adverse Drug Reactions from the Post-Marketing Setting

System Organ Class (SOC)	Zelboraf (%)	Frequency
Hepatobiliary disorders		
Liver injury[1]	< 1	Uncommon
Blood and lymphatic systems disorders		
Neutropenia	< 1	Uncommon
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Chronic myelomonocytic leukaemia (CMML)[1,2]	N/A	Frequency not known
Pancreatic adenocarcinoma[1,3]	N/A	Frequency not known
Skin and Subcutaneous Tissue Disorders		
Drug reaction with eosinophilia and systemic symptoms (DRESS)[1]	N/A	Frequency not known
Injury, poisoning and procedural complications		
Radiation injury[1,4]	N/A	Frequency not known
Gastrointestinal Disorders		
Pancreatitis	< 1	Uncommon
Stomatitis	<1	Common
Renal and Urinary Disorders		
Acute kidney injury	N/A	Frequency not known
Musculoskeletal and connective tissue Disorders		
Dupuytren's contracture	N/A	Frequency not known
Plantar fascial fibromatosis	N/A	Frequency not known
Immune System Disorders		
Sarcoidosis	N/A	Rare

1 see section 4.4 Special Warnings and Precautions for Use, Effects on laboratory tests
2 Progression of pre-existing chronic myelomonocytic leukaemia with NRAS mutation
3 Progression of pre-existing pancreatic adenocarcinoma with KRAS mutation
4 Includes recall phenomenon, radiation skin injury, radiation pneumonitis, radiation oesophagitis, radiation proctitis, radiation hepatitis, cystitis radiation, and radiation necrosis.

Description of selected ADRs from postmarketing experience

Acute kidney injury

A broad spectrum of renal ADR cases has been reported with Zelboraf ranging from mild/moderate creatinine elevations to acute interstitial nephritis and acute tubular necrosis, some observed in the setting of dehydration events. In most cases, creatinine elevations appear to be reversible in nature (see section 4.4 Special Warnings and Precautions for Use and 4.2 Dose and Method of Administration, Table 1).

Laboratory Abnormalities

Liver laboratory abnormalities including ≥ 5 times the upper limit of normal (ULN) for ALT, ≥ 2 times the ULN for ALP, and ≥ 3 times the ULN for ALT and simultaneous elevation of bilirubin concentration (> 2 times the ULN) have been reported in the post-marketing setting (see section 4.4 Special Warnings and Precautions for Use).

Creatinine lab abnormalities were reported in the post marketing setting (see section 4.4 Special Warnings and Precautions for Use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific treatment for Zelboraf overdose.

Patients who develop adverse reactions should receive appropriate symptomatic treatment. Dose limiting toxicities for Zelboraf include rash with pruritus and fatigue.

In the event of suspected overdose, Zelboraf should be withheld and treatment should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor, ATC code: L01XE15.

Mechanism of Action

Zelboraf is a protein kinase inhibitor, selective for the activating mutation of the oncogenic BRAF serine-threonine kinase enzyme.

Vemurafenib is an inhibitor of BRAF serine-threonine kinase, and other kinases, such as CRAF, ARAF, SRMS, ACK1, MAP4K5 and FGR. Mutations in the BRAF gene result in constitutive activation of BRAF proteins, which can cause cell proliferation without associated growth factors.

Preclinical data generated in biochemical assays demonstrated that vemurafenib can inhibit BRAF kinases with activating codon 600 mutations (see Table 7).

Table 7 Kinase Inhibitory Activity of Vemurafenib Against Different BRAF Kinases

Kinase	Anticipated frequency in V600 mutation-positive melanoma*	Inhibitory Concentration 50 (IC_{50}) (nM)
BRAFV600E	87.3%	10
BRAFV600K	7.9%	7
BRAFV600R	1%	9
BRAFV600D	<0.2%	7
BRAFV600G	<0.1%	8
BRAFV600M	0.1%	7
BRAFV600A	<0.1%	14
BRAFWT	NA	39

* Estimated from 16403 melanomas with annotated BRAF codon 600 mutations in the public COSMIC database, release 71 (November 2014.

This inhibitory effect was confirmed in the ERK phosphorylation and cellular anti-proliferation assays in available melanoma cell lines expressing V600-mutant BRAF. In cellular anti-proliferation assays the inhibitory concentration 50 (IC50) against V600 mutated cell lines (V600E, V600R, V600D and V600K mutated cell lines) ranged from approximately 0.015 to 1 µM whereas the IC50 against BRAF wild type cell lines were > 10 µM.

Clinical trials

The efficacy of Zelboraf has been evaluated in 337 patients from a phase III randomised, active-controlled clinical trial and 132 patients from a phase II single arm clinical trial. Prior to study enrolment, tumour specimens from all patients were tested for the presence of a BRAF V600 mutation using a real-time polymerase chain reaction assay. During clinical trials the cobas® 4800 BRAF V600 Mutation Test was used to assess the BRAF mutation status of DNA isolated from formalin-fixed, paraffin-embedded tumour tissue. Please refer to the package insert of the cobas® 4800 BRAF V600 Mutation Test, or other approved test kits for detailed information.

Among the tumour specimens sequenced retrospectively from enrolled patients, the majority (92%) were BRAF V600E mutation-positive and 8% carried non-E mutations (primarily V600K). The efficacy and safety of Zelboraf in patients with tumours expressing BRAF V600 non-E mutations have not been convincingly established.

Treatment-Naïve Patients (Study NO25026, BRIM3)

An open-label, multicenter, multinational, randomised phase III study supports the use of Zelboraf in previously untreated patients with BRAF V600 mutation-positive unresectable stage IIIC or stage IV melanoma. In this study, patients were randomised to treatment with Zelboraf (960 mg, orally, twice daily) or dacarbazine (1000 mg/m^2 every 3 weeks, intravenously).

A total of 675 patients were randomised to Zelboraf (n = 337) or dacarbazine (n = 338). Randomisation was stratified according to disease stage, lactate dehydrogenase (LDH), ECOG performance status and geographic region. Baseline characteristics were well balanced between treatment groups. For patients randomised to Zelboraf, most patients were male (59%) and Caucasian (99%), the median age was 56 years (28% were ≥ 65 years old), all patients had

ECOG performance status of 0 or 1, and the majority of patients had stage M1c disease (66%). The co-primary efficacy endpoints of the study were overall survival (OS) and progression-free survival (PFS). Key secondary endpoints included confirmed best overall response rate (BORR) and response duration.

Statistically significant and clinically meaningful improvements were observed in the co-primary endpoints of OS ($p < 0.0001$) and PFS ($p < 0.0001$) (unstratified log-rank test) based on the pre-specified interim analysis at the data cut-off of 30 December 2010. The median follow-up time for OS in the Zelboraf group at the 30 December 2010 data cut-off was 3.75 months (range 0.3 – 10.8 months) and in the dacarbazine group was 2.33 months (range < 0.1 – 10.3 months). At the time of analysis, Kaplan-Meier estimates of median OS for both treatment arms were considered unreliable due to the small number of patients in follow-up (< 10%) beyond month 7. The secondary endpoint of confirmed BORR [complete response (CR) + partial response (PR)], as assessed by the investigator, was significantly improved ($p < 0.0001$) in the Zelboraf arm (48.4%) (95% CI: 41.6%, 55.2%) compared to the dacarbazine arm (5.5%) (95% CI: 2.8%, 9.3%). There were 2 complete responses (0.9%) and 104 partial responses (47.4%) in the Zelboraf arm and all 12 responses were partial responses (5.5%) in the dacarbazine arm. Stable disease assessed according to RECIST 1.1 was observed in 37% of Zelboraf-treated patients and 24% of dacarbazine-treated patients.

Improvement in OS, PFS and confirmed BORR in favour of Zelboraf treatment were generally observed across subgroups (age, sex, baseline LDH, ECOG performance status, metastatic disease stage) and geographic regions.

The proportion of patients with improvement in the physician's assessment of performance status was higher in the Zelboraf group (63.4%) (95% CI: 57%, 69%) than in the dacarbazine group (20.2%) (95% CI: 15%, 26%).

After the pre-specified interim analysis with a December 30, 2010 data cut-off the study was modified to permit dacarbazine patients to cross over to receive Zelboraf. Post-hoc survival analyses were undertaken thereafter as described in Table 8. At the time of the December 20, 2012 data cut-off analysis the median follow-up time in the Zelboraf arm was 13.4 months (range 0.4 to 33.3 months). The Kaplan-Meier estimate of median OS for Zelboraf was 13.6 months (95% CI: 12.0, 15.3).

Table 8: Overall Survival in Treatment-Naïve Patients with BRAF V600 Mutation Positive Melanoma by Study Cut-Off date (*n* = 338 dacarbazine, *n* = 337 Zelboraf)

Cut-off dates	Treatment	Number of deaths (%)	Hazard Ratio (HR) (95% CI)	Number of cross-over patients (%)
December 30, 2010	dacarbazine	75 (22)	0.37 (0.26, 0.55)	0 (not applicable)
	Zelboraf	43 (13)		
March 31, 2011	dacarbazine	122 (36)	0.44 (0.33, 0.59)[#]	50 (15%)
	Zelboraf	78 (23)		
October 3, 2011	dacarbazine	175 (52)	0.62 (0.49, 0.77)[#]	81 (24%)
	Zelboraf	159 (47)		
December 20, 2012	dacarbazine	236 (70)	0.78 (0.64, 0.94)[#]	84 (25%)
	Zelboraf	242 (72)		

[#]Censored results at time of cross-over

Non-censored results at time of cross-over: March 31, 2011: HR (95% CI) = 0.47 (0.35, 0.62); October 3, 2011: HR (95% CI) = 0.67 (0.54, 0.84); December 20, 2012: HR (95% CI) = 0.79 (0.66, 0.95)

Figure 1: Kaplan-Meier Curves of Overall Survival: Treatment-Naïve Patients (December 20, 2012 cut-off)

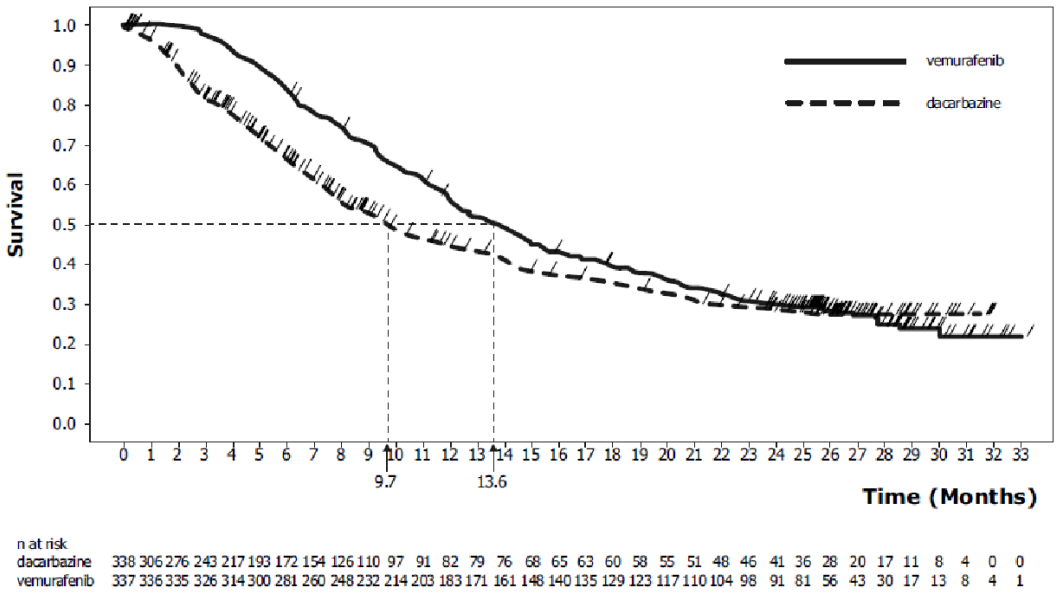


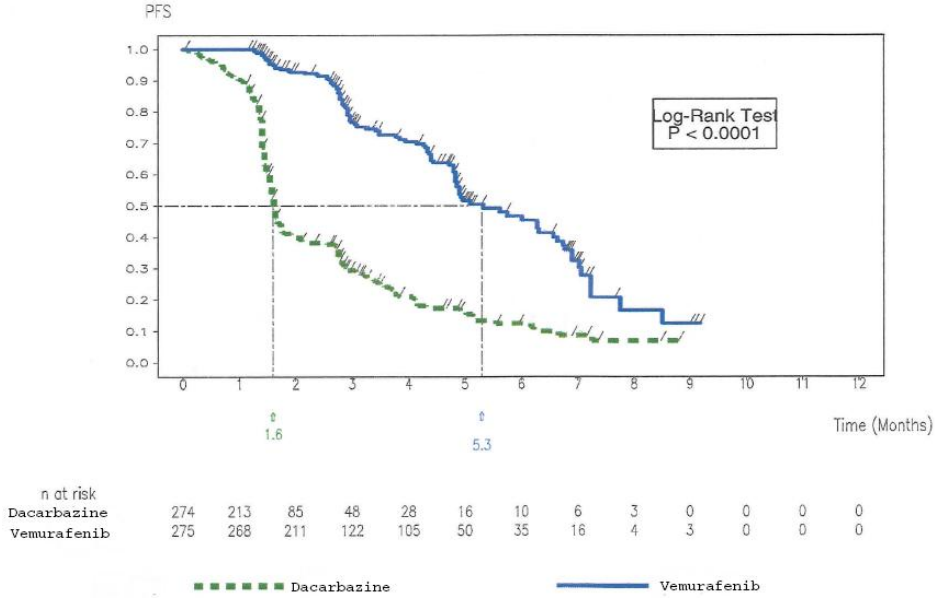
Table 9 and Figure 2 show the progression-free survival in treatment-naïve patients with BRAF V600 mutation positive melanoma.

Table 9: Progression-Free Survival in Treatment-Naïve Patients with BRAF V600 Mutation Positive Melanoma (December 30, 2010 cut-off)

	Zelboraf ***n*** **= 337**	**dacarbazine** ***n*** **= 338**	***p*-value[c]**
PFS Hazard Ratio (95% CI)[a]	0.26 (0.20, 0.33)		< 0.0001
6-month PFS rate (95 % CI)[b]	47% (38%, 55%)	12% (7%, 18%)	-
Median PFS (months) (95% CI)[b]	5.32 (4.86, 6.57)	1.61 (1.58, 1.74)	-

[a] Hazard ratio estimated using Cox model (a hazard ratio of < 1 favors Zelboraf); [b] Kaplan-Meier estimate; [c] Unstratified log-rank test. PFS = progression-free survival.

Figure 2: Kaplan-Meier Curves of Progression-Free Survival: Treatment-Naïve Patients (December 30, 2010 cut-off)



Patients Who Failed at Least One Prior Systemic Therapy (Study NP22657, BRIM2)
A phase II single-arm, multicenter, multinational study was conducted in 132 metastatic melanoma patients with BRAF V600-mutation-positive tumours who had received at least one prior therapy. Patients received 960 mg Zelboraf twice daily. The median age was 52 years old with 19% of patients being older than 65 years old. The majority of patients were male (61%), Caucasian (99%), and had stage M1c disease (61%). Forty-nine percent of patients had failed ≥ 2 prior therapies. The median duration of follow-up was 6.87 months (range, 0.6 – 11.3 months).

The primary endpoint of confirmed BORR (CR + PR) as assessed by an independent review committee (IRC) was 52% (95% CI: 43%, 61%). The median time to response was 1.4 months, with 75% of responses occurring by 1.6 months of treatment.

Efficacy results are summarised in Table 10.

Table 10: Efficacy Results for Phase II Study (NP22657)

	Independent Review Committee Assessment ***n* = 132**
BORR (*n*) [95% CI] **CR** (*n*) **PR** (*n*)	52% (69) [43%, 61%] 2% (3) 50% (66)
Time to response, median months [range]	1.4 months [1.2, 5.5]
Duration of response, median months [95% CI]	6.5 months [5.6, NR]
PFS, median months [95% CI] **6-month PFS** [95% CI]	6.1 months [5.5, 6.9] 52% [43%, 61%]
OS, median months [95% CI] **6-month survival rate** [95% CI] **1 year survival rate** [95% CI]	15.9 months [11.2, 19.3] 0.77 [0.69, 0.84] 0.58 [0.48, 0.66]

BORR = best overall response rate (confirmed); CR = complete response; PR = partial response; PFS = progression-free survival; OS = overall survival; NR = not reached.

Patients With Brain Metastases

An open-label, single-arm, multicenter, phase II study (n = 146) of Zelboraf was conducted in adult patients with histologically confirmed metastatic melanoma harbouring the BRAF V600 mutation and with brain metastases. Patients could be either symptomatic or asymptomatic for their brain metastases. The study included two simultaneously enrolling cohorts:

- Previously untreated patients (cohort 1: n = 90): Patients who had not received previous treatment for brain metastases; prior systemic therapy for metastatic melanoma was allowed.
- Previously treated patients (cohort 2: n = 56): Patients who had been previously treated for their brain metastases and had progressed following this treatment. For patients treated with stereotactic radiotherapy (SRT) or surgery, a new RECIST-assessable brain lesion must have developed following this prior therapy.

The median age of the patients was 54 years (range 26 to 83 years), and was similar in the two cohorts. The majority of patients were men (61.6%) and similarly distributed between the two cohorts. A total of 135 patients (92.5%) were reported as white, with the race of 11 patients (7.5%) not reported due to local regulations. The median number of brain target lesions at baseline was 2 (range 1 to 5), in both cohorts.

The primary objective of the study was to evaluate the efficacy of Zelboraf using best overall response rate (BORR) in the brain of metastatic melanoma patients with previously untreated brain metastases, as assessed by an independent review committee (IRC) using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1).

Secondary objectives included an evaluation of the efficacy of Zelboraf using BORR in the brain of previously treated patients, duration of response (DOR), progression-free survival (PFS) and overall survival (OS) in patients with melanoma metastatic to the brain.

Table 11 Efficacy of Zelboraf in patients with brain metastases

	Cohort 1 No Previous Treatment	Cohort 2 Previously Treated	Total
BORR[a] in brain (n)	90	56	146
Responders (n[%]) (95% CI)[b]	16 (17.8%) (10.5–27.3)	10 (17.9%) (8.9–30.4)	26 (17.8%) (12.0–25.0)
DOR[c] in brain (n)	16	10	26
Median (months) (95% CI)[d]	4.6 (2.9, 6.2)	6.6 (2.8, 10.7)	5.0 (3.7, 6.6)
PFS - overall (n)	90	56	146
Median (months)[e] (95% CI)[d]	3.7 (3.6, 3.7)	3.7 (3.6, 5.5)	3.7 (3.6, 3.7)
PFS - brain only (n)	90	56	146
Median (months)[e] (95% CI)[d]	3.7 (3.6, 4.0)	4.0 (3.6, 5.5)	3.7 (3.6, 4.2)
OS (n)	90	56	146
Median (months) (95% CI)[d]	8.9 (6.1, 11.5)	9.6 (6.4, 13.9)	9.6 (6.9, 11.5)

a Best Overall Response Rate as assessed by independent review committee, number of responders - n (%)
b two-sided 95% Clopper-Pearson Confidence Interval (CI)
c Duration of response as assessed by an Independent Review Committee
d Kaplan-Meier estimate
e assessed by investigator

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic (PK) parameters for vemurafenib were determined using non compartmental analysis in a phase I and a phase III study. Mean C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ were approximately 62 μg/mL, 53 μg/mL and 600 μg.h/mL, respectively. Population PK analysis using pooled data from 458 patients estimated the median of the steady-state C_{max}, C_{min} and AUC to be 62 μg/mL, 59 μg/mL and 734 μg.h/mL, respectively. The median accumulation ratio estimate for a twice daily regimen is 7.36. The PK of vemurafenib is shown to be dose proportional between 240 and 960 mg twice daily dosing, and population PK analysis also confirmed that the PK of vemurafenib is linear.

Absorption

Vemurafenib is absorbed with a median T_{max} of approximately 4 hours following a single 960 mg dose (four 240 mg tablets). Vemurafenib exhibits marked accumulation after repeat dosing at 960 mg twice daily with high inter-patient variability. In the phase II study mean vemurafenib plasma concentration at 4 hours post dose increased from 3.6 μg/mL on Day 1 to 49.0 μg/mL on Day 15 (range 5.4 – 118 μg/mL).

The bioavailability of vemurafenib at steady state was 57.8% (geometric mean).

At steady state (reached by day 15 in 80% of patients), the mean vemurafenib exposure in plasma is stable (concentrations before and 2 – 4 hours after the morning dose) as indicated by the mean ratio of 1.13. Similar marked inter-patient variability in plasma exposure was observed at steady-state independent of dose reduction.

Following oral dosing, the absorption rate constant for the population of metastatic melanoma patients is estimated to be 0.19 hr^{-1} (with 101% inter-patient variability).

Food (high fat meal) increases the relative bioavailability of a single 960 mg dose of vemurafenib. The geometric mean ratios between the fed and fasted states for C_{max} and AUC were 2.5 and 4.6 to 5.1 fold, respectively. The median T_{max} was increased from 4 to 7.5 hours when a single vemurafenib dose was taken with food. Safety and efficacy data from pivotal studies were collected from patients taking vemurafenib with or without food.

The effect of food on steady-state vemurafenib exposure is currently unknown.

Distribution

The population apparent volume of distribution for vemurafenib in metastatic melanoma patients is estimated to be 91 L (with 64.8% inter-patient variability). It is highly bound to human plasma proteins *in vitro* (> 99%).

Metabolism

The relative proportions of vemurafenib and its metabolites were characterised in a human mass balance study with a single dose of ^{14}C-labeled vemurafenib administered orally at steady state.

On average, 95% of the dose was recovered within 18 days. The majority (94%) in faeces, with < 1% recovered in urine. While CYP3A4 is the primary enzyme responsible for the metabolism of vemurafenib in vitro, conjugation metabolites (glucuronidation and glycosylation) were also identified in humans. However, the parent compound was the predominant component (95%) in plasma. Although metabolism does not appear to result in a relevant amount of metabolites in plasma, the importance of metabolism for excretion cannot be excluded. Coadministration of rifampin, a strong CYP3A4 inducer, significantly decreased the plasma exposure of vemurafenib (AUC) by approximately 40% following a single 960 mg dose of vemurafenib, suggesting CYP3A4 pathway could be important elimination pathway for vemurafenib. Coadministration of itraconazole, a strong CYP3A4 inhibitor, increased steady state vemurafenib AUC by approximately 40%.

Excretion

The population apparent clearance of vemurafenib in patients with metastatic melanoma is estimated to be 29.3 L/day (with 31.9% inter-patient variability). The median of the individual elimination half-life estimates for vemurafenib is 56.9 hours (the 5^{th} and 95^{th} percentile range

Pharmacokinetics in Special Populations

<u>Paediatrics</u>

Limited pharmacokinetic data from six adolescent patients aged 15 to 17 with stage IIIC or IV BRAF V600 mutation positive melanoma suggest that vemurafenib pharmacokinetic characteristics in adolescents are generally similar to those in adults. However, no conclusion can be made due to the limited amount of data (see section 4.2 Dose and Method of Administration - Special Dosage Instructions).

Elderly
Based on the population pharmacokinetic analysis, age has no statistically significant effect on vemurafenib pharmacokinetics.

Hepatic Impairment
Based on preclinical data and the human mass balance study, vemurafenib is eliminated primarily via the liver. No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of vemurafenib. In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, increases in AST, ALT, and total bilirubin up to three times the upper limit of normal did not influence the apparent clearance of vemurafenib. The potential need for dose adjustment in patients with severe hepatic impairment cannot be determined as clinical and pharmacokinetic data are insufficient to determine the effect of metabolic or excretory hepatic impairment on vemurafenib pharmacokinetics. Caution is recommended in these patients (see sections 4.2 Dose and Method of Administration and 4.4 Special Warnings and Precautions for Use).

Renal Impairment
No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of vemurafenib. In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, mild and moderate renal impairment did not influence the apparent clearance of vemurafenib (creatinine clearance > 30 mL/min). The potential need for dose adjustment in patients with severe renal impairment (creatinine clearance < 29 mL/min) cannot be determined as clinical and pharmacokinetic data are insufficient (see sections 4.2 Dose and Method of Administration and 4.4 Special Warnings and Precautions for Use).

Gender
In the population pharmacokinetic analysis, gender was found to be statistically significant in explaining the inter-patient variability, with a 17% greater apparent clearance (CL/F) and a 48% greater apparent volume of distribution (V/F) in males. However, results from the population analysis have shown that the differences in exposure are relatively small (with an estimated median 12-hour steady-state AUC and C_{max} of 792 µg.h/mL and 67 µg/mL in females and 696 µg.h/mL and 63 µg/mL in males, respectively), indicating that there is no need to dose adjust based on gender.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Standard genotoxicity studies in *in vitro* assays (bacterial mutation [Ames assay], human lymphocyte chromosome aberration) and in the *in vivo* rat bone marrow micronucleus test conducted with vemurafenib were all negative.

Carcinogenicity
No carcinogenicity studies have been performed to establish the carcinogenic potential of Zelboraf.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate
Hydroxypropylcellulose.

Film-coating
Polyvinyl alcohol
Titanium dioxide CI77891
Macrogol 3350
Talc (purified)
Iron oxide red CI77491.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C. Store in the original blister pack and outer carton. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Pack-size: 56 x 1 film-coated tablets (7 blisters of 8 x 1 tablet)

Zelboraf® is sold under licence from Plexxikon Inc., a member of the Daiichi Sankyo group.

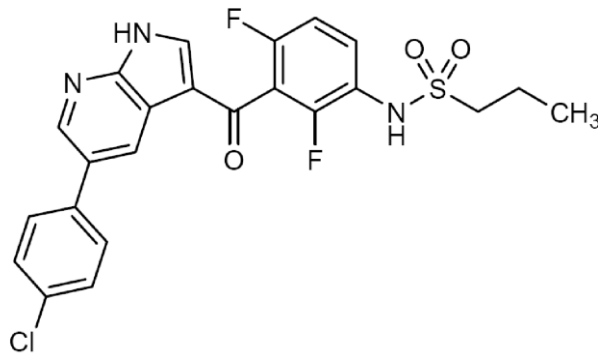
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



Vemurafenib is designated chemically as *N*-{3-[5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-b] pyridin-3-carbonyl]-2,4-difluorophenyl} propane-1-sulfonamide.

The empirical formula of vemurafenib is $C_{23}H_{18}ClF_2N_3O_3S$ and its molecular weight is 489.9.

Vemurafenib is a white to off-white crystalline solid. It is practically insoluble in aqueous media. The pKa (acidic) is 7.9 and 11.1 and the log P (water) is 3.0.

CAS number
918504-65-1

7. MEDICINE SCHEDULE (POISONS STANDARD)
Prescription Only Medicine (S4)

8. SPONSOR
Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30-34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL
10 May 2012

10. DATE OF REVISION OF THE TEXT
27 June 2025

Summary table of changes

Section Changed	Summary of new information
4.8	Addition of adverse reaction sarcoidosis