ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

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

4.2 Posology and method of administration

Treatment with vemurafenib should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.
Before taking vemurafenib, 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 vemurafenib is 960 mg (4 tablets of 240 mg) twice daily (equivalent to a total daily dose of 1,920 mg). Vemurafenib 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 vemurafenib 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 vemurafenib 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 vemurafenib (see sections 4.4 and 4.8).

Table 1: Dose modification schedule based on the grade of any AEs

Grade (CTC-AE) [(a)]	**Recommended dose modification**
Grade 1 or Grade 2 (tolerable)	Maintain vemurafenib at a dose of 960 mg twice daily.
Grade 2 (intolerable) or Grade 3	
1st occurence 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).
2nd occurence 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).
3rd occurence of any grade 2 or 3 AE or persistence after 2nd dose reduction	Discontinue permanently.
Grade 4	
1st occurence of any grade 4 AE	Discontinue permanently or interrupt vemurafenib 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).
2nd occurence of any grade 4 AE or persistence of any grade 4 AE after 1st 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.
1st occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures in section 4.4. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures 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).
3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	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 vemurafenib 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 vemurafenib has not been yet established in children and adolescents (<18 years). No data are available.

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

Method of administration
Vemurafenib tablets are to be swallowed whole with water. Vemurafenib tablets 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 vemurafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. The efficacy and safety of vemurafenib in patients with tumours expressing rare BRAF V600 mutations other than V600E and V600K have not been convincingly established (see section 5.1). Vemurafenib 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 vemurafenib (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, vemurafenib treatment should be permanently discontinued.

Dermatologic reactions
Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in the pivotal clinical trial. In patients who experience a severe dermatologic reaction, vemurafenib treatment should be permanently discontinued.

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 vemurafenib 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 vemurafenib, 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 vemurafenib is not recommended in

patients with QTc>500 milliseconds (ms). If during treatment the QTc exceeds 500 ms, vemurafenib 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 vemurafenib 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 vemurafenib (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 vemurafenib 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 vemurafenib. 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 vemurafenib, 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.

Liver injury
Liver laboratory abnormalities may occur with vemurafenib (see section 4.8). Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be monitored before initiation of treatment and monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption or with treatment discontinuation (see sections 4.2 and 4.4).

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). Vemurafenib 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 vemurafenib in clinical studies (see section 4.8). All patients should be advised to avoid sun exposure while taking vemurafenib. 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).

Effects of vemurafenib on other medicinal products
Vemurafenib may increase the plasma exposure of medicinal products predominantly metabolized by CYP1A2 and decrease the plasma exposure of medicines predominantly metabolized by CYP3A4, including oral contraceptives. Dose adjustments for medicinal products predominantly metabolized via CYP1A2 or CYP3A4 should be considered based on their therapeutic windows before concomitantly treating with vemurafenib (see sections 4.5 and 4.6).

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

Effect of other medicinal products on vemurafenib
Vemurafenib pharmacokinetics could be affected by medicines that inhibit or influence P-gp (e.g. verapamil, clarithromycin, cyclosporine, ritonavir, quinidine, dronedarone, amiodarone, itraconazole, ranolazine) (see section 4.5).
Concomitant administration of potent inducers of P-gp, glucuronidation, CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort [hypericin]) should be avoided when possible (see section 4.5). Alternative treatment with less inducing potential should be considered to maintain the efficacy of vemurafenib.

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of vemurafenib on CYP substrates
CYP1A2 inhibition was observed when a single dose of caffeine was co-administered after repeat dosing with vemurafenib for 15 days. This resulted in an average 2.5-fold increase (maximum up to 10-fold) in caffeine plasma exposure after vemurafenib treatment. Vemurafenib may increase the plasma exposure of substances predominantly metabolized by CYP1A2 and dose adjustments should be considered.

CYP3A4 induction was observed when a single dose of midazolam was co-administered after repeat dosing with vemurafenib for 15 days. This resulted in an average 32% decrease (maximum up to 80%) in midazolam plasma exposure after vemurafenib treatment. Vemurafenib may decrease the plasma exposure of substances predominantly metabolized by CYP3A4. On this basis, the efficacy of contraceptive pills metabolized by CYP3A4 used concomitantly with vemurafenib might be decreased. Dose adjustments for CYP3A4 substrates with narrow therapeutic window should be considered (see section 4.4 and 4.6).

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

When a single dose of warfarin was co-administered after repeat dosing with vemurafenib for 15 days, some patients exhibited increased warfarin exposure (mean 20%) (see section 4.4). Caution should be exercised when vemurafenib is co-administered with warfarin (CYP2C9) in patients with melanoma.

Vemurafenib 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.

Due to the long half-life of vemurafenib, the full inhibitory effect of vemurafenib on a concomitant medicinal product might not be observed before 8 days of vemurafenib treatment.
After cessation of vemurafenib treatment, a washout of 8 days might be necessary to avoid an interaction with a subsequent treatment.

Effects of vemurafenib on substance transport systems
In vitro studies have demonstrated that vemurafenib is an inhibitor of the efflux transporter (P-gp). The clinical relevance of this finding is unknown. It cannot be excluded that vemurafenib may increase the exposure of other medicines transported by P-gp.
The possible effect of vemurafenib on other transporters (e.g. BCRP) is currently unknown.

Effects of concomitant medicines on vemurafenib
In vitro studies suggest that CYP3A4 metabolism and glucuronidation are responsible for the metabolism of vemurafenib. Biliary excretion appears to be another important elimination pathway. There are no clinical data available showing the effect of strong inducers or inhibitors of CYP3A4 and/or transport protein activity on vemurafenib exposure. Vemurafenib should be used with caution in combination with potent inhibitors of CYP3A4, glucuronidation and/or transport proteins (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir).
Concomitant administration of potent 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 vemurafenib and should be avoided.

In vitro studies have demonstrated that vemurafenib is a substrate of the efflux transporter, P-gp. The effects of P-gp inducers and inhibitors on vemurafenib exposure are unknown. It cannot be excluded that vemurafenib pharmacokinetics could be affected by medicines that inhibit or influence P-gp (e.g. verapamil, clarithromycin, cyclosporine, ritonavir, quinidine, dronedarone, amiodarone, itraconazole, ranolazine).

It is currently unknown whether vemurafenib is a substrate also to other transport proteins.

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

Pregnancy
There are no data regarding the use of vemurafenib in pregnant women.
Vemurafenib revealed no evidence of teratogenicity in rat or rabbit embryo/foetuses (see section 5.3). In animal studies, vemurafenib was found to cross the placenta. Vemurafenib 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 vemurafenib 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 vemurafenib therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
No specific studies with vemurafenib 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 on reproductive organs (see section 5.3).

4.7 Effects on ability to drive and use machines

The effects of vemurafenib on the ability to drive and use machines have not been studied. 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) (> 30%) reported with vemurafenib include arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus. CuSCC was very commonly reported and was most commonly treated by local excision.

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 ≥ 1/10
Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1,000 to < 1/100
Rare ≥ 1/10,000 to < 1/1000
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 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 vemurafenib in the phase II or phase III study and events* originating from safety reports across all trials

System organ class	***Very Common***	***Common***	***Uncommon***
Infections and infestations		Folliculitis	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	SCC of the skin [(c)], seborrheic keratosis, skin papilloma	Basal cell carcinoma, new primary melanoma[+]	Non-cuSCC*[+]
Metabolism and nutrition disorders	Decreased appetite		
Nervous system disorders	Headache, dysgeusia	7th nerve paralysis, dizziness	Neuropathy peripheral
Eye disorders		Uveitis	Retinal vein occlusion
Vascular disorders			Vasculitis
Respiratory, thoracic and mediastinal disorders	Cough		
Gastrointestinal disorders	Diarrhoea, vomiting, nausea, constipation		
Skin and subcutaneous tissue disorders	Photosensitivity reaction, actinic keratosis, rash, rash maculo-papular, rash papular, pruritus, hyperkeratosis, erythema, alopecia, dry skin, sunburn	Palmar-plantar erythrodysaesthesia syndrome,erythema nodosum, keratosis pilaris	Toxic epidermal necrolysis [(d)], Stevens-Johnson syndrome [(e)]
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, pain in extremity, musculoskeletal pain, back pain	Arthritis	
General disorders and administration site conditions	Fatigue, pyrexia, oedema peripheral, asthenia		
Investigations	GGT increase [(b)]	ALT increase [(b)], alkaline phosphatase increase [(b)], bilirubin increase [(b),] weight decreased, QT prolongation	AST increase [(b)]

* Events originating from safety reports across all trials

[+] A causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.

Description of selected adverse reactions

Hepatic enzyme increase [(b)]
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.

Cutaneous squamous cell carcinoma [(c)] *(cuSCC)*
Cases of cuSCC have been reported in patients treated with vemurafenib. The incidence of cuSCC in vemurafenib-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 vemurafenib 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.

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

Dermatologic Reactions [(e)]
Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in the pivotal clinical trial. In patients who experience a severe dermatologic reaction, vemurafenib 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 vemurafenib 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).

Special populations

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

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

4.9 Overdose

There is no specific antidote for overdose of vemurafenib. Patients who develop adverse reactions should receive appropriate symptomatic treatment. No cases of overdose have been observed with vemurafenib in clinical trials. In case of suspected overdose, vemurafenib 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
Vemurafenib is a low molecular weight, orally available, inhibitor of BRAF serine-threonine kinase. Mutations in the BRAF gene which substitute the valine at amino acid position 600 result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation.
Preclinical data generated in biochemical assays demonstrated that vemurafenib can potently inhibit BRAF kinases with activating codon 600 mutations (Table 4).

Table 4: Kinase inhibitory activity of vemurafenib against different BRAF kinases

Kinase	Anticipated frequency in V600 mutation-positive melanoma [(f)]	Inhibitory Concentration 50 (nM)
$BRAF^{V600E}$	93.2%	10
$BRAF^{V600K}$	5.6%	7
$BRAF^{V600R}$	1%	9
$BRAF^{V600D}$	<0.1%	7
$BRAF^{V600G}$	<0.1%	8
$BRAF^{V600M}$	<0.1%	7
$BRAF^{V600A}$	0	14
$BRAF^{WT}$	NA	39

[(f)] Estimated from 2099 melanomas with annotated BRAF codon 600 mutations in the public COSMIC database, release 54 (July 2011).

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 IC50 against V600 mutated cell lines (V600E, V600R, V600D and V600K mutated cell lines) ranged from 0.016 to 1.131 μM whereas the inhibitory concentration 50 against BRAF wild type cell lines were 12.06 and 14.32 μM, respectively.

Determination of BRAF mutation status

Before taking vemurafenib, 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 vemurafenib has been evaluated in 336 patients from a phase III clinical trial (NO25026) and 132 patients from a phase II clinical trial (NP 22657). 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 vemurafenib in previously untreated patients with BRAF V600E mutation-positive unresectable or metastatic melanoma. Patients were randomized to treatment with vemurafenib (960 mg twice daily) or dacarbazine (1000 mg/m2 on day 1 every 3 weeks).

A total of 675 patients were randomized to vemurafenib (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 vemurafenib. Post-hoc survival analyses were undertaken thereafter as described in table 5.

Table 5: Overall survival in previously untreated patients with BRAF V600 mutation positive melanoma by study cut-off date (N=338 dacarbazine, N=337 vemurafenib)

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)
	vemurafenib	43 (13)		
March 31, 2011	dacarbazine	122 (36)	0.44 (0.33, 0.59) [(g)]	50 (15%)
	vemurafenib	78 (23)		
October 3, 2011	dacarbazine	175 (52)	0.62 (0.49, 0.77) [(g)]	81 (24%)
	vemurafenib	159 (47)		
February 1, 2012	dacarbazine	200 (59)	0.70 (0.57, 0.87) [(g)]	83 (25%)
	vemurafenib	199 (59)		

[(g)] Censored results at time of cross-over

Non-censored results at time of cross-over: March 31: HR (95% CI) = 0.47 (0.35, 0.62); October 3: HR (95% CI) = 0.67 (0.54, 0.84); February 1: HR (95% CI) = 0.76 (0.63, 0.93)

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

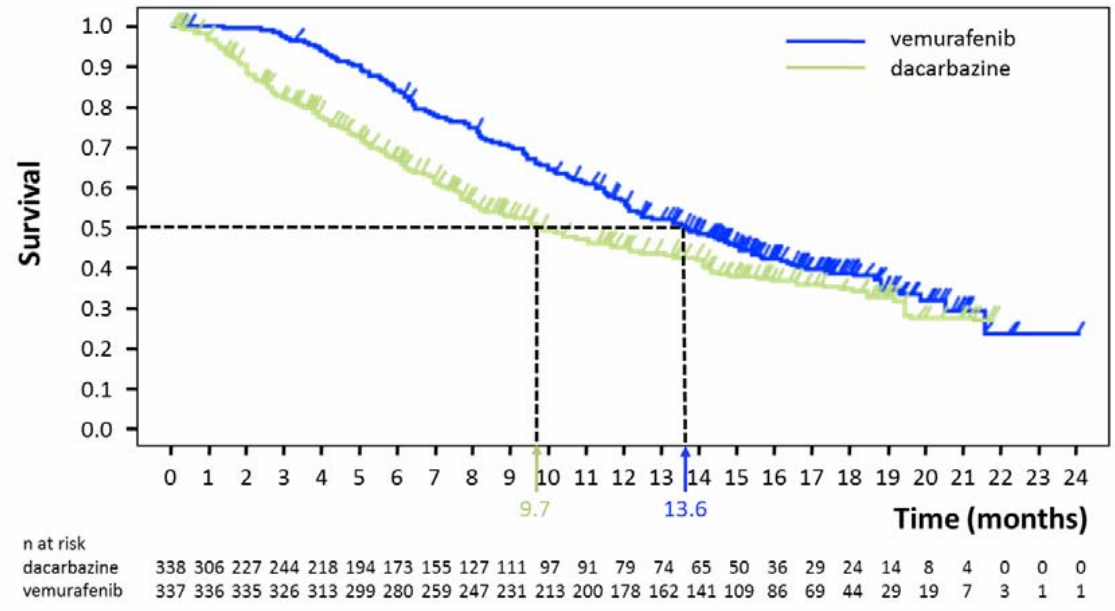

Table 6 shows the treatment effect for all pre-specified stratification variables which are established as prognostic factors.

Table 6: Overall survival in previously untreated patients with BRAF V600 mutation positive melanoma by LDH, tumour stage and ECOG status (February 1, 2012 cut-off, censored results at time of cross over)

Stratification variable	N	Hazard Ratio	95% Confidence Interval
LDH normal	391	0.77	0.57; 1.05
LDH >ULN	284	0.55	0.41; 0.73
Stage IIIc/M1A/M1B	234	1.02	0.69; 1.51
Stage MIC	441	0.57	0.45; 0.73
ECOG PS=0	459	0.75	0.57; 0.98
ECOG PS=1	216	0.56	0.41; 0.78

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

Table 7 shows the overall response rate and progression-free survival in previously untreated patients with BRAF V600 mutation positive melanoma.

Table 7: Overall response rate and progression-free survival in previously untreated patients with BRAF V600 mutation positive melanoma

	vemurafenib	dacarbazine	p-value [h]
December 30, 2010 data cut-off date [i]			
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 [j]			
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) (95% CI)	6.87 (6.14, 6.97)	1.64 (1.58, 2.07)	

[h] Unstratified log-rank test for PFS and Chi-squared test for Overall Response Rate.
[i] As of December 30, 2010, a total of 549 patients were evaluable for PFS and 439 patients were evaluable for overall response rate.
[j] 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 vemurafenib 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.

5.2 Pharmacokinetic properties

Vemurafenib is a Class IV substance (low solubility and permeability), using the criteria described in the Biopharmaceutics Classification System. The pharmacokinetic parameters for vemurafenib 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 absolute bioavailability of the vemurafenib 240 mg tablet is unknown.

Vemurafenib at 960 mg twice daily is absorbed with a median Tmax of approximately 4 hours. Vemurafenib exhibits high inter-patient variability. In the phase II study, AUC_{0-8h} and C_{max} at day 1 were 22.1 ± 12.7 µg·h/mL and 4.1 ± 2.3 µg/mL. Accumulation occurs upon multiple twice daily dosing of vemurafenib. In the non compartmental analysis, after dosing with 960 mg vemurafenib 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 ± 143.6 µg·h/mL and 56.7 ± 21.8 µg/mL, respectively, under steady-state conditions.

Food (high fat meal) increases the relative bioavailability of a single 960 mg dose of vemurafenib. The geometric mean ratios between the fed and fasted states for C_{max} and AUC were 2.6 and 4.7 fold, respectively. The median T_{max} was increased from 4 to 8 hours when a single vemurafenib dose was taken with food.

The effect of food on steady state vemurafenib exposure is currently unknown. Consistent intake of vemurafenib on an empty stomach may lead to significantly lower steady state exposure than consistent intake of vemurafenib with or a short time after a meal. Occasional intake of vemurafenib on an empty stomach is expected to have limited influence on steady state exposure due to the high accumulation of vemurafenib at steady state. Safety and efficacy data from pivotal studies were collected from patients taking vemurafenib 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 vemurafenib 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 vemurafenib 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 vemurafenib and its metabolites were characterized in a human mass balance study with a single dose of ^{14}C-labeled vemurafenib administered orally. 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.

Elimination

The population apparent clearance of vemurafenib 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 vemurafenib 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 vemurafenib administered orally, on average 95% of the dose was recovered within 18 days. The majority of vemurafenib-related material (94%) was recovered in faeces, and <1% in urine. Biliary excretion of unchanged compound may be an important route of elimination. However, due to the unknown absolute bioavailability, the importance of hepatic and renal excretion for the clearance of parent vemurafenib is uncertain. Vemurafenib 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 vemurafenib 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 vemurafenib (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 vemurafenib 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 vemurafenib. Data are insufficient to determine the effect of metabolic or excretory hepatic impairment on vemurafenib pharmacokinetics (see sections 4.2 and 4.4).

Paediatric population
No studies have been conducted to investigate the pharmacokinetics of vemurafenib in paediatric patients.

5.3 Preclinical safety data

The preclinical safety profile of vemurafenib 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.

Vemurafenib 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 vemurafenib 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 embryofoetal 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 embryofoetal 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 vemurafenib 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 vemurafenib.

Carcinogenicity studies have not been conducted with vemurafenib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 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)

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/751/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 February 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal and every three years once an indefinite licence is granted.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zelboraf 240 mg film-coated tablets
vemurafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/751/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zelboraf

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE PERFORATED BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Zelboraf 240 mg tablets
vemurafenib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zelboraf 240 mg film-coated tablets
vemurafenib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Zelboraf is and what it is used for
2. What you need to know before you take Zelboraf
3. How to take Zelboraf
4. Possible side effects
5. How to store Zelboraf
6. Contents of the pack and other information

1. What Zelboraf is and what it is used for

Zelboraf is an anticancer medicine that contains the active substance vemurafenib. It is used to treat adult patients with melanoma that has spread to other parts of the body or cannot be removed by surgery.

It can only be used in patients whose cancer has a change (mutation) in the "BRAF" gene. This change may have led to the development of melanoma.

Zelboraf targets proteins made from this modified gene and slows down or stops the development of your cancer.

2. What you need to know before you take Zelboraf

Do not take Zelboraf:
- If you are **allergic** to vemurafenib or any of the other ingredients of this medicine (listed in section 6 of this leaflet). Symptoms of allergic reactions may include swelling of the face, lips or tongue, difficulty breathing, rash, or fainting sensation.

Warnings and precautions
Talk to your doctor before taking Zelboraf.

Allergic reactions
- **Allergic reactions can happen while taking Zelboraf and may be severe.** Stop taking Zelboraf and get medical help immediately if you have any symptoms of an allergic reaction such as swelling of the face, lips or tongue, difficulty breathing, rash, or fainting sensation.

Severe skin reactions

- **Severe skin reactions can happen while taking Zelboraf.** Stop taking Zelboraf and talk to your doctor immediately if you get a skin rash with any of the following symptoms: blisters on your skin, blisters or sores in your mouth, peeling of your skin, fever, redness or swelling of your face, hands, or soles of your feet.

Heart disorder

- **Tell your doctor if you have a heart disorder, such as an alteration of the electrical activity of your heart called "QT prolongation".** Your doctor will run tests to check that your heart is working properly before and during your treatment with Zelboraf. If necessary, your doctor may decide to interrupt your treatment temporarily or stop it altogether.

Eye problems

- **You should have your eyes examined by your doctor while you are taking Zelboraf.** Tell your doctor immediately if you get eye pain, swelling, redness, blurred vision or other vision changes during your treatment.

Checks of your skin before, during and after treatment

- **If you notice any changes in your skin while taking this medicine, please talk to your doctor as soon as possible.**
- Regularly during your treatment and up to 6 months after your treatment, your doctor needs to check your skin for a type of cancer called "cutaneous squamous cell carcinoma".
- Usually, this lesion appears on sun-damaged skin, remains local and can be cured by surgical removal.
- If your doctor finds this type of skin cancer, he or she will treat it or send you to another doctor for treatment.
- Additionally, your doctor needs to inspect your head, your neck, your mouth, your lymph glands and you will undergo CT scans regularly. This is a precautionary measure in case a squamous cell carcinoma lesion would develop inside your body. Genital examinations (for women) and anal examinations are also recommended before and at the end of your treatment.
- You may develop new melanoma lesions while taking Zelboraf. These lesions are usually removed by surgery and patients continue their treatment. Monitoring of these lesions occurs as outlined above for cutaneous squamous cell carcinoma.

Kidney or liver problems

- **Tell your doctor if you have kidney or liver problems.** This may affect the activity of Zelboraf. Your doctor will also do some blood tests to monitor your liver functions.

Sun protection

- If you are taking Zelboraf, you may become more sensitive to sunlight and get sunburns that can be severe. During treatment, **avoid exposing your skin to direct sunlight**
- If you do plan to go into the sun:
  - wear clothing which protects your skin, including your head and face, arms and legs;
  - use a lip balm and a broad spectrum sunscreen (minimum of Sun Protection Factor(SPF) 30, re-applied every 2 to 3 hours).
- This will help to protect you against sunburn.

Children and adolescents
Zelboraf is not recommended for children and adolescents. The effects of Zelboraf in people younger than 18 years old are not known.

Other medicines and Zelboraf
Before starting treatment, tell your doctor if you are taking, have recently taken or might use any other medicines (including those you have bought for yourself from a pharmacy, supermarket or health store). This is very important, as using more than one medicine at the same time can strengthen or weaken the effect of medicines.

In particular, tell your doctor if you are taking:

- Medicines that are known to affect the way your heart beats:
  - medicines for heart rhythm problems (e.g. quinidine, amiodarone)
  - medicines for depression (e.g. amitriptyline, imipramine)
  - medicines for bacterial infections (e.g. azithromycin, clarithromycin)
  - medicines for nausea and vomiting (e.g. ondansetron, domperidone).
- Medicines that are mainly eliminated by metabolising proteins called CYP1A2 (e.g caffeine, olanzapine, theophylline), CYP3A4 (e.g. some oral contraceptives) or called CYP2C8.
- Medicines that influence a protein called P-gp (e.g. verapamil, clarithromycin, cyclosporine, ritonavir, quinidine, dronedarone, amiodarone, itraconazole, ranolazine, amitriptyline, cisplatin).
- Medicines that stimulate the metabolising proteins called CYP3A4 or a metabolising process called glucuronidation (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort)
- A medicine used to prevent blood clots called warfarin
- A medicine called YERVOY (ipilimumab, another medicine for the treatment of melanoma). The combination of this medicine with Zelboraf is not recommended due to increased toxicity to the liver.

If you are taking any of these medicines (or if you are not sure), please talk to your doctor before taking Zelboraf.

Pregnancy and breast-feeding

- **Use an appropriate method of contraception during your treatment** and for at least 6 months after the end of your treatment. Zelboraf may decrease the efficacy of some oral contraceptives. Please tell your doctor if you are taking an oral contraceptive.
- Zelboraf is not recommended for use during pregnancy unless your doctor considers that the benefit for the mother outweighs the risk for the baby. There is no information about the safety of Zelboraf in pregnant women. Tell your doctor if you are pregnant or planning to become pregnant.
- It is not known whether the ingredients in Zelboraf pass into human milk. Breast-feeding is not recommended during treatment with Zelboraf.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines

It is not known whether Zelboraf will affect your ability to drive or to operate machines. Beware of fatigue or eye problems that could be a reason for not driving.

3. How to take Zelboraf

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

How many tablets should you take

- The recommended dose is 4 tablets twice a day (a total of 8 tablets).
- Take 4 tablets in the morning. Then take 4 tablets in the evening.
- If you experience side effects, your doctor may decide to carry on your treatment but lower your dose. Always take Zelboraf exactly as your doctor has told you.
- In case of vomiting, continue to take Zelboraf as usual and do not take an additional dose.

Taking your tablets

- Do not take Zelboraf regularly on an empty stomach.
- Swallow the tablets whole with a glass of water.

If you take more Zelboraf than you should
If you take more Zelboraf than you should, talk to your doctor immediately. Taking too much Zelboraf may increase the likelihood and severity of side effects. No cases of overdose have been observed with Zelboraf.

If you forget to take Zelboraf
- If you forget a dose and it is more than 4 hours before your next dose, just take your dose as soon as you remember it. Take the next dose at the usual time.
- If it is less than 4 hours before your next dose, skip the missed dose. Then take the next dose at the usual time.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Zelboraf
It is important to keep taking Zelboraf for as long as your doctor prescribes it for you. If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, Zelboraf can cause side effects, although not everybody gets them.

Serious allergic reactions
If you get any of these:
- Swelling of the face, lips or tongue
- Difficulty breathing
- Rash
- Fainting sensation.

Call a doctor immediately. Do not use any more Zelboraf until you have spoken to a doctor.

Please talk to your doctor as soon as possible if you notice any changes in your skin.

Side effects are listed below by frequency:

Very common: may affect more than 1 in 10 people
- Rash, itching, dry or scaly skin
- Skin problems including warts
- A type of skin cancer (cutaneous squamous cell carcinoma)
- Sunburn, being more sensitive to sunlight
- Loss of appetite
- Headache
- Changes in the way things taste
- Diarrhoea
- Constipation
- Feeling sick (nausea), vomiting
- Hair loss
- Joint or muscle pain, musculoskeletal pain
- Pain in the extremities
- Back pain
- Feeling tired (fatigue)
- Fever
- Swelling usually in the legs (peripheral oedema)
- Change in liver tests results (GGT increase)
- Cough.

Common: may affect up to 1 in 10 people
- Types of skin cancers (basal cell carcinoma, new primary melanoma)
- Palmar plantar syndrome (i.e. redness, skin peeling or blisters on hands and feet)
- Inflammation of the eye (uveitis)
- Bell's palsy (a form of facial paralysis that is often reversible)
- Tingling or burning feelings in hands and feet
- Inflammation of joints
- Inflammation of hair's roots
- Weight loss
- Change in liver tests results (ALT, alkaline phosphatase and bilirubin increase)
- Dizziness
- Changes in electrical activity of the heart (QT prolongation).

Uncommon: may affect up to 1 in 100 people
- Allergic reactions that may include swelling of the face and difficulty breathing
- Blockage of blood flow to part of the eye (retinal vein occlusion)
- Problem with the nerves that can produce pain, loss of sensation and/or muscle weakness (neuropathy peripheral)
- Inflammation of blood vessels
- Change in liver tests results (AST increase)
- A type of cancer (non-cutaneous squamous cell carcinoma**)**.

If you get any side effects, talk to you doctor. This includes any possible side effects not listed in this leaflet.

5. How to store Zelboraf

Keep this medicine out of the sight and reach of children.

Do not use Zelboraf after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of the month.

Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Zelboraf contains
- The active substance is vemurafenib. Each film-coated tablet contains 240 milligrams (mg) of vemurafenib (as a co-precipitate of vemurafenib and hypromellose acetate succinate).
- The other ingredients are:
    - Colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl cellulose and magnesium stearate
    - Film-coat: Iron oxide red, macrogol 3350, polyvinyl alcohol, Talc-and titanium dioxide.

What Zelboraf looks like and contents of the pack
Zelboraf 240 mg film-coated tablets are pinkish white to orange white. They are oval with "VEM" engraved on one side.
They are available in aluminium perforated unit dose blisters in packs of 56 x 1 tablets.

Marketing Authorisation Holder
Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

Manufacturer
Roche Pharma AG
Emil-Barell-Strasse 1
D-79639
Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

България
Рош България ЕООД
Тел: +359 2 818 44 44

Česká republika
Roche s. r. o.
Tel: +420 - 2 20382111

Danmark
Roche a/s
Tlf: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα
Roche (Hellas) A.E.
Τηλ: +30 210 61 66 100

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

France
Roche
Tél: +33 (0) 1 47 61 40 00

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Luxembourg/Luxemburg
(Voir/siehe Belgique/Belgien)

Magyarország
Roche (Magyarország) Kft.
Tel: +36 - 23 446 800

Malta
(ara Renju Unit)

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438050

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

Hrvatska
Roche d.o.o
Tel: +385 1 4722 333

Ireland
Roche Products (Ireland) Ltd.
Tel: +353 (0) 1 469 0700

Ísland
Roche a/s
c/o Icepharma hf
Sími: +354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

Κύπρος
Γ.Α.Σταμάτης & Σια Λτδ.
Τηλ: +357 - 22 76 62 76

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

United Kingdom
Roche Products Ltd.
Tel: +44 (0) 1707 366000

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.