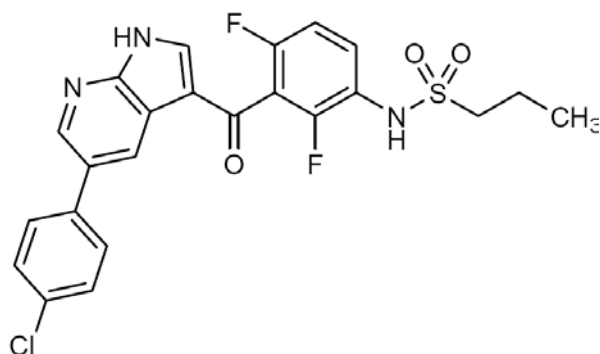


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## ZELBORAF<sup>®</sup>

Vemurafenib

CAS 918504-65-1



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<sub>23</sub>H<sub>18</sub>ClF<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S and its molecular weight is 489.9.

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

## DESCRIPTION

ZELBORAF film-coated 240 mg tablets are oval, biconvex, pinkish white to orange white tablets with “VEM” engraved on one side. Each tablet contains 240 mg of vemurafenib (as a co-precipitate of vemurafenib and hypromellose acetate succinate). ZELBORAF tablets contain the following excipients: croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, and hydroxypropylcellulose. The film-coating contains polyvinyl alcohol, titanium dioxide CI77891, macrogol 3350, talc (purified), and iron oxide red CI77491.

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

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## PHARMACOLOGY

### PHARMACODYNAMICS

#### Mechanism of Action

Vemurafenib is a low molecular weight, oral inhibitor of some mutated forms of the BRAF serine-threonine kinase enzyme. In biochemical assays, vemurafenib also inhibits other kinases, such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5 and FGR at higher concentrations. Some mutations in the BRAF gene result in constitutively activated BRAF kinases, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib had anti-tumour effects in xenograft models of melanomas with mutated BRAF V600E.

### PHARMACOKINETICS

The pharmacokinetic (PK) parameters for vemurafenib were determined using non compartmental analysis in a phase I and a phase III study (20 patients after 15 days of dosing at 960 mg twice daily, and 204 patients in steady state day 22, respectively). Mean  $C_{max}$ ,  $C_{min}$  and  $AUC_{0-12hr}$  were approximately 60  $\mu\text{g/mL}$ , 53  $\mu\text{g/mL}$  and 600  $\mu\text{g.h/mL}$ , 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  $\mu\text{g/mL}$ , 59  $\mu\text{g/mL}$  and 734  $\mu\text{g.h/mL}$ , 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 and Bioavailability

Vemurafenib at 960 mg twice daily as a 240 mg tablet is absorbed with a median  $T_{max}$  of approximately 4 hours. 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  $\mu\text{g/mL}$  on Day 1 to 49.0  $\mu\text{g/mL}$  on Day 15 (range 5.4 – 118  $\mu\text{g/mL}$ ).

At steady state, 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  $0.19 \text{ hr}^{-1}$  (with 101% inter-patient variability).

The absolute bioavailability of vemurafenib has not been determined.

The effect of food on vemurafenib has not been determined.

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### **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 characterized in a human mass balance study.

On average, 95% of the dose was recovered within 18 days. The majority (94%) in faeces, with < 1% recovered in urine. The parent compound was the predominant component (95%) in plasma.

### **Elimination**

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<sup>th</sup> and 95<sup>th</sup> percentile range is 29.8 – 119.5 hours).

### **Pharmacokinetics in Special Populations**

*Paediatrics:* No studies have been conducted to investigate the pharmacokinetics of vemurafenib in children or adolescents.

*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 studies have been conducted to investigate the pharmacokinetics of vemurafenib in patients with hepatic impairment. Caution is recommended in these patients.

*Renal Impairment:* No studies have been conducted to investigate the pharmacokinetics of vemurafenib in patients with renal impairment.

*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<sub>max</sub> 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.

## **CLINICAL TRIALS**

The efficacy of ZELBORAF has been evaluated in 336 patients from a phase III randomized, active-controlled clinical trial and 132 patients from a phase II single arm clinical trial. Prior

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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<sup>®</sup> 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<sup>®</sup> 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)**

An open-label, multicenter, multinational, randomized 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 randomized to treatment with ZELBORAF (960 mg, orally, twice daily) or dacarbazine (1000 mg/m<sup>2</sup> every 3 weeks, intravenously).

A total of 675 patients were randomized to ZELBORAF ( $n = 337$ ) or dacarbazine ( $n = 338$ ). Randomization 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 randomized to ZELBORAF, most patients were male (59%) and Caucasian (99%), the median age was 56 years (28% were  $\geq 65$  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.

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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 1.

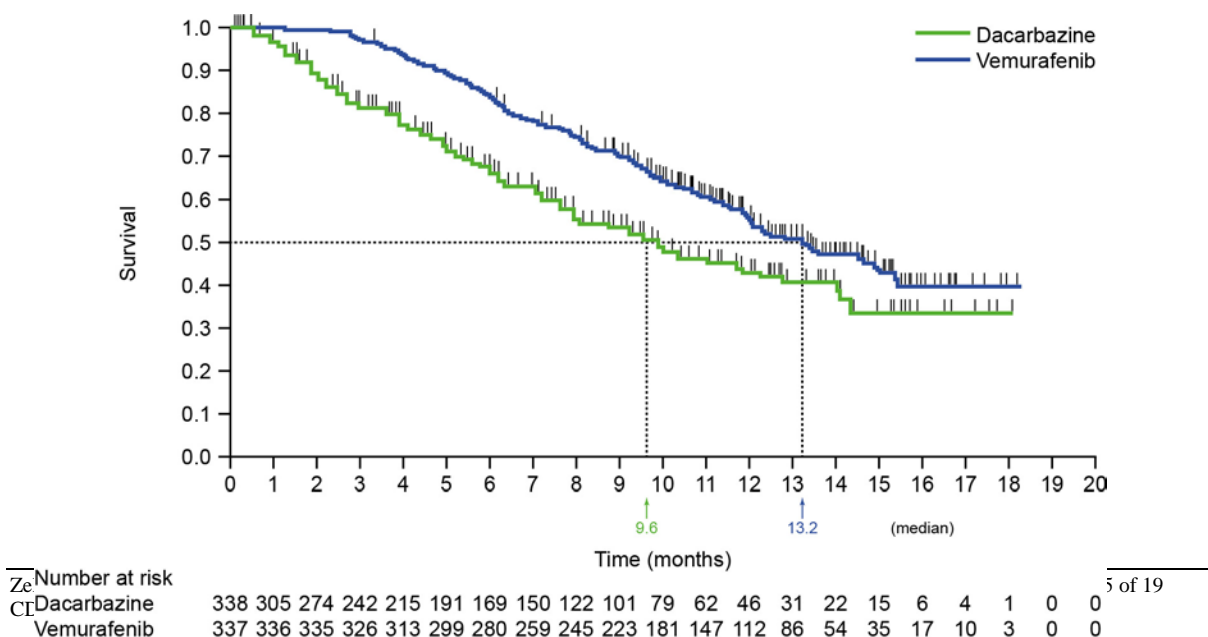
**Table 1 Overall Survival in Treatment-Naïve Patients with BRAF V600 Mutation Positive Melanoma by Study Cut-Off date (n = 338 dacarbazine, n = 337 ZELBORAF)**

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) <sup>#</sup>	50 (15%)
	ZELBORAF	78 (23)		
October 3, 2011	dacarbazine	175 (52)	0.62 (0.49, 0.77) <sup>#</sup>	81 (24%)
	ZELBORAF	159 (47)		

<sup>#</sup>Censored results at time of cross-over

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

**Figure 1 Kaplan-Meier Curves of Overall Survival: Treatment-Naïve Patients (October 3, 2011 cut-off)**



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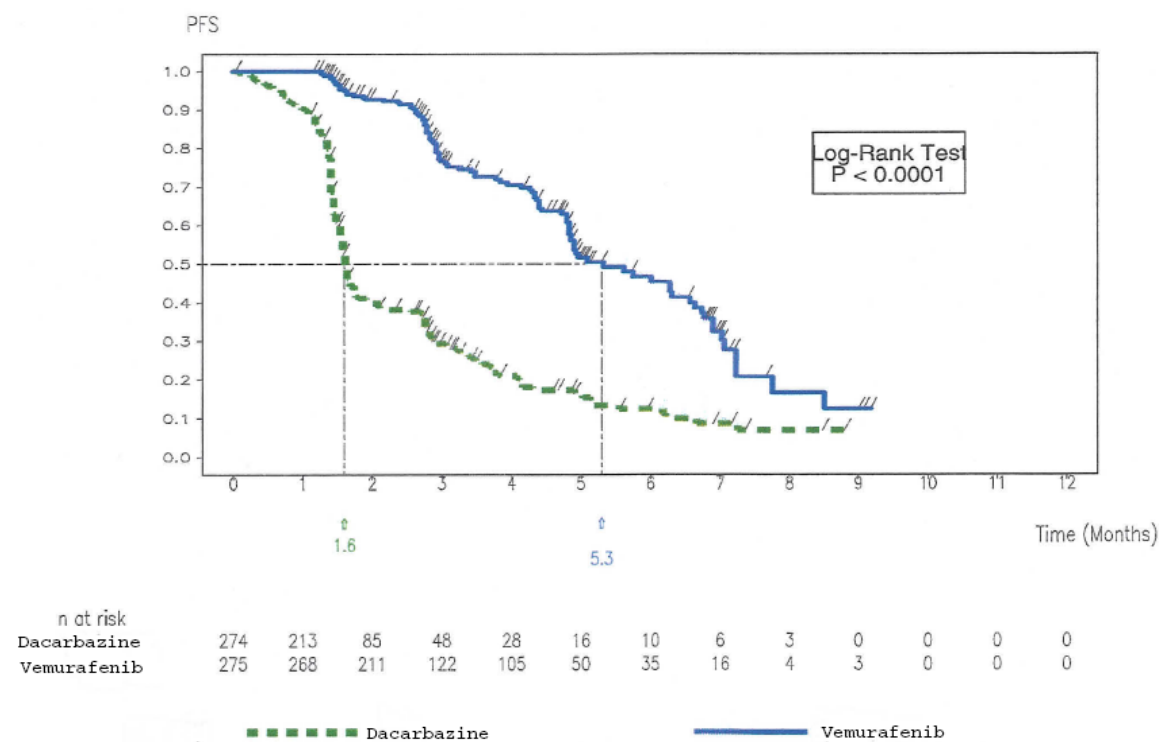
Table 2 and Figure 2 show the progression-free survival in treatment-naïve patients with BRAF V600 mutation positive melanoma.

**Table 2 Progression-Free Survival in Treatment-Naïve Patients with BRAF V600 Mutation Positive Melanoma (December 30, 2010 cut-off)**

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

\*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)**



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### **Patients Who Failed at Least One Prior Systemic Therapy (Study NP22657)**

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  $\geq 2$  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 summarized in Table 3.

**Table 3 Efficacy Results for Phase II Study (NP22657)**

	<b>Independent Review Committee Assessment <i>n</i> = 132</b>
<b>BORR</b> ( <i>n</i> )	52% (69)
[95% CI]	[43%, 61%]
<b>CR</b> ( <i>n</i> )	2% (3)
<b>PR</b> ( <i>n</i> )	50% (66)
<b>Time to response</b> , median months	1.4 months
[range]	[1.2, 5.5]
<b>Duration of response</b> , median months	6.5 months
[95% CI]	[5.6, NR]
<b>PFS</b> , median months	6.1 months
[95% CI]	[5.5, 6.9]
<b>6-month PFS</b>	52%
[95% CI]	[43%, 61%]
<b>OS</b> , median months	NR
[95% CI]	[9.5, NR]
<b>6-month survival rate</b>	77 %
[95% CI]	[70%, 85%]

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

## **INDICATIONS**

ZELBORAF is indicated for the treatment of unresectable stage IIIC or stage IV metastatic melanoma positive for a BRAF V600 mutation.

## **CONTRAINDICATIONS**

ZELBORAF is contraindicated in patients with:

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- hypersensitivity to the active substance or to any of the excipients.

## PRECAUTIONS

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 *CLINICAL TRIALS*).

### 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 *ADVERSE EFFECTS*). CuSCC usually occurred early in the course of treatment. Potential risk factors associated with cuSCC in ZELBORAF clinical trials included age ( $\geq 65$  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 should also be done prior to initiation of treatment and periodically during treatment as 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



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Serious hypersensitivity reactions, including anaphylaxis have been reported in association with ZELBORAF and upon re-initiation of treatment (see *ADVERSE EFFECTS*). Severe hypersensitivity reactions included generalized 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. 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 *ADVERSE 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  $\geq$  30+) when outdoors to help protect against sunburn.

For photosensitivity, grade 2 (intolerable) or greater adverse events, dose modifications are recommended (see *DOSAGE AND ADMINISTRATION; Dose Modifications*).

### **Ophthalmologic Reactions**

In study NO25026, rare cases of uveitis have been reported in patients treated with ZELBORAF. Treatment with steroid and mydriatic ophthalmic drops may be required to manage uveitis. Patients should be routinely monitored for signs and symptoms of uveitis. Additionally, there were rare cases of blurry vision, iritis and photophobia. There was one case of retinal vein occlusion in study NP22657.

### **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 *ADVERSE 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  $\geq$  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

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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 *DOSAGE AND 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.

### **Liver Laboratory Abnormalities**

Liver laboratory abnormalities may occur with ZELBORAF (see *ADVERSE EFFECTS*). Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be monitored before initiation of treatment and monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption, or with treatment discontinuation (see *DOSAGE AND ADMINISTRATION; Dose Modifications*).

### **Effects on Fertility**

No fertility studies have been conducted with ZELBORAF.

### **Use in Pregnancy - Category D**

Pregnant women have not been studied in clinical trials with ZELBORAF.

Women of childbearing potential and men are recommended to use appropriate contraceptive measures during ZELBORAF therapy and for at least 6 months after discontinuation of ZELBORAF.

ZELBORAF should not be administered to pregnant women unless the possible benefit for the mother outweighs the possible risk to the fetus.

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 1.3 times the human clinical exposure based on AUC) and rabbits at doses up to 450 mg/kg/day (approximately 0.6 times the human clinical exposure based on AUC).

### **Use in Lactation**

It is not known whether vemurafenib is excreted in human 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.

### **Paediatric Use**

The safety and efficacy of ZELBORAF in children 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  $\geq 65$  years old. Elderly patients ( $\geq 65$  years

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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 *PHARMACOKINETICS; Pharmacokinetics in Special Populations*).

### **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**

Carcinogenicity studies have not been conducted with vemurafenib.

### **Ability to Drive and Use Machines**

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

## **INTERACTIONS WITH OTHER MEDICINES**

### *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. 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.

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.

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Based on *in vitro* data, vemurafenib may inhibit the efflux transporter P-glycoprotein (P-gp). The clinical relevance is unknown. Vemurafenib may increase the exposure of other medicines transported by P-gp.

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*

Based on *in vitro* data, vemurafenib is a substrate of CYP3A4 and, therefore, concomitant administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, saquinavir, ritonavir, indinavir, voriconazole) and inducers (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital, St John's Wort [hypericin]) should be used with caution when co-administered with ZELBORAF.

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, cyclosporin, 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.

It is unknown if vemurafenib is a substrate to other transport proteins.

## **ADVERSE EFFECTS**

The adverse drug reactions (ADRs) described in this section were identified from two clinical trials, a phase III randomized, active-controlled study in treatment-naïve patients ( $n = 336$ ) with BRAF V600 mutation-positive unresectable or metastatic melanoma and a phase II study 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 randomized to the ZELBORAF arm received a twice-daily oral starting dose of 960 mg, and patients randomized to the active control arm received dacarbazine 1000 mg/m<sup>2</sup> administered intravenously every 3 weeks. At the time of analysis, the median duration of ZELBORAF treatment was 3.1 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.

Table 4 summarises the ADRs occurring in at least 10% of patients treated with ZELBORAF in either the phase III or phase II studies.

**Table 4 Summary of ADRs\* Occurring in  $\geq 10\%$  of Patients**

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ADRs	Phase III Study: Treatment-naïve patients						Phase II Study: Patients who failed at least one prior systemic therapy		
	ZELBORAF <i>n</i> = 336			Dacarbazine <i>n</i> = 282			ZELBORAF <i>n</i> = 132		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
<b>Skin and subcutaneous tissue disorders</b>									
Rash	37	8	-	2	-	-	52	7	-
Photosensitivity reaction	33	3	-	4	-	-	49	3	-
Alopecia	45	< 1	-	2	-	-	36	-	-
Pruritis	23	1	-	1	-	-	30	2	-
Hyperkeratosis	24	1	-	< 1	-	-	28	-	-
Rash maculo-papular	9	2	-	< 1	-	-	21	6	-
Actinic keratosis	8	-	-	3	-	-	17	-	-
Dry skin	19	-	-	1	-	-	16	-	-
Rash papular	5	< 1	-	-	-	-	13	-	-
Erythema	14	-	-	2	-	-	8	-	-
<b>Musculoskeletal and connective tissue disorders</b>									
Arthralgia	53	4	-	3	< 1	-	67	8	-
Myalgia	13	-	-	1	-	-	24	< 1	-
Pain in extremity	18	< 1	-	6	2	-	9	-	-
Musculoskeletal pain	8	< 1	-	4	< 1	-	11	-	-
Back pain	8	-	-	5	< 1	-	11	< 1	-
<b>General disorders and administration site conditions</b>									
Fatigue	38	2	-	33	2	-	54	4	-
Oedema peripheral	17	< 1	-	5	-	-	23	-	-
Pyrexia	19	< 1	-	9	< 1	-	17	2	-
Asthenia	11	< 1	-	9	< 1	-	2	-	-
<b>Gastrointestinal disorders</b>									
Nausea	35	2	-	43	2	-	37	2	-
Diarrhoea	28	< 1	-	13	< 1	-	29	< 1	-
Vomiting	18	1	-	26	1	-	26	2	-
Constipation	12	< 1	-	24	-	-	16	-	-
<b>Nervous system disorders</b>									
Headache	23	< 1	-	10	-	-	27	-	-
Dysgeusia	14	-	-	3	-	-	11	-	-
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>									

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ADRs	Phase III Study: Treatment-naïve patients						Phase II Study: Patients who failed at least one prior systemic therapy		
	ZELBORAF n = 336			Dacarbazine n = 282			ZELBORAF n = 132		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Skin papilloma	21	< 1	-	-	-	-	30	-	-
Cutaneous SCC <sup>†#</sup>	24	22	-	< 1	< 1	-	24	24	-
Seborrhoeic keratosis	10	< 1	-	1	-	-	14	-	-
<b>Investigations</b>									
Gamma-glutamyltransferase increased	5	3	< 1	1	-	-	15	6	4
<b>Metabolism and nutrition disorders</b>									
Decreased appetite	18	-	-	8	< 1	-	21	-	-
<b>Respiratory, thoracic and mediastinal disorders</b>									
Cough	8	-	-	7	-	-	12	-	-
<b>Injury, poisoning and procedural complications</b>									
Sunburn	10	-	-	-	-	-	14	-	-

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

† Includes both squamous cell carcinoma of the skin and keratoacanthoma.

# 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.

The following clinically relevant ADRs were reported in < 10% (*uncommon*: ≥ 0.1% – < 1%; *common*: ≥ 1% – < 10%) of the ZELBORAF-treated group in the phase III and phase II studies:

*Skin and subcutaneous tissue disorders*: palmar-plantar erythrodysesthesia syndrome (*common*), keratosis pilaris (*common*), erythema nodosum (*common*), Stevens-Johnson syndrome (*uncommon*), toxic epidermal necrolysis (*uncommon*)

*Musculoskeletal and connective tissue disorders*: arthritis (*common*)

*Nervous system disorders*: dizziness (*common*), neuropathy peripheral (*common*), VII<sup>th</sup> nerve paralysis (*uncommon*)

*Neoplasms benign, malignant and unspecified (includes cysts and polyps)*: basal cell carcinoma (*common*)

*Infections and infestations*: folliculitis (*common*)

*Investigations*: weight decreased (*common*)

*Eye disorders*: retinal vein occlusion (*uncommon*), uveitis (*common*)

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*Vascular disorders:* vasculitis (*uncommon*)

*Cardiac disorders:* atrial fibrillation (*uncommon*)

## **Gender**

The grade 3 adverse events reported more frequently in females than males were rash, arthralgia and photosensitivity (see *PHARMACOKINETICS; Gender*).

## **Further Information on Selected Adverse Reactions**

*Cutaneous squamous cell carcinoma (cuSCC)* (see *PRECAUTIONS*)

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 with a median time to the first appearance of 7 - 8 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 *PRECAUTIONS*)

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 *PRECAUTIONS*)

Analysis of centralized 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<sup>2</sup>. The percentage of patients with a change from baseline in QTcP greater than 60 ms was predicted to be 0.043% for males and

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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 summarized in Table 5 below as the proportion of patients who experienced a shift from baseline to grade 3 or 4.

**Table 5 Change From Baseline to Grade 3/4 Liver Enzyme Abnormalities\***

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

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

## DOSAGE AND ADMINISTRATION

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

### Recommended Dosage

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 1 hour before or 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 Table 6).

### Missed Doses

If a 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.

### Dose Modifications

Management of symptomatic adverse events or prolongation of QTc may require dose reduction, temporary interruption or treatment discontinuation of ZELBORAF (see *PRECAUTIONS*). Dose modifications or interruptions are not recommended for cutaneous



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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 Table 6.

**Table 6 Dose Modifications**

<b>Grade (CTC-AE)*</b>	<b>Recommended ZELBORAF Dose Modification</b>
<b>Grade 1 or Grade 2 (tolerable)</b>	Maintain treatment at a dose of 960 mg twice daily
<b>Grade 2 (intolerable) or Grade 3</b>	
1 <sup>st</sup> Appearance	Interrupt treatment until grade 0 – 1 Resume dosing at 720 mg twice daily.
2 <sup>nd</sup> Appearance	Interrupt treatment until grade 0 – 1 Resume dosing at 480 mg twice daily
3 <sup>rd</sup> Appearance	Discontinue permanently
<b>Grade 4</b>	
1 <sup>st</sup> Appearance	Discontinue permanently or interrupt treatment until grade 0 – 1 Resume dosing at 480 mg twice daily
2 <sup>nd</sup> Appearance	Discontinue permanently

\*The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)

### Special Dose Instructions

*Paediatrics:* The safety and efficacy of ZELBORAF have not been studied in children and adolescents (< 18 years old).

*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 *PRECAUTIONS; Use in the Elderly*).

*Hepatic Impairment:* The safety and efficacy of ZELBORAF have not been studied in patients with hepatic impairment.

*Renal Impairment:* The safety and efficacy of ZELBORAF have not been studied in patients with renal impairment.

### OVERDOSAGE

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.

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

Contact the Poisons Information Centre (in Australia call 13 11 26; in New Zealand call 0800 764 766) for advice on management of overdosage.

## **PRESENTATION AND STORAGE CONDITIONS**

ZELBORAF film-coated 240 mg tablets are available in packages of 56 tablets (7 blisters of 8 tablets).

ZELBORAF film-coated 240 mg tablets are oval, biconvex, pinkish white to orange white tablets with “VEM” engraved on one side.

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

Do not use after the expiry date (EXP) shown on the pack.

### **Disposal of Medicines**

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. Unused or expired medicine should be returned to a pharmacy for disposal.

## **POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine (S4)

## **NAME AND ADDRESS OF THE SPONSOR**

### **Australia**

Roche Products Pty Limited  
ABN 70 000 132 865  
4–10 Inman Road  
Dee Why NSW 2099  
AUSTRALIA

Customer enquiries: 1800 233 950

### **New Zealand**

Roche Products (New Zealand) Limited  
PO Box 12492 Penrose  
Auckland 1642  
NEW ZEALAND

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Customer enquiries: 0800 656 464

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

10 May 2012

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