Zelboraf ®

Vemurafenib

Composition

Active substance: vemurafenib

Excipients: croscarmellose sodium (produced from genetically modified cotton), excipients for coated tablets

Pharmaceutical Form and Quantity of Active Substance per Unit

Film-coated tablets containing 240 mg

Indications and Potential Uses

Treatment of unresectable or metastatic melanoma patients with BRAF V600 mutation.

Dosage and Administration

Only patients in whom BRAF V600 mutation has been demonstrated by a validated test may be treated with vemurafenib.

Usual dosage

The recommended dose is 960 mg (four 240 mg tablets) twice daily. The first dose should be taken in the morning. The second dose should be taken in the evening about 12 hours after the first dose. Both doses should be taken either one hour before or two hours after a meal. Bioavailability in combination with food has not yet been studied. These times should therefore be strictly adhered to.

The film-coated tablets should be swallowed whole with a glass of water and not chewed or crushed.

It is recommended that treatment be continued until disease progression or occurrence of unacceptable toxicity.

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

Dose adjustments

Adverse drug reactions or QT prolongation may necessitate temporary dose reduction, treatment interruption or treatment discontinuation.

The long elimination half-life of vemurafenib must be borne in mind. Severe undesirable effects should prompt consideration of the possibility of enhancing elimination with activated charcoal.

In the event of grade 3 or intolerable grade 2 toxicity, treatment should be interrupted, with dosing resumed at 720 mg twice daily on reaching grade 0–1. Following a repeated episode, treatment should be resumed after interruption at 480 mg twice daily. On the third occurrence of grade 3/intolerable grade 2 or any incident of grade 4 toxicity, treatment should be discontinued.

Dose adjustment or treatment interruption on the appearance of cutaneous squamous cell carcinoma (cuSCC) is not recommended. Dose reductions resulting in a dose below 480 mg twice daily are not recommended.

Special dosage instructions

Elderly patients

No dose adjustment is necessary in patients aged ≥65 years.

Pediatric use

The safety and efficacy of Zelboraf have not been studied in children and adolescents (<18 years of age).

Renal impairment

The safety and efficacy of Zelboraf have not been studied in patients with renal impairment.

Hepatic impairment

The safety and efficacy of Zelboraf have not been studied in patients with hepatic impairment.

Contraindications

Hypersensitivity to the active substance or any of the excipients.

Warnings and Precautions

Cutaneous squamous cell carcinoma (cuSCC)

Cases of cutaneous squamous cell carcinoma (including ones classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported very frequently during treatment with Zelboraf, usually early in the course of treatment. Potential risk factors were age (≥65 years), prior skin cancer and chronic sun exposure. In most cases it was possible to excise the squamous cell carcinoma and continue vemurafenib therapy without dose adjustment. It is recommended that all patients undergo a dermatological examination before the start of treatment and routine monitoring during treatment. Any suspicious skin lesion should be excised, submitted for pathological evaluation and treated according to the local standard of care.

It is recommended that all patients undergo a head and neck examination involving at least visual inspection of the oral mucosa and lymph node palpation before the start of treatment and every 3 months during treatment. Computed tomography of the chest should also be performed in all patients before the start of treatment and every 6 months during treatment. After the end of treatment with vemurafenib, patients should be monitored for the development of skin tumours for at least 6 months or until the start of another antineoplastic therapy. Patients should be urged to tell their doctor about any skin changes, including rash or photosensitivity. Abnormal findings should be investigated further if clinically indicated.

Hypersensitivity

Severe hypersensitivity reactions, including anaphylaxis, have occurred in association with Zelboraf. Severe hypersensitivity reactions may lead, among other things, to Stevens-Johnson syndrome, generalised rash and erythema or hypotension. In patients who experience a severe hypersensitivity reaction, Zelboraf treatment should be permanently discontinued (see "Contraindications").

QT prolongation

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label, phase 2 QT substudy in previously treated patients with metastatic melanoma. QT prolongation may result in an increased risk of ventricular arrhythmias and torsade de pointes. Treatment with Zelboraf is not recommended in patients with uncorrectable electrolyte disturbances, long QT syndrome or who are taking medicinal products known to prolong the QT interval.

ECG and electrolytes should be monitored before starting treatment with Zelboraf and after dose adjustment, then monthly during the first 3 months of treatment and every 3 months thereafter, or more often if clinically indicated. The ECG should be checked after every dose adjustment. Initiation of treatment with Zelboraf is not recommended in patients with QTc >500 ms. If QTc exceeds 500 ms (CTCAE ≥ grade 3) during treatment, Zelboraf should be temporarily interrupted, electrolyte disturbances corrected, and cardiac risk factors for QT prolongation (e.g. heart failure, bradyarrhythmias) controlled. Treatment should be restarted at a lower dose once QTc falls below 500 ms.

Permanent discontinuation of Zelboraf is recommended if QTc is both >500 ms and increased by >60 ms compared to baseline after correction of all associated risk factors.

Hepatic impairment

Elevation of hepatic enzymes may occur during treatment with Zelboraf (see "Undesirable effects—Hepatobiliary system". Hepatic function (transaminases and alkaline phosphatase) and bilirubin should be monitored before starting treatment and monthly during treatment, or as clinically indicated. Laboratory changes should be managed by treatment interruption, dose reduction or, in rare cases, treatment discontinuation.

Photosensitivity

Mild to severe cases of photosensitivity have been reported in patients given doses of Zelboraf in clinical trials (see "Undesirable effects"). All patients should be instructed to avoid sun exposure during treatment with Zelboraf. Patients receiving Zelboraf should wear light-protective clothing and use a broad-spectrum UVA/UVB sun cream and lip balm (SPF ≥30).

If ≥ grade 2 (intolerable) photosensitivity occurs, dose adjustment is recommended.

Interactions

Effects of Zelboraf on CYP substrates

Results of drug interaction studies in patients with metastatic melanoma produced no evidence of drug interactions between Zelboraf and CYP2C19, CYP2D6 and CYP2C9 substrates. Vemurafenib is a CYP1A2 inhibitor and a CYP3A4 inducer.

CYP1A2 inhibition: On administration of a single dose of caffeine after dosing with vemurafenib for 15 days, there was a mean 2.5-fold (maximum up to 10-fold) increase in caffeine exposure (AUC_{last}). Patients should be advised to reduce their coffee, tea and chocolate consumption accordingly. This should also be borne in mind when taking CYP1A2 substrates such as theophylline, lidocaine, clozapine, clomipramine, duloxetine, flutamide, imipramine, mianserin, olanzapine, ondansetron, terbinafine, tizanidine and zolmitriptan.

CYP3A4 induction: On coadministration of a single dose of midazolam after repeated dosing with Zelboraf for 15 days, midazolam plasma exposure (AUC_{last}) was reduced by a mean 32% (maximum up to 80%). This should be borne in mind during concomitant treatment with CYP3A4 substrates, particularly those with narrow therapeutic windows such as vitamin K antagonists, clopidogrel, prasugrel, clomipramine, ifosfamide, ondansetron, vinca alkaloids, etc.

Dose adjustment of drugs metabolised predominantly by CYP1A2 or CYP3A4 should be considered before coadministration with Zelboraf, depending on their therapeutic range. On coadministration of a single dose of warfarin (not licensed in Switzerland) after repeated dosing with Zelboraf for 15 days, increased exposure to warfarin (mean 20%)

was observed in some patients. Coadministration of Zelboraf with vitamin K antagonists must be undertaken with caution.

Effects of coadministered drugs on Zelboraf

There are no clinical data showing an effect of potent inducers or inhibitors of CYP3A4 activity on Zelboraf exposure.

Effects of Zelboraf on drug transport systems

In vitro studies have shown that Zelboraf is both an inhibitor and a substrate of the efflux transporter P-glycoprotein (P-gp). Neither the effects of Zelboraf on drugs that are substrates of P-gp, nor the effects of P-gp inducers or inhibitors on Zelboraf exposure are known. Cautious dosing of Zelboraf is required when taking drugs that affect P-gp (e.g. verapamil).

Pregnancy and Lactation

Pregnancy

No clinical data are available on use in pregnant women. There was no evidence of a teratogenic effect on embryos and fetuses when vemurafenib was administered to pregnant rats and rabbits (see "Preclinical data—Teratogenicity").

Zelboraf should not be administered during pregnancy unless clearly necessary. Women of child-bearing age and men are advised to use a reliable method of contraception during treatment and for at least 6 months after the end of Zelboraf therapy.

Lactation

It is not known whether Zelboraf is excreted in human milk. A risk to neonates/infants cannot be excluded. A decision must be taken whether to discontinue breast-feeding or Zelboraf therapy, weighing the benefit of breast-feeding to the child against the benefit of treatment to the mother.

Effects on Ability to Drive and Use Machines

No studies have been performed on the effects on driving ability and the operation of machinery. Because of undesirable effects such as nausea and vomiting, however, caution is required when driving vehicles and operating machinery.

Undesirable Effects

The commonest (>30%) undesirable effects are arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus. Cutaneous squamous cell carcinoma was observed very frequently, and in most cases was surgically resectable.

The undesirable effects observed in the phase II (BRIM2) and phase III (BRIM3) studies have been classified by organ type and incidence into the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100).

Immune response

Very rare: hypersensitivity reactions

Infections and infestations

Common: folliculitis

Neoplasms

Very common: skin papilloma 30%, cutaneous squamous cell carcinoma 21%, seborrheic keratosis 14%

Common: basal cell carcinoma

Metabolism and nutrition disorders

Very common: decreased appetite 21%

Common: weight loss

Nervous system disorders

Very common: headache 27%, dysgeusia 13%

Common: dizziness, peripheral neuropathy, facial palsy

Eye disorders

Common: retinal vein occlusion, uveitis

Cardiovascular disorders

Common: vasculitis

Very rare: QTc prolongation

Respiratory organs

Very common: cough 12%

Gastrointestinal disorders

Very common: nausea 37%, diarrhea 29%, vomiting 26%, constipation 16%

Hepatobiliary system

Very common: elevation of gamma-GT 15%

Common: elevated ALT, elevated bilirubin, elevated alkaline phosphatase

Uncommon: elevated AST

Skin

Very common: rash 52%, photosensitivity reaction 49%, alopecia 36%, pruritus 30%, hyperkeratosis 28%, maculopapular rash 21%, actinic keratosis 17%, dry skin 16%, papular rash 13%, erythema 11%

Common: palmar-plantar erythrodysesthesia syndrome, keratosis pilaris, erythema nodosum, Stevens-Johnson syndrome

Musculoskeletal system

Very common: arthralgia 67%, myalgia 24%, limb pain 13%, musculoskeletal pain 11%, back pain 11%

Common: arthritis

General disorders

Very common: fatigue 54%, peripheral edema 23%, fever 18%, sunburn 14%

Further information on selected undesirable effects

Hypersensitivity

A case of hypersensitivity reaction involving skin rash, fever, chills and hypotension occurred 8 days after starting treatment with Zelboraf 960 mg twice daily in a clinical trial. Similar symptoms recurred after rechallenge with a single 240 mg dose. The patient permanently discontinued Zelboraf therapy and recovered without sequelae.

QT prolongation (see "Warnings and precautions")

Central tendency analysis of ECG data from an open-label, uncontrolled, phase 2 QT substudy in 132 patients treated with Zelboraf at a dose of 960 mg twice daily showed a mean increase in QTc compared to the day-1 baseline (3.3 ms; upper 95% confidence interval [CI]: 5 ms) by day 15 (12.8 ms; upper 95% CI: 14.9 ms). Exposure-dependent QT prolongation was observed in this study; the mean effect on QTc was stable at 12–15 ms after the first month of treatment. The greatest mean QTc prolongation (15.1 ms; upper 95% CI: 17.7 ms) was observed within the first 6 months of treatment (n=90). Two patients (1.5%) showed treatment-emergent absolute QTc values of >500 ms (CTCAE grade 3), and only one patient (0.8%) developed QTc prolongation of >60 ms compared to baseline. Modelling and simulation of QT prolongation yielded the following estimates: at a dosage of 960 mg twice daily the percentage of patients with QTcP prolongation of over 60 ms compared to baseline is assumed to be 0.05%. This percentage increases to 0.2% for overweight patients with a BMI of 45 kg/m^2. The proportion of patients with a change from baseline QTcP of more than 60 ms is assumed to be 0.043% for men and 0.046% for women. The proportion of patients with QTcP values of over 500 ms is assumed to be 0.05% for men and 1.1% for women.

Use in elderly patients

Of the patients with unresectable or metastatic melanoma who were treated with Zelboraf in the phase 3 study, 28% were 65 years or older.

Gender

The following grade 3 adverse drug reactions were observed in women more often than in men: rash, arthralgia and photosensitivity.

Overdosage

There is no specific antidote for overdosage with Zelboraf. Patients exhibiting undesirable effects after overdosage should receive appropriate symptomatic treatment. Dose-limiting toxicities for Zelboraf include rash with pruritus, exhaustion and arthralgia. In cases of suspected overdosage, treatment with Zelboraf should be suspended and supportive treatment initiated. The long elimination half-life of vemurafenib must be borne in mind. Severe undesirable effects should prompt consideration of the possibility of enhancing elimination with activated charcoal.

Properties and Effects

ATC code: L01XE15

Mechanism of action and pharmacodynamics

Vemurafenib is a low-molecular-weight, orally available inhibitor of the activated form of the BRAF serine-threonine kinase enzyme. Mutations in the BRAF gene lead to constitutive activation of the BRAF protein, which may result in overactivated signal transduction and cell proliferation, even in the absence of typical growth factors. As a potent and selective BRAF inhibitor, vemurafenib suppresses the mitogen-activated protein kinase (MAPK) signalling pathway. The best-characterised BRAF substrate in this signalling pathway is MEK. Phosphorylation of MEK by BRAF leads to MEK activation, and pMEK in turn phosphorylates ERK. After translocation to the nucleus, pERK activates transcription factors responsible for stimulating cell proliferation and survival. *In vitro* studies have shown that vemurafenib inhibits phosphorylation and activation of MEK and ERK, resulting in suppression of uncontrolled cell proliferation in tumour cells due to V600 BRAF mutation.

Clinical efficacy

The efficacy of Zelboraf was evaluated in a clinical phase 3 study (BRIM3) in 675 patients and a clinical phase 2 study (BRIM2) in 132 patients with BRAF mutation (cobas® 4800 BRAF V600 Mutation Test).

Treatment-naïve patients (BRIM3, NO25026)

A total of 675 patients were randomised to treatment with either Zelboraf (960 mg twice daily; n=337) or dacarbazine (1000 mg/m^2 every 3 weeks; n=338). Randomisation was stratified according to disease stage, LDH, ECOG performance status and geographical region. Baseline characteristics were balanced between the two treatment groups. Most patients randomised to Zelboraf were male (59%) and Caucasian (99%). The median age was 56 years (28% were ≥65 years), all patients had an ECOG performance status of 0 or 1, and the majority of patients (66%) had M1c disease stage. The co-primary efficacy endpoints of the study were overall survival (OS) and progression-free survival (PFS). After a mean follow-up of 5 months, median overall survival was 7.9 months in the dacarbazine arm and had not yet been reached in the vemurafenib arm. The hazard ratio was 0.37 (95% CI: 0.26–0.55). Progression-free survival (PFS) differed significantly (5.3 vs 1.6 months); hazard ratio 0.26 (95% CI: 0.20–0.33) ($p<0.0001$). The confirmed overall response was 48.4% vs 5.5%.

Non-responders to at least one prior systemic therapy (BRIM2, NP22657)

An uncontrolled, phase 2 study in 132 patients with metastatic melanoma who had received at least one prior systemic therapy showed a response rate of 52% in the primary endpoint (95% CI: 43%–61%; confirmed overall response assessed by an independent review committee [IRC]). The median time to response was 1.4 months, with 75% of responses achieved within the first 1.6 months of treatment. The median duration of response (assessed by IRC) was 6.5 months. Median overall survival has not yet been reached. Median PFS was 6.1 months.

Pharmacokinetics

The pharmacokinetics of vemurafenib are dose-linear in the range 240 to 960 mg twice daily. T_{max} is 4 hours. Steady state is reached after approximately 14 days of continuous dosing. The accumulation factor is approximately 7.4.

Absorption

The absolute bioavailability of vemurafenib has not been studied.

Distribution

Based on the metastatic melanoma patient population, vemurafenib has an apparent volume of distribution of 91 litres. Vemurafenib is highly protein-bound (>99%). Only a small proportion of vemurafenib passes into red blood cells, and preclinical studies suggest that vemurafenib does not enter the cerebrospinal fluid (CSF).

Metabolism

Vemurafenib is metabolised to only a small extent (conjugation and oxidation).

The major component in the blood is the unchanged parent compound.

Elimination

Elimination is mainly biliary, with 73% recovered in the feces as unchanged parent compound and 13% as characterised metabolites. Less than 1% of radioactivity is recovered in the urine (ADME study). Vemurafenib has an apparent clearance of 29.3 litres/day. The median elimination half-life of vemurafenib is 56.9 hours.

Pharmacokinetics in special patient populations

Elderly patients

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

Gender

Apparent clearance (CL/F) was 17% higher, and apparent volume of distribution (V/F) 48% higher in men than in women. However, no relevant differences were found in exposure, so that gender-based dose adjustment is not required.

Children and adolescents

No studies of vemurafenib pharmacokinetics have been performed in pediatric patients.

Renal impairment

No studies of vemurafenib pharmacokinetics have been performed in patients with renal impairment.

Hepatic impairment

No studies of vemurafenib pharmacokinetics have been performed in patients with hepatic impairment.

Preclinical Data

Carcinogenicity

No carcinogenicity studies have been performed.

Mutagenicity

All standard genotoxicity studies with vemurafenib were consistently negative.

Fertility

No preclinical fertility studies have been performed. No effects on reproductive organs were observed in repeated-dose toxicology studies.

Teratogenicity

Vemurafenib was associated with no teratogenic effects on rat embryos or fetuses (at doses up to 250 mg/kg/day, corresponding to approximately 1.7 times human clinical exposure, based on AUC) or on rabbit embryos or fetuses (at doses up to 450 mg/kg/day, corresponding to approximately 0.8 times human clinical exposure, based on AUC).

Fetal drug levels were 2–6% of maternal levels, suggesting possible transmission of vemurafenib from the mother to the developing fetus.

Other

Repeated-dose dog toxicology studies identified the liver and bone marrow as target organs. In a 13-week study in dogs with twice-daily dosing, partly reversible toxic effects (hepatocellular necrosis and degeneration) were observed in the liver at exposures below clinical exposure (based on AUC comparisons). In a prematurely discontinued 39-week study with twice-daily dosing, focal bone marrow necrosis was observed in a dog at exposures below clinical exposure (based on AUC comparisons).

In vitro phototoxicity was demonstrated for vemurafenib on cultured murine fibroblasts after UVA irradiation; this effect was not confirmed in an *in vivo* rat study. CYP isoenzyme inhibition was observed *in vitro* (mainly CYP2C9 with IC50 5.9 µM, as well as CYP1A2, CYP2C19 and CYP2D6 less marked, with IC50 >20 µM).

Additional Information

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Disposal

Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Special instructions for storage

Do not store above 30°. Store in the original pack and protected from moisture. Keep out of the reach of children.

Packs

Film-coated tablets 240 mg 56

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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