Zelboraf®
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 \(C_{23}H_{18}ClF_2N_3O_3S\) and its molecular weight is 489.9.

Vemurafenib is a white to off-white crystalline solid. It is practically insoluble in aqueous media.

**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.

**Pharmacology**

**Pharmacodynamics**

**Mechanism of Action**

Vemurafenib is an inhibitor BRAF serine-threonine kinase. Mutations in the BRAF gene result in constitutive activation of BRAF proteins, which can cause cell proliferation without associated growth factors.

Pre-clinical data generated in biochemical assays demonstrated that vemurafenib can potently inhibit BRAF kinases with activating codon 600 mutations (see Table 1).
Table 1  Kinase Inhibitory Activity of Vemurafenib Against Different BRAF Kinases

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Anticipated frequency in V600 mutation-positive melanoma*</th>
<th>Inhibitory Concentration 50 (IC50) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAFV600E</td>
<td>87.3%</td>
<td>10</td>
</tr>
<tr>
<td>BRAFV600K</td>
<td>7.9%</td>
<td>7</td>
</tr>
<tr>
<td>BRAFV600R</td>
<td>1%</td>
<td>9</td>
</tr>
<tr>
<td>BRAFV600D</td>
<td>&lt;0.2%</td>
<td>7</td>
</tr>
<tr>
<td>BRAFV600G</td>
<td>&lt;0.1%</td>
<td>8</td>
</tr>
<tr>
<td>BRAFV600M</td>
<td>0.1%</td>
<td>7</td>
</tr>
<tr>
<td>BRAFV600A</td>
<td>&lt;0.1%</td>
<td>14</td>
</tr>
<tr>
<td>BRAFWT</td>
<td>N/A</td>
<td>39</td>
</tr>
</tbody>
</table>

* Estimated from 16,403 melanomas with annotated BRAF codon 600 mutations in the public COSMIC database, release 71 (Nov 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 0.016 to 1.131 µM whereas the IC50 against BRAF wild type cell lines were 12.06 and 14.32 µM, respectively.

Pharmacokinetics

The pharmacokinetic (PK) parameters for vemurafenib were determined using non-compartmental analysis in a phase I and a phase III study. Mean Cmax, Cmin and AUC0-12hr 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 Cmax, Cmin 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 and Bioavailability

Vemurafenib is absorbed with a median Tmax 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).

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 Cmax and AUC were 2.5 and 4.6 to 5.1 fold, respectively. The median Tmax 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.

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).

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 with a single dose of 14C-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. Co-administration 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.

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 5th and 95th 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, the majority of vemurafenib is eliminated via the liver. 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 (see DOSAGE AND ADMINISTRATION; Special Dose Instructions and PRECAUTIONS; Hepatic Impairment).

Renal Impairment: 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 DOSAGE AND ADMINISTRATION; Special Dose Instructions and PRECAUTIONS; 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_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.

Clinical Trials
The efficacy of Zelboraf has been evaluated in 337 patients from a phase III randomized, 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. The efficacy and safety of Zelboraf have not been established in patients with tumours in which BRAF V600 mutations were not detected.

**Treatment-Naïve Patients (Study NO25026, BRIM3)**

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 twice daily) or dacarbazine (1000 mg/m² every 3 weeks).

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 ≥ 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. Overall survival was longer with Zelboraf compared to dacarbazine with a hazard ratio of 0.37 (95% CI: 0.26, 0.55), which represents a 63% decrease in the hazard of death with Zelboraf compared to dacarbazine. Kaplan-Meier estimates of the 6-month survival rates were 84% (95% CI: 78%, 89%) for Zelboraf and 64% (95% CI: 56%, 73%) for dacarbazine. 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.

PFS by investigator assessment was longer with Zelboraf compared to dacarbazine with a hazard ratio for progression or death (PFS) of 0.26 (95% CI: 0.20, 0.33), which represents a 74% decrease in the hazard of progression or death for Zelboraf compared to dacarbazine. The Kaplan-Meier estimate of the 6-month PFS rates were 47% (95% CI: 38%, 55%) for Zelboraf and 12% (95% CI: 7%, 18%) for dacarbazine. 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%). 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. At the 30 December 2010 data cut-off, the median follow-up time for OS in the Zelboraf group 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).

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 2. 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).

Zelboraf 170222
Table 2  Overall Survival in Treatment-Naïve Patients with BRAF V600 Mutation Positive Melanoma by Study Cut-Off date (n = 338 dacarbazine, n = 337 Zelboraf)

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

*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 3 and Figure 2 show the progression-free survival in treatment-naïve patients with BRAF V600 mutation positive melanoma.
Table 3  Progression-Free Survival in Treatment-Naïve Patients with BRAF V600 Mutation Positive Melanoma (December 30, 2010 cut-off)

<table>
<thead>
<tr>
<th></th>
<th>Zelboraf n = 337</th>
<th>Dacarbazine n = 338</th>
<th>p-value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS Hazard Ratio</td>
<td>0.26 (0.20, 0.33)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>(95% CI)(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-month PFS rate</td>
<td>47% (38%, 55%)</td>
<td>12% (7%, 18%)</td>
<td></td>
</tr>
<tr>
<td>(95% CI)(^b)</td>
<td>(4.86, 6.57)</td>
<td>(1.58, 1.74)</td>
<td></td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.32</td>
<td>1.61</td>
<td></td>
</tr>
<tr>
<td>(95% CI)(^b)</td>
<td>(6.19, 6.17)</td>
<td>(1.58, 1.74)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 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

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 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. The median duration of response by IRC was 6.5 months (95% CI: 5.6, not reached). Stable disease as assessed by RECIST 1.1 was
observed in 30% of patients. The median overall survival was 15.9 months (95% CI: 11.2, 19.3), the
6-month survival rate was 0.77 (95% CI: 0.69, 0.84) and at 1 year was 0.58 (95% CI: 0.48, 0.66). The
median PFS was 6.1 months (95% CI: 5.5, 6.9), and the 6-month PFS rate was 52% (95% CI: 43%,
61%).

Efficacy results are summarized in Table 4.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Efficacy Results for Phase II Study (NP22657)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Independent Review Committee Assessment</td>
</tr>
<tr>
<td></td>
<td>Assessment n = 132</td>
</tr>
<tr>
<td>BORR (n)</td>
<td>52% (69)</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[43%, 61%]</td>
</tr>
<tr>
<td>CR (n)</td>
<td>2% (3)</td>
</tr>
<tr>
<td>PR (n)</td>
<td>50% (66)</td>
</tr>
<tr>
<td>Duration of response, median months [95% CI]</td>
<td>6.5 months [5.6, NR]</td>
</tr>
<tr>
<td>PFS, median months [95% CI]</td>
<td>6.1 months [5.5, 6.9]</td>
</tr>
<tr>
<td>6-month PFS [95% CI]</td>
<td>52% [43%, 61%]</td>
</tr>
<tr>
<td>OS, median months [95% CI]</td>
<td>15.9 months [11.2, 19.3]</td>
</tr>
<tr>
<td>6-month survival rate [95% CI]</td>
<td>77% [69%, 84%]</td>
</tr>
</tbody>
</table>

BORR = best overall response rate (confirmed); CR = complete response; PR = partial response;
PFS = progression-free survival; OS = overall survival.

Indications

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

Contraindications

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

Precautions

Before taking Zelboraf, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated molecular pathology laboratory. The efficacy and safety of Zelboraf have not been established in patients with tumours in which BRAF mutations were not detected (see 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 ADVERSE 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)
Reports of non-cuSCC have been received involving patients receiving Zelboraf. 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. Chest CT scans, which are performed as part of the disease management prior to initiation of treatment and every 6 months during treatment, should also be reviewed for non-cuSCC. Pelvic examinations (for women) and anal examinations are recommended before and at the end of treatment or when considered clinically indicated.

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 Melanoma
New primary 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 cuSCC.

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

Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylaxis have been reported in association with Zelboraf (see CONTRAINDICATIONS and 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. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with Zelboraf (see ADVERSE EFFECTS; Post-Marketing Experience). In patients who experience a severe dermatologic reaction, Zelboraf treatment should be permanently discontinued.
**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 INTERACTIONS WITH OTHER MEDICINES and ADVERSE EFFECTS, Post-Marketing Experience). Most cases were cutaneous in nature but some cases involving visceral organs had fatal outcome.

Zelboraf should be used with caution when given concomitantly or sequentially with radiation treatment.

**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 ≥ 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).

**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 ADVERSE EFFECTS, Post-Marketing Experience).

Events should be managed with dose reduction, treatment interruption, or with treatment discontinuation (see DOSAGE AND ADMINISTRATION; Dose Modifications).

**QT Prolongation**

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase II QT substudy 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 ≥ 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 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.

**Ophthalmologic Reactions**

Serious ophthalmologic reactions including uveitis have been reported. Patients should be monitored routinely for ophthalmologic reactions (see ADVERSE EFFECTS).

**Concurrent Administration with ipilimumab**

The concurrent administration of ipilimumab and Zelboraf is not recommended. 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).
Liver Injury
Liver injury, including cases of severe liver injury, has been reported with Zelboraf (see ADVERSE EFFECTS; Post-Marketing Experience).

Liver laboratory abnormalities may occur with Zelboraf (see ADVERSE 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 DOSAGE AND ADMINISTRATION; Dose Modifications).

Creatinine
Lab abnormalities have been reported, mostly cases of mild (> 1-1.5 x ULN) to moderate (> 1.5 – 3 x ULN) creatinine elevation. In most cases, creatinine elevations appear to be reversible in nature (see ADVERSE EFFECTS).

Serum creatinine should be measured before initiation of treatment and periodically monitored during treatment as clinically indicated. For recommended dose modifications, see DOSAGE AND ADMINISTRATION.

Hepatic Impairment
There are only very limited data available in patients with moderate to severe hepatic impairment. Patients with moderate to severe hepatic impairment may have increased exposure. Zelboraf should be used with caution in patients with hepatic impairment (see DOSAGE AND ADMINISTRATION; Special Dose Instructions and PHARMACOKINETICS; Pharmacokinetics in Special Populations).

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. Zelboraf should be used with caution in patients with severe renal impairment (see DOSAGE AND ADMINISTRATION; Special Dose Instructions and PHARMACOKINETICS; Pharmacokinetics in Special Populations).

Effects on Fertility
No specific studies with vemurafenib have been conducted in animals to evaluate the effect on fertility; nevertheless, no histopathological findings were noted in reproductive organs in males and females in repeat-dose toxicology studies in rats at doses up to 450 mg/kg/day (approximately 0.6 and 1.6 times the human exposure based on AUC in males and females, respectively) and dogs at doses up to 450 mg/kg/day (approximately 0.4 times the human clinical exposure based on AUC in both males and females, respectively).

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 foetus.

Vemurafenib revealed no evidence of teratogenicity in rat embryo/foetuses at doses up to 250 mg/kg/day (approximately 1.7 times the human clinical exposure based on AUC) or rabbit embryo/foetuses at doses up to 450 mg/kg/day (approximately 0.7 times the human clinical exposure based on AUC). Foetal drug levels were 3 – 5% of maternal levels, indicating that vemurafenib has the potential to be transmitted from the mother to the developing foetus.
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 ≥ 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 PHARMACOKINETICS; Pharmacokinetics in Special
Populations).

Carcinogenicity
Carcinogenicity studies have not been conducted with vemurafenib.

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.

Other
Repeat-dose toxicology studies identified the liver and bone marrow as target organs in the dog.
Reversible toxic effects (hepatocellular necrosis and degeneration) on the liver at exposures below the
anticipated clinical exposure (based on AUC comparisons) were noted in the 13-week dog study with
twice-daily dosing. Focal bone marrow necrosis was noted in one dog in a prematurely terminated 39-
week dog study with twice-daily dosing at exposures within the range of clinical exposures.
Vemurafenib was shown to be phototoxic in vitro in cultured murine fibroblasts after UVA irradiation
but not in vivo in a rat study.

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 Drug Metabolizing Enzymes
Results from an in vivo drug-drug interaction study in metastatic melanoma patients demonstrated that
vemurafenib is a moderate CYP1A2 inhibitor and a CYP3A4 inducer.
Concomitant use of vemurafenib with agents metabolised by CYP1A2 and CYP3A4 with narrow
therapeutic windows is not recommended. If co-administration cannot be avoided, exercise caution as
vemurafenib may increase plasma exposure of CYP1A2 substrate drugs and decrease plasma
exposure of CYP3A4 substrate drugs. Dose reduction of the concomitant CYP1A2 substrate drug may
be considered, if clinically indicated. Co-administration of vemurafenib increased the AUC of caffeine
(CYP1A2 substrate) 2.6-fold, while it decreased the AUC of midazolam (CYP3A4 substrate) by 39% in
a clinical trial. In another clinical trial, vemurafenib increased AUCinf of a single 2mg dose
of tizanidine (CYP1A2 substrate) approximately 4.2 and 4.7 fold, respectively. The AUC of dextromethorphan (CYP2D6 substrate) and its metabolite dextrorphan were increased by approximately 47% indicating an effect on dextromethorphan kinetics that may not be mediated by inhibition of CYP2D6.

Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate). Exercise caution and consider additional INR (international normalised ratio) 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.

**Medicines that Inhibit or Induce CYP3A4**

Vemurafenib is a substrate of CYP3A4, and therefore, concomitant administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Co-administration 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 PHARMACOKINETICS, Metabolism). Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, voriconazole) and inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) should be used with caution when co-administered with vemurafenib.

**Interaction of Vemurafenib with Drug Transport Systems**

*In vitro* studies have demonstrated that vemurafenib is both a substrate and an inhibitor of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

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.

The effects of vemurafenib on medicines which are substrates of BCRP, and the effects of BCRP inducers and inhibitors on vemurafenib exposure are unknown.

*In vitro* studies have also demonstrated that vemurafenib is an inhibitor of the bile salt export pump (BSEP). The in vivo relevance of this finding is unknown.

**Radiation Toxicity**

Potentiation of radiation treatment toxicity has been reported in patients receiving Zelboraf (see PRECAUTIONS and ADVERSE EFFECTS, Post-Marketing Experience). In the majority of cases, patients received radiotherapy regimens greater than or equal to 2 Gy/day (hypofractionated regimens).

---

**Adverse Effects**

**Clinical Trials**

The adverse drug reactions (ADRs) described in this section were identified from two clinical trials, a phase III randomized, active-controlled study in treatment-naive 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/m² administered intravenously every 3 weeks. 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 5 summarises the ADRs occurring in at least 10% of patients treated with Zelboraf in either the phase III or phase II studies.

**Table 5 Summary of ADRs* Occurring in ≥ 10% of Patients in the Zelboraf Treatment Arm**

<table>
<thead>
<tr>
<th>ADRs</th>
<th>Phase III Study: Treatment-naive patients</th>
<th>Phase II Study: Patients who failed at least one prior systemic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zelboraf ( n = 336 )</td>
<td>Dacarbazine ( n = 287 )</td>
</tr>
<tr>
<td></td>
<td>All Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>37 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>33 (3)</td>
<td>-</td>
</tr>
<tr>
<td>Alopecia</td>
<td>45 (&lt;1)</td>
<td>-</td>
</tr>
<tr>
<td>Pruritus</td>
<td>23 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>24 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>9 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>8 (-)</td>
<td>-</td>
</tr>
<tr>
<td>Dry skin</td>
<td>19 (-)</td>
<td>-</td>
</tr>
<tr>
<td>Rash papular</td>
<td>5 (&lt;1)</td>
<td>-</td>
</tr>
<tr>
<td>Erythema</td>
<td>14 (-)</td>
<td>-</td>
</tr>
<tr>
<td>Palmar-plantar erythodysaesthesia syndrome</td>
<td>8 (&lt;1)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>53 (3)</td>
<td>-</td>
</tr>
<tr>
<td>Myalgia</td>
<td>13 (-)</td>
<td>-</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>18 (&lt;1)</td>
<td>-</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>8 (&lt;1)</td>
<td>-</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (-)</td>
<td>-</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2 (&lt;1)</td>
<td>-</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>17 (&lt;1)</td>
<td>-</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19 (&lt;1)</td>
<td>-</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11 (&lt;1)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Phase III Study: Treatment-naïve patients

<table>
<thead>
<tr>
<th>ADRs</th>
<th>Zelboraf $n = 336$</th>
<th>Dacarbazine $n = 287$</th>
<th>Zelboraf $n = 132$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>28</td>
<td>&lt; 1</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
<td>&lt; 1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>&lt; 1</td>
<td>-</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>14</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuropathy peripheral</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>21</td>
<td>&lt; 1</td>
<td>-</td>
</tr>
<tr>
<td>SCC of skin*</td>
<td>24</td>
<td>22</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Seborrhoeic keratosis</td>
<td>10</td>
<td>&lt; 1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma-glutamyltransferase</td>
<td>5</td>
<td>3</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>8</td>
<td>&lt; 1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunburn</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* 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.

The following clinically relevant ADRs were reported in < 10% of the Zelboraf-treated group in the phase III and phase II studies:

**Skin and subcutaneous tissue disorders:** keratosis pilaris, panniculitis, erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders: Dupuytren’s contracture
Nervous system disorders: dizziness, VIIth nerve paralysis
Neoplasms benign, malignant and unspecified (includes cysts and polyps): basal cell carcinoma
Infections and infestations: folliculitis
Eye disorders: retinal vein occlusion, uveitis
Vascular disorders: vasculitis

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 keratos is, 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 CONTRAINDICATIONS and 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/m². 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 summarized in Table 6 below as the proportion of patients who experienced a shift from baseline to grade 3 or 4.
Table 6  Change From Baseline to Grade 3/4 Liver Enzyme Abnormalities*

<table>
<thead>
<tr>
<th></th>
<th>Change From Baseline to Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zelboraf (%)</td>
</tr>
<tr>
<td>GGT</td>
<td>11.5</td>
</tr>
<tr>
<td>AST</td>
<td>0.9</td>
</tr>
<tr>
<td>ALT</td>
<td>2.8</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>2.9</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.9</td>
</tr>
</tbody>
</table>

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

Table 7  Creatinine change from baseline

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

<table>
<thead>
<tr>
<th></th>
<th>Vemurafenib (%)</th>
<th>Dacarbazine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change &gt;= 1 grade from baseline (all grade)</td>
<td>27.9</td>
<td>6.1</td>
</tr>
<tr>
<td>Change &gt;= 1 grade from baseline to grade 3 or higher</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>• To grade 3</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>• To grade 4</td>
<td>0.9</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Post-Marketing Experience

Table 8  Adverse Drug Reactions Reported in the Post-Marketing Setting

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>ADR</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Liver Injury (see Laboratory Abnormalities above and below and PRECAUTIONS)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Blood and lymphatic systems disorders</td>
<td>Neutropenia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</td>
<td>Chronic myelomonocytic leukaemia (CMML)<em>, pancreatic adenocarcinoma</em> (see PRECAUTIONS)</td>
<td>Frequency not known</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Drug reaction with eosinophilia and systemic symptoms (DRESS) (see PRECAUTIONS)</td>
<td>Frequency not known</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Radiation injury (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES)</td>
<td>Frequency not known</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Pancreatitis</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
Disorders

<table>
<thead>
<tr>
<th>Renal and Urinary Disorders</th>
<th>Acute kidney injury see further information below</th>
<th>Frequency not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Dupuytren’s contracture Plantar fascial fibromatosis (see PRECAUTIONS)</td>
<td>Frequency not known</td>
</tr>
</tbody>
</table>

*Progression of pre-existing chronic myelomonocytic leukaemia with NRAS mutation

# Progression of pre-existing pancreatic adenocarcinoma with KRAS mutation

^ Includes recall phenomenon, radiation skin injury, radiation pneumonitis, radiation oesophagitis, radiation proctitis, radiation hepatitis, cystitis radiation, and radiation necrosis.

Further information on selected adverse reactions

Acute kidney injury

A broad spectrum of renal 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.

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.

Creatinine lab abnormalities were reported in the post marketing setting.

Dosage and Administration

Before taking Zelboraf, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated molecular pathology 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 7).

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.

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 PRECAUTIONS). 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 9 and 10.

**Table 9  Dose Modifications**

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

*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 10  Dose Modification Schedule Based On Prolongation Of The QT Interval**

<table>
<thead>
<tr>
<th>Prolongation of the QT interval - QTc value</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc &gt; 500 ms at baseline</td>
<td>Treatment not recommended.</td>
</tr>
<tr>
<td>QTc increase meets values of both &gt; 500 ms and &gt; 60 ms change from pre-treatment values</td>
<td>Discontinue permanently.</td>
</tr>
<tr>
<td>1st occurrence of QTc &gt; 500 ms during treatment and change from pre-treatment value remains ≤ 60 ms</td>
<td>Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures in section PRECAUTIONS, QT Prolongation. Reduce dose by 240 mg twice daily.</td>
</tr>
<tr>
<td>2nd occurrence of QTc &gt; 500 ms during treatment and change from pre-treatment value remains ≤ 60ms</td>
<td>Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures in in section PRECAUTIONS, QT Prolongation. Reduce dose by 240 mg twice daily.</td>
</tr>
<tr>
<td>3rd occurrence of QTc &gt; 500 ms during treatment and change from pre-treatment value remains ≤ 60ms</td>
<td>Discontinue permanently.</td>
</tr>
</tbody>
</table>
**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:** No adjustment to the starting dose is needed for patients with mild or moderate hepatic impairment (see PRECAUTIONS; Hepatic Impairment and PHARMACOKINETICS; Pharmacokinetics in Special Populations). The potential need for dose adjustment in patients with severe hepatic impairment cannot be determined due to insufficient data.

**Renal Impairment:** No adjustment to the starting dose is needed for patients with mild or moderate renal impairment (see PRECAUTIONS; Renal Impairment and PHARMACOKINETICS; Pharmacokinetics in Special Populations). The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data.

---

**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.

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.

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**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.

Do not store Zelboraf tablets above 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.
Medicine Classification

Prescription Medicine.

Name and Address of the Sponsor

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Customer enquiries: 0800 656 464

Date of Preparation

22 February 2017

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