

Zelboraf[®]

Vemurafenib



1. NAME OF THE MEDICINAL PRODUCT

Zelboraf 240 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 240 mg of vemurafenib (as a co-precipitate of vemurafenib and hypromellose acetate succinate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pinkish white to orange white, oval, biconvex film-coated tablets of approximately 19 mm, with 'VEM' engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zelboraf is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma (see section 5.1).

A validated test is required to identify BRAF V600 mutation status.

4.2 Posology and method of administration

Treatment with Zelboraf should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.

Before taking Zelboraf, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test (see sections 4.4 and 5.1).

Posology

The recommended dose of Zelboraf is 960 mg (4 tablets of 240 mg) twice daily (equivalent to a total daily dose of 1,920 mg). Zelboraf may be taken with or without food, but consistent intake of both daily doses on an empty stomach should be avoided (see Section 5.2).

Duration of treatment

Treatment with Zelboraf should continue until disease progression or the development of unacceptable toxicity (see tables 1 and 2 below).

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 medicinal product but the treatment should be continued as usual.

Posology adjustments

Management of adverse drug reactions or QTc prolongation may require dose reduction, temporary interruption and/or treatment discontinuation (see tables 1 and 2). Posology adjustments resulting in a dose below 480 mg twice daily are not recommended.

In the event the patient develops Cutaneous Squamous Cell Carcinoma (cuSCC), it is recommended to continue the treatment without modifying the dose of Zelboraf (see sections 4.4 and 4.8).

Table 1: Dose modification schedule based on the grade of any Adverse Events (AEs)

Grade (CTC-AE) ^(a)	Recommended dose modification
Grade 1 or Grade 2 (tolerable)	Maintain Zelboraf at a dose of 960 mg twice daily.
Grade 2 (intolerable) or Grade 3	
1 st occurrence of any grade 2 or 3 AE	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2 nd occurrence of any grade 2 or 3 AE or persistence after treatment interruption	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3 rd occurrence of any grade 2 or 3 AE or persistence after 2 nd dose reduction	Discontinue permanently.
Grade 4	
1 st occurrence of any grade 4 AE	Discontinue permanently or interrupt Zelboraf treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
2 nd occurrence of any grade 4 AE or persistence of any grade 4 AE after 1 st dose reduction	Discontinue permanently.

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

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase II study in previously treated patients with metastatic melanoma. Management of QTc prolongation may require specific monitoring measures (see section 4.4).

Table 2: Dose modification schedule based on prolongation of the QT interval

QTc value	Recommended dose modification
QTc > 500 ms at baseline	Treatment not recommended.
QTc increase meets values of both > 500 ms and > 60 ms change from pre-treatment values	Discontinue permanently.
1 st occurrence of QTc > 500 ms during treatment and change from pre-treatment value remains < 60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures in section 4.4. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2 nd occurrence of QTc > 500 ms during treatment and change from pre-treatment value remains < 60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures in section 4.4. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3 rd occurrence of QTc > 500 ms during treatment and change from pre-treatment value remains < 60 ms	Discontinue permanently.

Special population

Elderly

No special dose adjustment is required in patients aged > 65 years old.

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. Patients with severe renal impairment should be closely monitored (see sections 4.4 and 5.2).

Hepatic impairment

Limited data are available in patients with hepatic impairment. As Zelboraf is cleared by the liver, patients with moderate to severe hepatic impairment may have increased exposure and should be closely monitored (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Zelboraf in children less than 18 years old have not been established. Currently available data are described in sections 4.8, 5.1, and 5.2, but no recommendation on a posology can be made.

Non-Caucasian patients

The safety and efficacy of Zelboraf has not been established in non-Caucasian patients. No data are available.

Method of administration

Zelboraf is for oral use. The tablets are to be swallowed whole with water. They should not be chewed or crushed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Before taking Zelboraf, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. The efficacy and safety of Zelboraf in patients with tumours expressing rare BRAF V600 mutations other than V600E and V600K have not been convincingly established (see section 5.1). Zelboraf should not be used in patients with wild type BRAF malignant melanoma.

Hypersensitivity reaction

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with Zelboraf (see sections 4.3 and 4.8). Severe hypersensitivity reactions may include Stevens-Johnson syndrome, generalized rash, erythema or hypotension. In patients who experience severe hypersensitivity reactions, 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 in the post marketing setting (see section 4.8). In patients who experience a severe dermatologic reaction, Zelboraf treatment should be permanently discontinued.

Potentiation of Radiation Toxicity

Cases of radiation recall and radiation sensitization have been reported in patients treated with radiation either prior, during, or subsequent to Zelboraf treatment. Most cases were cutaneous in nature but some cases involving visceral organs had fatal outcomes (see sections 4.5 and 4.8).

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

QT prolongation

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase II study in previously treated patients with metastatic melanoma (see section 4.8). 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 (including magnesium), long QT syndrome or who are taking medicinal products known to prolong the QT interval.

Electrocardiogram (ECG) and electrolytes (including magnesium) must be monitored in all patients before treatment with Zelboraf, after one month of treatment and after dose modification.

Further monitoring is recommended in particular in patients with moderate to severe hepatic impairment 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 $QTc > 500$ milliseconds (ms). If during treatment the QTc exceeds 500 ms, Zelboraf treatment should be temporarily interrupted, electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur once the QTc decreases below 500 ms and at a lower dose as described in Table 2. Permanent discontinuation of Zelboraf treatment is recommended if the QTc increase meets values of both > 500 ms and > 60 ms change from pre-treatment values.

Ophthalmologic reactions

Serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion, have been reported. Monitor patients routinely for ophthalmologic reactions.

Cutaneous Squamous Cell Carcinoma (cuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with Zelboraf (see section 4.8).

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. The prescriber should examine the patient monthly during and up to six months after treatment for cuSCC. In patients who develop cuSCC, it is recommended to continue the treatment without dose adjustment. Monitoring should continue for 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.

Non-Cutaneous Squamous Cell Carcinoma (non-cuSCC)

Cases of non-cuSCC have been reported in clinical trials where patients received 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.

In addition, patients should undergo a chest Computerised Tomography (CT) scan, prior to treatment and every 6 months during treatment.

Anal examinations and pelvic examinations (for women) 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 managed according to clinical practices.

New primary melanoma

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

Other malignancies

Based on mechanism of action, Zelboraf may cause progression of cancers associated with RAS mutations (see section 4.8). Carefully consider benefits and risks before administering Zelboraf to patients with a prior or concurrent cancer associated with RAS mutation.

Pancreatitis

Pancreatitis has been reported in Zelboraf-treated subjects. Unexplained abdominal pain should be promptly investigated (including measurement of serum amylase and lipase). Patients should be closely monitored when re-starting Zelboraf after an episode of pancreatitis.

Liver injury

Liver injury, including cases of severe liver injury, has been reported with Zelboraf (see section 4.8). 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 sections 4.2 and 4.8).

Renal toxicity

Renal toxicity, ranging from serum creatinine elevations to acute interstitial nephritis and acute tubular necrosis, has been reported with Zelboraf. Serum creatinine should be measured before initiation of treatment and monitored during treatment as clinically indicated (see sections 4.2 and 4.8).

Hepatic impairment

No adjustment to the starting dose is needed for patients with hepatic impairment. Patients with mild hepatic impairment due to liver metastases without hyperbilirubinaemia may be monitored according to the general recommendations. 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 (see section 5.2). Thus close monitoring is warranted especially after the first few weeks of treatment as accumulation may occur over an extended period of time (several weeks). In addition ECG monitoring every month during the first three months is recommended.

Renal impairment

No adjustment to the starting dose is needed for patients with mild or moderate renal impairment. There are only limited data available in patients with severe renal impairment (see section 5.2). Zelboraf should be used with caution in patients with severe renal impairment and patients should be closely monitored.

Photosensitivity

Mild to severe photosensitivity was reported in patients who received Zelboraf in clinical studies (see section 4.8). All patients should be advised to avoid sun exposure while taking Zelboraf. While taking the medicinal product, patients should be advised to wear protective clothing and use a broad spectrum Ultraviolet A (UVA)/Ultraviolet B (UVB) sunscreen and lip balm (Sun Protection Factor \geq 30) when outdoors to help protect against sunburn.

For photosensitivity grade 2 (intolerable) or greater, dose modifications are recommended (see section 4.2).

Dupuytren's contracture and plantar fascial fibromatosis

Dupuytren's contracture and plantar fascial fibromatosis have been reported with Zelboraf. The majority of cases were mild to moderate, but severe, disabling cases of Dupuytren's contracture have also been reported (see section 4.8). Events should be managed with dose reduction with treatment interruption or with treatment discontinuation (see section 4.2).

Effects of Zelboraf on other medicinal products

Zelboraf may increase the plasma exposure of medicinal products predominantly metabolized by CYP1A2 and decrease the plasma exposure of medicines predominantly metabolized by CYP3A4. Concomitant use of Zelboraf with agents metabolized by CYP1A2 and CYP3A4 with narrow therapeutic windows is not recommended. Dose adjustments for medicinal products predominantly metabolized via CYP1A2 or CYP3A4 should be considered based on their therapeutic windows before concomitantly treating with Zelboraf (see sections 4.5 and 4.6).

Exercise caution and consider additional INR (International Normalized Ratio) monitoring when Zelboraf is used concomitantly with warfarin.

Zelboraf may increase the plasma exposure of medicinal products that are P-gp substrates. Caution should be exercised when dosing Zelboraf concurrently with P-gp substrates. Dose reduction and/or additional drug level monitoring for P-gp substrate medicinal products with narrow therapeutic index (NTI) (e.g. digoxin, dabigatran etexilate, aliskiren) may be considered if these medicinal products are used concomitantly with Zelboraf (see section 4.5).

Effect of other medicinal products on Zelboraf

Concomitant administration of strong inducers of CYP3A4, P-gp and glucuronidation (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort [hypericin]) might lead to decreased exposure of Zelboraf and should be avoided when possible (see section 4.5). Alternative treatment with less inducing potential should be considered to maintain the efficacy of Zelboraf. Caution should be used when administering Zelboraf with strong CYP3A4/PgP inhibitors. Patients should be carefully monitored for safety and dose modifications applied if clinically indicated (see Table 1 in section 4.2).

Concurrent administration with ipilimumab

In a Phase I trial, asymptomatic grade 3 increases in transaminases (ALT/AST >5 x ULN) and bilirubin (total bilirubin >3 x ULN) were reported with concurrent administration of ipilimumab (3 mg/kg) and Zelboraf (960 mg BID or 720 mg BID). Based on these preliminary data, the concurrent administration of ipilimumab and Zelboraf is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Zelboraf on Drug Metabolizing Enzymes

Results from an *in vivo* drug-drug interaction study in metastatic melanoma patients demonstrated that Zelboraf is a moderate CYP1A2 inhibitor and a CYP3A4 inducer. Concomitant use of Zelboraf with agents metabolized by CYP1A2 with narrow therapeutic windows (e.g. agomelatine, alosetron, duloxetine, melatonin, ramelteon,

tacrine, tizanidine, theophylline) is not recommended. If co-administration cannot be avoided, exercise caution, as Zelboraf may increase plasma exposure of CYP1A2 substrate drugs. Dose reduction of the concomitant CYP1A2 substrate drug may be considered, if clinically indicated. Co-administration of Zelboraf increased the plasma exposure (AUC) of caffeine (CYP1A2 substrate) 2.6-fold. In another clinical trial, Zelboraf increased C_{max} and AUC of a single 2 mg dose of tizanidine (CYP1A2 substrate) approximately 2.2-fold and 4.7-fold, respectively.

Concomitant use of Zelboraf with agents metabolized by CYP3A4 with narrow therapeutic windows is not recommended. If co-administration cannot be avoided, it needs to be considered that Zelboraf may decrease plasma concentrations of CYP3A4 substrates and thereby their efficacy may be impaired. On this basis, the efficacy of contraceptive pills metabolized by CYP3A4 used concomitantly with Zelboraf might be decreased. Dose adjustments for CYP3A4 substrates with narrow therapeutic window may be considered, if clinically indicated (see sections 4.4 and 4.6).

In a clinical trial, co-administration of Zelboraf decreased the AUC of midazolam (CYP3A4 substrate) by an average 39% (maximum decrease up to 80%).

Mild induction of CYP2B6 by Zelboraf was noted *in vitro* at a Zelboraf concentration of 10 μ M. It is currently unknown whether Zelboraf at a plasma level of 100 μ M observed in patients at steady state (approximately 50 μ g/ml) may decrease plasma concentrations of concomitantly administered CYP2B6 substrates, such as bupropion.

Co-administration of Zelboraf resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate). Exercise caution and consider additional INR (international normalized ratio) monitoring when Zelboraf is used concomitantly with warfarin (see section 4.4).

Zelboraf 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 Zelboraf may increase their concentrations.

Due to the long half-life of Zelboraf, the full inhibitory effect of Zelboraf on a concomitant medicinal product might not be observed before 8 days of Zelboraf treatment.

After cessation of Zelboraf treatment, a washout of 8 days might be necessary to avoid an interaction with a subsequent treatment.

Radiation treatment

Potential of radiation treatment toxicity has been reported in patients receiving Zelboraf (see sections 4.4 and 4.8). In the majority of cases, patients received radiotherapy regimens greater than or equal to 2 Gy/day (hypofractionated regimens).

Effects of Zelboraf on drug transport systems

In vitro studies have demonstrated that Zelboraf is an inhibitor of the efflux transporter P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

A clinical drug interaction study demonstrated that multiple oral doses of Zelboraf (960 mg twice daily) increased the exposure of a single oral dose of the P-gp substrate digoxin, approximately 1.8 and 1.5 fold for digoxin AUC_{last} and C_{max} , respectively.

Caution should be exercised when dosing Zelboraf concurrently with P-gp substrates (e.g. aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, sirolimus, sitagliptin, talinolol, topotecan) and dose reduction of the concomitant medicinal product may be considered, if clinically indicated. Consider additional drug level monitoring for P-gp substrate medicinal products with a narrow therapeutic index (NTI) (e.g. digoxin, dabigatran etexilate, aliskiren) (see section 4.4).

The effects of Zelboraf on medicinal products that are substrates of BCRP are unknown. It cannot be excluded that Zelboraf may increase the exposure of medicines transported by BCRP (e.g. methotrexate, mitoxantrone, rosuvastatin).

Many anticancer drugs are substrates of BCRP and therefore there is a theoretical risk for an interaction with Zelboraf.

The possible effect of Zelboraf on other transporters is currently unknown.

Effects of concomitant medicines on Zelboraf

In vitro studies suggest that CYP3A4 metabolism and glucuronidation are responsible for the metabolism of Zelboraf. Biliary excretion appears to be another important elimination pathway. *In vitro* studies have demonstrated that Zelboraf is a substrate of the efflux transporters P-gp and BCRP. It is currently unknown whether Zelboraf is a substrate also to other transport proteins. Concomitant administration of strong CYP3A4 inhibitors or inducers or inhibitors/inducer of transport protein activity may alter Zelboraf concentrations.

Co-administration of itraconazole, a strong CYP3A4/Pgp inhibitor, increased steady state Zelboraf AUC by approximately 40%. Zelboraf should be used with caution in combination with strong inhibitors of CYP3A4, glucuronidation and/or transport proteins (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir). Patients co-treated with such agents should be carefully monitored for safety and dose modifications applied if clinically indicated (see Table 1 in section 4.2).

In a clinical study, co-administration of a single dose 960 mg of Zelboraf with rifampicin, significantly decreased the plasma exposure of Zelboraf by approximately 40%. Concomitant administration of strong inducers of P-gp, glucuronidation, and/or CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort [*Hypericum perforatum*]) may lead to suboptimal exposure to Zelboraf and should be avoided.

The effects of P-gp and BCRP inhibitors that are not also strong CYP3A4 inhibitors are unknown. It cannot be excluded that Zelboraf pharmacokinetics could be affected by such medicines through influence on P-gp (e.g. verapamil, cyclosporine, quinidine) or BCRP (e.g. cyclosporine, gefitinib).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females

Women of childbearing potential have to use effective contraception during treatment and for at least 6 months after treatment.

Zelboraf might decrease the efficacy of hormonal contraceptives (see section 4.5).

Pregnancy

There are no data regarding the use of Zelboraf in pregnant women.

Zelboraf revealed no evidence of teratogenicity in rat or rabbit embryo/foetuses (see section 5.3). In animal studies, Zelboraf was found to cross the placenta. Based on its mechanism of action, Zelboraf could cause fetal harm when administered to a pregnant woman. Zelboraf should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the foetus.

Breast-feeding

It is not known whether Zelboraf is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Zelboraf therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

No specific studies with Zelboraf have been conducted in animals to evaluate the effect on fertility. However, in repeat-dose toxicity studies in rats and dogs, no histopathological findings were noted in reproductive organs in males and females (see section 5.3).

4.7 Effects on ability to drive and use machines

Zelboraf has minor influence on the ability to drive and use machines. Patients should be made aware of the potential fatigue or eye problems that could be a reason for not driving.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (ADR) of any grade (> 30%) reported with Zelboraf include arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia, diarrhea, headache, pruritus, vomiting, skin papilloma and hyperkeratosis. The most common (≥ 5%) Grade 3 ADRs were cuSCC, keratoacanthoma,

rash, arthralgia and gamma-glutamyltransferase (GGT) increased. CuSCC was most commonly treated by local excision.

Potential of radiation toxicity: Radiation recall and radiation sensitization have been observed from postmarketing sources. However the frequency of this adverse reaction is unknown since radiation treatment information including radiation dosage information is not routinely collected in spontaneous safety reports.

Tabulated summary of adverse reactions

ADRs which were reported in melanoma patients are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been used for the classification of frequency:

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare $\geq 1/10,000$ to $< 1/1,000$

Very rare $< 1/10,000$

In this section, ADRs are based on results in 468 patients from a phase III randomized open label study in adult patients with BRAF V600 mutation-positive unresectable or stage IV melanoma, as well as a phase II single-arm study in patients with BRAF V600 mutation-positive stage IV melanoma who had previously failed at least one prior systemic therapy (see section 5.1). In addition ADRs originating from safety reports across all clinical trials and post-marketing sources are reported. All terms included are based on the highest percentage observed among phase II and phase III clinical trials. Within each frequency grouping, ADRs are presented in order of decreasing severity and were reported using NCI-CTCAE v 4.0 (common toxicity criteria) for assessment of toxicity.

Table 3: ADRs occurring in patients treated with Zelboraf in the phase II or phase III study and events originating from safety reports across all trials⁽¹⁾ and post-marketing sources⁽²⁾

System organ class	Very Common	Common	Uncommon	Rare
Infections and infestations		Folliculitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)	SCC of the skin ^(d) , keratoacanthoma, seborrheic keratosis, skin papilloma	Basal cell carcinoma, new primary melanoma ⁽³⁾	Non-cuSCC ⁽¹⁾⁽³⁾	Chronic myelomonocytic leukaemia ⁽²⁾⁽⁴⁾ , pancreatic adenocarcinoma ⁽⁵⁾
Blood and lymphatic system disorders		Neutropenia		
Immune system disorders				Sarcoidosis ⁽¹⁾⁽²⁾⁽ⁱ⁾
Metabolism and nutrition disorders	Decreased appetite			
Nervous system disorders	Headache, dysgeusia, dizziness	7 th nerve paralysis, neuropathy peripheral		
Eye disorders		Uveitis	Retinal vein occlusion, iridocyclitis	
Vascular disorders		Vasculitis		
Respiratory, thoracic and mediastinal disorders	Cough			
Gastrointestinal disorders	Diarrhoea, vomiting, nausea, constipation		Pancreatitis ⁽²⁾	
Hepatobiliary disorders			Liver injury ^{(1)(2)(g)}	
Skin and subcutaneous tissue disorders	Photosensitivity reaction, actinic keratosis, rash, rash maculo-papular, pruritus, hyperkeratosis, erythema, palmar-plantar erythrodysesthesia syndrome, alopecia, dry skin, sunburn	Rash papular, panniculitis (including erythema nodosum), keratosis pilaris	Toxic epidermal necrolysis ^(e) , Stevens-Johnson syndrome ^(f)	Drug reaction with eosinophilia and systemic symptoms ⁽¹⁾⁽²⁾
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, pain in extremity, musculoskeletal pain, back pain	Arthritis	Plantar fascial fibromatosis ⁽¹⁾⁽²⁾ Dupuytren's contracture ⁽¹⁾⁽²⁾	
Renal and urinary disorders				Acute interstitial nephritis ^{(1)(2)(h)} , acute tubular necrosis ^{(1)(2)(h)}
General disorders and administration site conditions	Fatigue, pyrexia, oedema peripheral, asthenia			

System organ class	Very Common	Common	Uncommon	Rare
Investigations		ALT increased ^(c) , alkaline phosphatase increased ^(c) , AST increased ^(c) , bilirubin increased ^(c) , GGT increase ^(c) , weight decreased, electrocardiogram QT prolonged, blood creatinine increased ^{(1)(2)(h)}		
Injury, poisoning and procedural complications		Potential of radiation toxicity ⁽¹⁾⁽²⁾⁽ⁱ⁾		

(1) Events originating from safety reports across all trials

(2) Events originating from post-marketing sources.

(3) A causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.

(4) Progression of pre-existing chronic myelomonocytic leukaemia with NRAS mutation.

(5) Progression of pre-existing pancreatic adenocarcinoma with KRAS mutation.

Description of selected adverse reactions

Hepatic enzyme increase^(c)

Liver enzyme abnormalities reported in the phase III clinical study are expressed below as the proportion of patients who experienced a shift from baseline to a grade 3 or 4 liver enzyme abnormalities:

- Very common: GGT
- Common: ALT, alkaline phosphatase, bilirubin
- Uncommon: AST

There were no increases to Grade 4 ALT, alkaline phosphatase or bilirubin.

Liver injury^(g)

Based on the criteria for drug induced liver injury developed by an international expert working group of clinicians and scientists, liver injury was defined as any one of the following laboratory abnormalities:

- $\geq 5x$ ULN ALT
- $\geq 2x$ ULN ALP (without other cause for ALP elevation)
- $\geq 3x$ ULN ALT with simultaneous elevation of bilirubin concentration $> 2x$ ULN

Cutaneous squamous cell carcinoma^(d) (cuSCC)

Cases of cuSCC have been reported in patients treated with Zelboraf. The incidence of cuSCC in Zelboraf-treated patients across studies was approximately 20%. The majority of the excised lesions reviewed by an independent central dermatopathology laboratory were classified as SCC-keratoacanthoma subtype or with mixed-keratoacanthoma features (52%). 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 to 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 (see sections 4.2 and 4.4).

Non-cutaneous squamous cell carcinoma (non-cuSCC)

Cases of non-cuSCC have been reported in patients receiving Zelboraf while enrolled in clinical trials. Surveillance for non-cuSCC should occur as outlined in section 4.4.

New primary melanoma

New primary melanomas have been reported in clinical trials. These cases were managed with excision, and patients continued treatment without dose adjustment. Monitoring for skin lesions should occur as outlined in section 4.4.

Potentiation of radiation toxicity⁽ⁱ⁾

Cases reported include recall phenomenon, radiation skin injury, radiation pneumonitis, radiation esophagitis, radiation proctitis, radiation hepatitis, cystitis radiation, and radiation necrosis.

In a phase III clinical trial (MO25515, N= 3219), a higher incidence of potentiation of radiation toxicity was reported when Zelboraf patients received radiation prior to and during Zelboraf therapy (9.1%) compared to those patients who received radiation and Zelboraf concomitantly (5.2%) or to those whose radiation treatment was prior to Zelboraf (1.5%).

Hypersensitivity reactions^(e)

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with Zelboraf. Severe hypersensitivity reactions may include Stevens-Johnson syndrome, generalized rash, erythema or hypotension. In patients who experience severe hypersensitivity reactions, Zelboraf treatment should be permanently discontinued (see section 4.4).

Dermatologic reactions^(f)

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.

QT prolongation

Analysis of centralized ECG data from an open-label uncontrolled phase II QT sub-study in 132 patients dosed with Zelboraf 960 mg twice daily (NP22657) showed an exposure-dependent QTc prolongation. The mean QTc effect remained stable between 12-15 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 (n=90 patients). Two patients (1.5%) developed treatment-emergent absolute QTc values >500 ms (CTC Grade 3), and only one patient (0.8%) exhibited a QTc change from baseline of >60 ms (see section 4.4).

Acute kidney injury^(h)

Cases of renal toxicity have been reported with Zelboraf ranging from creatinine elevations to acute interstitial nephritis and acute tubular necrosis, some observed in the setting of dehydration events. Serum creatinine elevations were mostly mild (>1-1.5x ULN) to moderate (>1.5-3x ULN) and observed to be reversible in nature (see table 4).

Table 4: Creatinine changes from baseline in the phase III study

	Zelboraf (%)	Dacarbazine (%)
Change ≥ 1 grade from baseline to any grade	27.9	6.1
Change ≥ 1 grade from baseline to grade 3 or higher	1.2	1.1
• To grade 3	0.3	0.4
• To grade 4	0.9	0.8

Table 5: Acute kidney injury cases in the phase III study

	Zelboraf (%)	Dacarbazine (%)
Acute kidney injury cases*	10.0	1.4
Acute kidney injury cases associated with dehydration events	5.5	1.0
Dose modified for acute kidney injury	2.1	0

All percentages are expressed as cases out of total patients exposed to each medicinal product.

* Includes acute kidney injury, renal impairment, and laboratory changes consistent with acute kidney injury.

Sarcoidosis⁽ⁱ⁾

Cases of sarcoidosis have been reported in patients treated with vemurafenib, mostly involving the skin, lung and eye. In majority of the cases, Zelboraf was maintained and the event of sarcoidosis either resolved or persisted.

Special populations

Elderly

In the phase III study, ninety-four (28%) of 336 patients with unresectable or metastatic melanoma treated with Zelboraf were ≥ 65 years. Older patients (≥ 65 years) may be more likely to experience adverse reactions, including cuSCC, decreased appetite, and cardiac disorders.

Gender

During clinical trials with Zelboraf, grade 3 adverse reactions reported more frequently in females than males were rash, arthralgia and photosensitivity.

Paediatric population

The safety of Zelboraf in children and adolescents has not been established. No new safety signals were observed in a clinical study with six adolescent patients.

4.9 Overdose

There is no specific antidote for overdose of Zelboraf. Patients who develop adverse reactions should receive appropriate symptomatic treatment. No cases of overdose have been observed with Zelboraf in clinical trials. In case of suspected overdose, Zelboraf should be withheld and supportive care initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action and pharmacodynamic effects

Zelboraf is an inhibitor of 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.

Preclinical data generated in biochemical assays demonstrated that Zelboraf can potently inhibit BRAF kinases with activating codon 600 mutations (table 6).

Table 6: Kinase inhibitory activity of Zelboraf against different BRAF kinases

Kinase	Anticipated frequency in V600 mutation-positive melanoma ⁽ⁱ⁾	Inhibitory Concentration 50 (nM)
BRAF ^{V600E}	87.3%	10
BRAF ^{V600K}	7.9%	7
BRAF ^{V600R}	1%	9
BRAF ^{V600D}	<0.2%	7
BRAF ^{V600G}	<0.1%	8
BRAF ^{V600M}	<0.1%	7
BRAF ^{V600A}	<0.1%	14
BRAF ^{WT}	NA	39

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

This inhibitory effect was confirmed in the ERK phosphorylation and cellular anti-proliferation assays in available melanoma cell lines expressing V600-mutant BRAF. In cellular anti-proliferation assays the inhibitory concentration 50 (IC₅₀) against V600 mutated cell lines (V600E, V600R, V600D and V600K mutated cell lines) ranged from 0.016 to 1.131 µM whereas the IC₅₀ against BRAF wild type cell lines were 12.06 and 14.32 µM, respectively.

Determination of BRAF mutation status

Before taking Zelboraf, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. In the phase II and phase III clinical trials, eligible patients were identified using a real-time polymerase chain reaction assay (the cobas 4800 BRAF V600 Mutation Test). This test has CE marking and is used to assess the BRAF mutation status of DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumour tissue. It was designed to detect the predominant BRAF V600E mutation with high sensitivity (down to 5% V600E sequence in a background of wild-type sequence from FFPE-derived DNA). Non-clinical and clinical studies with retrospective sequencing analyses have shown that the test also detects the less common BRAF V600D mutations and V600K mutations with lower sensitivity. Of the specimens available from the non-clinical and clinical studies (n=920), that were mutation-positive by the cobas test and additionally analyzed by sequencing, no specimen was identified as being wild type by both Sanger and 454 sequencing.

Clinical efficacy and safety

The efficacy of Zelboraf has been evaluated in 336 patients from a phase III clinical trial (NO25026) and 278 patients from two phase II clinical trials (NP22657 and MO25743). All patients were required to have advanced melanoma with BRAF V600 mutations according to the cobas 4800 BRAF V600 Mutation Test.

Results from the Phase III study (NO25026) in previously untreated patients

An open-label, multicenter, international, randomized phase III study supports the use of Zelboraf in previously untreated patients with BRAF V600E mutation-positive unresectable or metastatic melanoma. Patients were randomized to treatment with Zelboraf (960 mg twice daily) or dacarbazine (1000 mg/m² on day 1 every 3 weeks).

A total of 675 patients were randomized to Zelboraf (n=337) or dacarbazine (n=338). Most patients were male (56%) and Caucasian (99%), the median age was 54 years (24% were ≥ 65 years), all patients had ECOG performance status of 0 or 1, and the majority of patients had stage M1c disease (65%). The co-primary efficacy endpoints of the study were overall survival (OS) and progression-free survival (PFS).

At the pre-specified interim analysis with a December 30, 2010 data cut-off, significant improvements in the co-primary endpoints of OS (p<0.0001) and PFS (p<0.0001) (unstratified log-rank test) were observed. Upon Data Safety Monitoring Board (DSMB) recommendation, those results were released in January 2011 and 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 7.

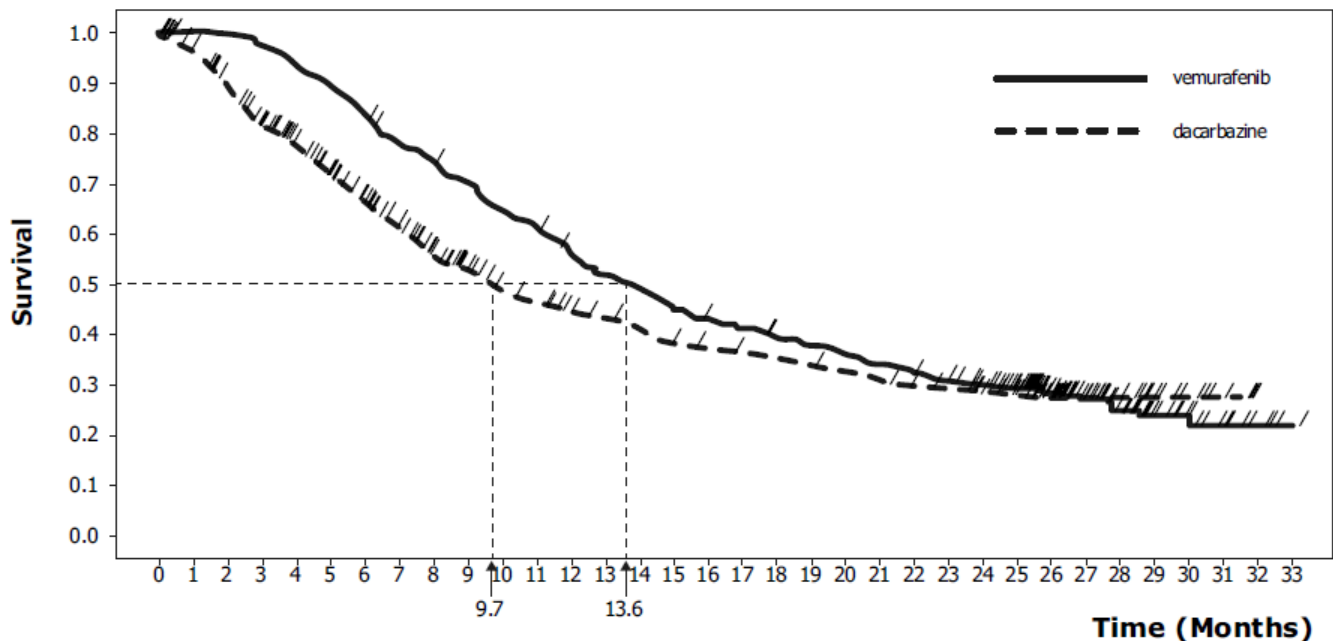
Table 7: Overall survival in previously untreated patients with BRAF V600 mutation positive melanoma by study cut-off date (N=338 dacarbazine, N=337 Zelboraf)

Cut-off dates	Treatment	Number of deaths (%)	Hazard Ratio (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) ^(w)	50 (15%)
	Zelboraf	78 (23)		
October 3, 2011	dacarbazine	175 (52)	0.62 (0.49, 0.77) ^(w)	81 (24%)
	Zelboraf	159 (47)		
February 1, 2012	dacarbazine	200 (59)	0.70 (0.57, 0.87) ^(w)	83 (25%)
	Zelboraf	199 (59)		
December 20, 2012	dacarbazine	236 (70)	0.78 (0.64, 0.94) ^(w)	84 (25%)
	Zelboraf	242 (72)		

^(w) 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); February 1 2012: HR (95% CI) = 0.76 (0.63, 0.93); December 20 2012: HR (95% CI) = 0.79 (0.66, 0.95)

Figure 1: Kaplan-Meier curves of overall survival – previously untreated patients (December 20, 2012 cut-off)



n at risk	338	306	276	243	217	193	172	154	126	110	97	91	82	79	76	68	65	63	60	58	55	51	48	46	41	36	28	20	17	11	8	4	0	0
dacarbazine	337	336	335	326	314	300	281	260	248	232	214	203	183	171	161	148	140	135	129	123	117	110	104	98	91	81	56	43	30	17	13	8	4	1
vemurafenib																																		

Table 8 shows the treatment effect for all pre-specified stratification variables which are established as prognostic factors.

Table 8: Overall survival in previously untreated patients with BRAF V600 mutation-positive melanoma by LDH, tumour stage and ECOG status post hoc analysis, December 20, 2012 cut-off, censored results at time of cross over)

Stratification variable	N	Hazard Ratio	95% Confidence Interval
LDH normal	391	0.88	0.67; 1.16
LDH >ULN	284	0.57	0.44; 0.76
Stage IIIc/M1A/M1B	234	1.05	0.73; 1.52
Stage MIC	441	0.64	0.51; 0.81
ECOG PS=0	459	0.86	0.67; 1.10
ECOG PS=1	216	0.58	0.42; 0.9

LDH: Lactate Dehydrogenase, ECOG PS: Eastern Cooperative Oncology Group Performance Status

Table 9 shows the overall response rate and progression-free survival in previously untreated patients with BRAF V600 mutation positive melanoma.

Table 9: Overall response rate and progression-free survival in previously untreated patients with BRAF V600 mutation positive melanoma

	Zelboraf	dacarbazine	p-value ^(x)
December 30, 2010 data cut-off date ^(y)			
Overall Response Rate (95% CI)	48.4% (41.6%, 55.2%)	5.5% (2.8%, 9.3%)	<0.0001
Progression-free survival Hazard Ratio (95% CI)	0.26 (0.20, 0.33)		<0.0001
Number of events (%)	104 (38%)	182 (66%)	
Median PFS (months) (95% CI)	5.32 (4.86, 6.57)	1.61 (1.58, 1.74)	
February 01, 2012 data cut-off date ^(z)			
Progression-free survival Hazard Ratio (95% CI)	0.38 (0.32, 0.46)		<0.0001
Number of events (%)	277 (82%)	273 (81%)	
Median PFS (months)	6.87	1.64	

(95% CI)	(6.14, 6.97)	(1.58, 2.07)	
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(x) Unstratified log-rank test for PFS and Chi-squared test for Overall Response Rate.

(y) As of December 30, 2010, a total of 549 patients were evaluable for PFS and 439 patients were evaluable for overall response rate.

(z) As of February 01, 2012, a total of 675 patients were evaluable for the post-hoc analysis update of PFS.

A total of 57 patients out of 673 whose tumours were analysed retrospectively by sequencing were reported to have BRAF V600K mutation-positive melanoma in NO25026. Although limited by the low number of patients, efficacy analyses among these patients with V600K-positive tumours suggested similar treatment benefit of Zelboraf in terms of OS, PFS and confirmed best overall response. No data are available in patients with melanoma harbouring rare BRAF V600 mutations other than V600E and V600K.

Results from the phase II study (NP22657) in patients who failed at least one prior therapy

A phase II single-arm, multi-center, multinational study was conducted in 132 patients who had BRAF V600E mutation-positive metastatic melanoma according to the cobas 4800 BRAF V600 Mutation Test and had received at least one prior therapy. The median age was 52 years with 19% of patients being older than 65 years. The majority of patients was male (61%), Caucasian (99%), and had stage M1c disease (61%). Forty-nine percent of patients failed ≥ 2 prior therapies.

With a median follow-up of 12.9 months (range, 0.6 to 20.1), the primary endpoint of confirmed best overall response rate (CR + PR) as assessed by an independent review committee (IRC) was 53% (95% CI: 44%, 62%). Median overall survival was 15.9 months (95% CI: 11.6, 18.3). The overall survival rate at 6 months was 77% (95% CI: 70%, 85%) and at 12 months was 58% (95% CI: 49%, 67%).

Nine of the 132 patients enrolled into NP22657 had V600K mutation positive tumours according to retrospective Sanger sequencing. Amongst these patients, 3 had a PR, 3 had SD, 2 had PD and one was not evaluable.

Results from the phase II study (MO25743) in patients with brain metastases

A single-arm, multicentre study (N = 146) of Zelboraf was conducted in adult patients with histologically confirmed metastatic melanoma harbouring the BRAF V600 mutation (according to the cobas 4800 BRAF V600 Mutation Test) and with brain metastases. The study included two simultaneously enrolling cohorts:

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

A total of 146 patients were enrolled. The majority of patients were male (61.6%), and Caucasian (92.5%), and the median age was 54 years (range 26 to 83 years), similarly distributed between the two cohorts. The median number of brain target lesions at baseline was 2 (range 1 to 5), in both cohorts.

The primary efficacy objective of the study was best overall response rate (BORR) in the brain of metastatic melanoma patients with previously untreated brain metastases, as assessed by an independent review committee (IRC).

Secondary objectives included an evaluation of the efficacy of Zelboraf using BORR in the brain of previously treated patients, duration of response (DOR), progression-free survival (PFS) and overall survival (OS) in patients with melanoma metastatic to the brain (see table 10).

Table 10: Efficacy of Zelboraf in patients with brain metastases

	Cohort 1 No previous treatment n = 90	Cohort 2 Previously treated n = 56	Total n = 146
BORR ^a in brain Responders n (%) (95% CI) ^b	16 (17.8%) (10.5, 27.3)	10 (17.9%) (8.9, 30.4)	26 (17.8%) (12.0, 25.0)
DOR ^c in brain (n) Median (months) (95% CI) ^d	(n = 16) 4.6 (2.9, 6.2)	(n = 10) 6.6 (2.8, 10.7)	(n = 26) 5.0 (3.7, 6.6)
BORR extra-cranial n (%) ^a	26 (32.9%)	9 (22.5%)	35 (29.4%)

PFS - overall Median (months) ^e (95% CI) ^d	3.7 (3.6, 3.7)	3.7 (3.6, 5.5)	3.7 (3.6, 3.7)
PFS - brain only Median (months) ^e (95% CI) ^d	3.7 (3.6, 4.0)	4.0 (3.6, 5.5)	3.7 (3.6, 4.2)
OS Median (months) (95% CI) ^d	8.9 (6.1, 11.5)	9.6 (6.4, 13.9)	9.6 (6.9, 11.5)

^a Best overall confirmed response rate as assessed by independent review committee, number of responders n (%)

^b Two-sided 95% Clopper-Pearson Confidence Interval (CI)

^c Duration of response as assessed by an Independent Review Committee

^d Kaplan-Meier estimate

^e Assessed by investigator

5.2 Pharmacokinetic properties

Zelboraf is a Class IV substance (low solubility and permeability), using the criteria described in the Biopharmaceutics Classification System. The pharmacokinetic parameters for Zelboraf were determined using non compartmental analysis in a phase I and phase III studies (20 patients after 15 days of dosing at 960 mg twice daily, and 204 patients in steady state day 22) as well as by population PK analysis using pooled data from 458 patients. Among these patients, 457 were Caucasians.

Absorption

The bioavailability at steady state ranged between 32 and 115% (mean 64%) relative to an intravenous microdose, in a phase I study with uncontrolled food conditions in 4 patients with BRAF V600 positive malignancies.

Zelboraf is absorbed with a median T_{max} of approximately 4 hours following a single 960 mg dose (four 240 mg tablets). Zelboraf exhibits high inter-patient variability. In the phase II study, AUC_{0-8h} and C_{max} at day 1 were $22.1 \pm 12.7 \mu\text{g}\cdot\text{h}/\text{mL}$ and $4.1 \pm 2.3 \mu\text{g}/\text{mL}$. Accumulation occurs upon multiple twice daily dosing of Zelboraf. In the non-compartmental analysis, after dosing with 960 mg Zelboraf twice daily the Day 15 / Day 1 ratio ranged from 15- to 17-fold for AUC, and 13- to 14-fold for C_{max} , yielding AUC_{0-8h} and C_{max} of $380.2 \pm 143.6 \mu\text{g}\cdot\text{h}/\text{mL}$ and $56.7 \pm 21.8 \mu\text{g}/\text{mL}$, respectively, under steady-state conditions.

Food (high fat meal) increases the relative bioavailability of a single 960 mg dose of Zelboraf. The geometric mean ratios between the fed and fasted states for C_{max} and AUC were 2.5 and 4.6 to 5.1 fold, respectively. The median T_{max} was increased from 4 to 7.5 hours when a single Zelboraf dose was taken with food.

The effect of food on steady state Zelboraf exposure is currently unknown. Consistent intake of Zelboraf on an empty stomach may lead to significantly lower steady state exposure than consistent intake of Zelboraf with or a short time after a meal. Occasional intake of Zelboraf on an empty stomach is expected to have limited influence on steady state exposure due to the high accumulation of Zelboraf at steady state. Safety and efficacy data from pivotal studies were collected from patients taking Zelboraf with or without food.

Variability in exposure may also occur due to differences in gastro-intestinal fluid content, volumes, pH, motility and transition time and bile composition.

At steady state, the mean Zelboraf exposure in plasma is stable during the 24-hour interval as indicated by the mean ratio of 1.13 between the plasma concentrations before and 2-4 hours after the morning dose. Following oral dosing, the absorption rate constant for the population of metastatic melanoma patients is estimated to be 0.19 hr^{-1} (with 101% between patient variability).

Distribution

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

Biotransformation

The relative proportions of Zelboraf and its metabolites were characterized in a human mass balance study with a single dose of ^{14}C -labeled Zelboraf administered orally. CYP3A4 is the primary enzyme responsible for the metabolism of Zelboraf *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.

Elimination

The population apparent clearance of Zelboraf in patients with metastatic melanoma is estimated to be 29.3 L/day (with 31.9% between patient variability). The population elimination half-life estimated by the population PK analysis for Zelboraf is 51.6 hours (the 5th and 95th percentile range of the individual half life estimates is 29.8 - 119.5 hours).

In the human mass balance study with Zelboraf administered orally, on average 95% of the dose was recovered within 18 days. The majority of Zelboraf-related material (94%) was recovered in faeces, and <1% in urine. Renal elimination does not appear to be of importance for Zelboraf elimination, whereas biliary excretion of unchanged compound may be an important route of elimination. Zelboraf is a substrate and inhibitor of P-gp *in vitro*.

Special populations

Elderly

Based on the population PK analysis, age has no statistically significant effect on Zelboraf pharmacokinetics.

Gender

The population pharmacokinetic analysis indicated a 17% greater apparent clearance (CL/F) and a 48% greater apparent volume of distribution (V/F) in males than in females. It is unclear whether this is a gender or a body size effect. However, the differences in exposure are not large enough to warrant dose adjustment based on body size or gender.

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 Zelboraf (creatinine clearance >40 ml/min). There are no data in patients with severe renal impairment (see sections 4.2 and 4.4).

Hepatic impairment

Based on preclinical data and the human mass balance study, major part of Zelboraf is eliminated via the liver. In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, increases in AST and ALT up to three times the upper limit of normal did not influence the apparent clearance of Zelboraf. Data are insufficient to determine the effect of metabolic or excretory hepatic impairment on Zelboraf pharmacokinetics (see sections 4.2 and 4.4).

Paediatric population

Limited pharmacokinetic data from six adolescent patients aged between 15 and 17 years with stage IIIC or IV BRAF V600 mutation positive melanoma suggest that Zelboraf pharmacokinetic characteristics in adolescents are generally similar to those in adults. See section 4.2 for information on paediatric use.

5.3 Preclinical safety data

The preclinical safety profile of Zelboraf was assessed in rats, dogs, and rabbits.

Repeat-dose toxicology studies identified the liver and bone marrow as target organs in the dog. Reversible toxic effects (hepatocellular necrosis and degeneration) in the liver at exposures below the anticipated clinical exposure (based on AUC comparisons) were noted in the 13-week dog study. Focal bone marrow necrosis was noted in one dog in a prematurely terminated 39-week BID dog study at exposures similar to the anticipated clinical exposure (based on AUC comparisons). In an *in vitro* bone marrow cytotoxicity study, slight cytotoxicity was observed in some lympho-hematopoietic cell populations of rat, dog and human at clinically relevant concentrations.

Zelboraf was shown to be phototoxic, *in vitro*, on cultured murine fibroblasts after UVA irradiation, but not *in vivo* in a rat study at doses up to 450 mg/kg/day (at exposures below the anticipated clinical exposure (based on AUC comparison). No specific studies with Zelboraf have been conducted in animals to evaluate the effect on fertility. However, in repeat-dose toxicity studies, no histopathological findings were noted on reproductive organs in males and females in rats and dogs at doses up to 450 mg/kg/day (at exposures below the anticipated clinical exposure based on AUC comparison). No teratogenicity was observed in embryofetal development studies in rats and rabbits at doses up to respectively 250 mg/kg/day and 450 mg/kg/day leading to exposures below the anticipated clinical exposure (based on AUC comparison). However, exposures in the embryofetal

development studies were below the clinical exposure based on AUC comparison, it is therefore difficult to define to what extent these results can be extrapolated to humans. Therefore an effect of Zelboraf on the foetus cannot be excluded. No studies were performed regarding pre- and postnatal development.

No signs of genotoxicity were identified in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) nor in the *in vivo* rat bone marrow micronucleus test conducted with Zelboraf.

Carcinogenicity studies have not been conducted with Zelboraf.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate
Hydroxypropylcellulose

Film-coating

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.4 Nature and contents of container

Aluminium / Aluminium perforated unit dose blisters
Pack-size: 56 x 1 film-coated tablets (7 blisters of 8 x 1 tablet)

6.5 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Medicine: keep out of reach of children

MYZelboraf20191126/CDS10.0



Revision Date: November 2019

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Delpharm Milano S.r.l, production site Segrate, Italy

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