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 Adverse Events (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 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).
2nd 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).
3rd occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction	Discontinue permanently.
Grade 4	
1st occurrence 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 occurrence 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 <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).
3rd 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 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 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 vemurafenib has not been established in non-Caucasian patients. No data are available.

Method of administration
Vemurafenib 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 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, generalised 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. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with vemurafenib in the post-marketing setting (see section 4.8). In patients who experience a severe dermatologic reaction, vemurafenib 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 vemurafenib treatment. Most cases were cutaneous in nature but some cases involving visceral organs had fatal outcomes (see sections 4.5 and 4.8). Vemurafenib 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 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.

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

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

Liver injury
Liver injury, including cases of severe liver injury, has been reported with vemurafenib (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 vemurafenib. 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). 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).

Dupuytren's contracture and plantar fascial fibromatosis
Dupuytren's contracture and plantar fascial fibromatosis have been reported with vemurafenib. 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 vemurafenib on other medicinal products
Vemurafenib may increase the plasma exposure of medicinal products predominantly metabolised by CYP1A2 and decrease the plasma exposure of medicines predominantly metabolised by CYP3A4. Concomitant use of vemurafenib with agents metabolized by CYP1A2 and CYP3A4 with narrow therapeutic windows is not recommended. Dose adjustments for medicinal products predominantly metabolised 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 Normalised Ratio) monitoring when vemurafenib is used concomitantly with warfarin.

Vemurafenib may increase the plasma exposure of medicinal products that are P-gp substrates. Caution should be exercised when dosing vemurafenib 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 vemurafenib (see section 4.5).

Effect of other medicinal products on vemurafenib

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 vemurafenib and should be avoided when possible (see section 4.5). Alternative treatment with less inducing potential should be considered to maintain the efficacy of vemurafenib. Caution should be used when administering Vemurafenib 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 >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 Drug Metabolizing Enzymes
Results from an in vivo drug-drug interaction study in metastatic melanoma patients demonstrated that vemurafenib is a moderate CYP1A2 inhibitor and a CYP3A4 inducer.

Concomitant use of vemurafenib with agents 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 vemurafenib 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 vemurafenib increased the plasma exposure (AUC) of caffeine (CYP1A2 substrate) 2.6-fold. In another clinical trial, vemurafenib 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 vemurafenib with agents metabolized by CYP3A4 with narrow therapeutic windows is not recommended. If co-administration cannot be avoided, it needs to be considered that vemurafenib 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 vemurafenib 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 vemurafenib decreased the AUC of midazolam (CYP3A4 substrate) by an average 39% (maximum decrease up to 80%).

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.

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

Vemurafenib moderately inhibited CYP2C8 *in vitro*. The *in vivo* relevance of this finding is unknown, but a risk for a clinically relevant effect on concomitantly administered CYP2C8 substrates cannot be excluded. Concomitant administration of CYP2C8 substrates with a narrow therapeutic window should be made with caution since vemurafenib may increase their concentrations.

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.

Radiation treatment
Potentiation of radiation treatment toxicity has been reported in patients receiving vemurafenib (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 vemurafenib on drug transport systems
In vitro studies have demonstrated that vemurafenib is an inhibitor of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

A clinical drug interaction study demonstrated that multiple oral doses of vemurafenib (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 vemurafenib 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 vemurafenib on medicinal products that are substrates of BCRP are unknown. It cannot be excluded that vemurafenib may increase the exposure of medicines transported by BCRP (e.g. methotrexate, mitoxantrone, rosuvastatin).
Many anticancer medicinal products are substrates of BCRP and therefore there is a theoretical risk for an interaction with vemurafenib.

The possible effect of vemurafenib on other transporters 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. *In vitro* studies have demonstrated that vemurafenib is a substrate of the efflux transporters P-gp and BCRP. It is currently unknown whether vemurafenib 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 vemurafenib concentrations.

Co-administration of itraconazole, a strong CYP3A4/Pgp inhibitor, increased steady state vemurafenib AUC by approximately 40%. Vemurafenib 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 vemurafenib with rifampicin, significantly decreased the plasma exposure of vemurafenib 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 vemurafenib 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 vemurafenib 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.
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. Based on its mechanism of action, vemurafenib could cause fetal harm when administered to a pregnant woman. 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 breast-feeding 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 in reproductive organs in males and females (see section 5.3).

4.7 Effects on ability to drive and use machines

Vemurafenib 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 vemurafenib include arthralgia, fatigue, rash, photosensitivity reaction, alopecia, nausea 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.

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 < 1/1,000
Very rare < 1/10,000

In this section, ADRs are based on results in 468 patients from a phase III randomised 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 vemurafenib in the phase II or phase III studyand 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, seborrhoeic 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, thrombocytopenia[(6)]		
Immune System Disorders				Sarcoidosis[(1)(2)(j)]
Metabolism and nutrition disorders	Decreased appetite			
Nervous system disorders	Headache, dysgeusia, dizziness	7th 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	Stomatitis	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 erythrodysaesthesia 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)]

System organ class	***Very Common***	***Common***	***Uncommon***	***Rare***
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			
Investigations		ALT increased[(c)], alkaline phosphatase increased[(c)], AST increased[(c)], bilirubin increased[(c)] GGT increased[(c)], weight decreased, electrocardiogram QT prolonged, blood creatinine increased[(1)(2)(h)]		
Injury, Poisoning, and Procedural Complications		Potentiation 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.
[(6)] Calculated based on phase II and phase III studies.

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:

- ≥ 5x ULN ALT
- ≥ 2x ULN ALP (without other cause for ALP elevation)
- ≥ 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 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.

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 vemurafenib patients received radiation prior to and during vemurafenib therapy (9.1%) compared to those patients who received radiation and vemurafenib concomitantly (5.2 %) or to those whose radiation treatment was prior to vemurafenib (1.5%).

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

Dermatologic reactions [(f)]
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 centralised 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).

Acute kidney injury [(h)]
Cases of renal toxicity have been reported with vemurafenib 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

	Vemurafenib (%)	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

	Vemurafenib (%)	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 [j]
Cases of sarcoidosis have been reported in patients treated with vemurafenib, mostly involving the skin, lung and eye. In majority of the cases, vemurafenib 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 vemurafenib 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 vemurafenib, grade 3 adverse reactions reported more frequently in females than males were rash, arthralgia and photosensitivity.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: L01EC01

Mechanism of action and pharmacodynamic effects
Vemurafenib 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 vemurafenib can potently inhibit BRAF kinases with activating codon 600 mutations (table 6).

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

Kinase	Anticipated frequency in V600 mutation-positive melanoma [t]	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
$BRAF^{WT}$	N/A	39

[t] Estimated from 16,403 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 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 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, multicentre, international, randomised phase III study supports the use of vemurafenib in previously untreated patients with BRAF V600E mutation-positive unresectable or metastatic melanoma. Patients were randomised to treatment with vemurafenib (960 mg twice daily) or dacarbazine (1000 mg/m^2 on day 1 every 3 weeks).

A total of 675 patients were randomised 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 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 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) [w]	50 (15%)
	vemurafenib	78 (23)		
October 3, 2011	dacarbazine	175 (52)	0.62 (0.49, 0.77) [w]	81 (24%)
	vemurafenib	159 (47)		
February 1, 2012	dacarbazine	200 (59)	0.70 (0.57, 0.87) [w]	83 (25%)
	vemurafenib	199 (59)		
December 20, 2012	dacarbazine	236 (70)	0.78 (0.64, 0.94) [w]	84 (25%)
	vemurafenib	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)

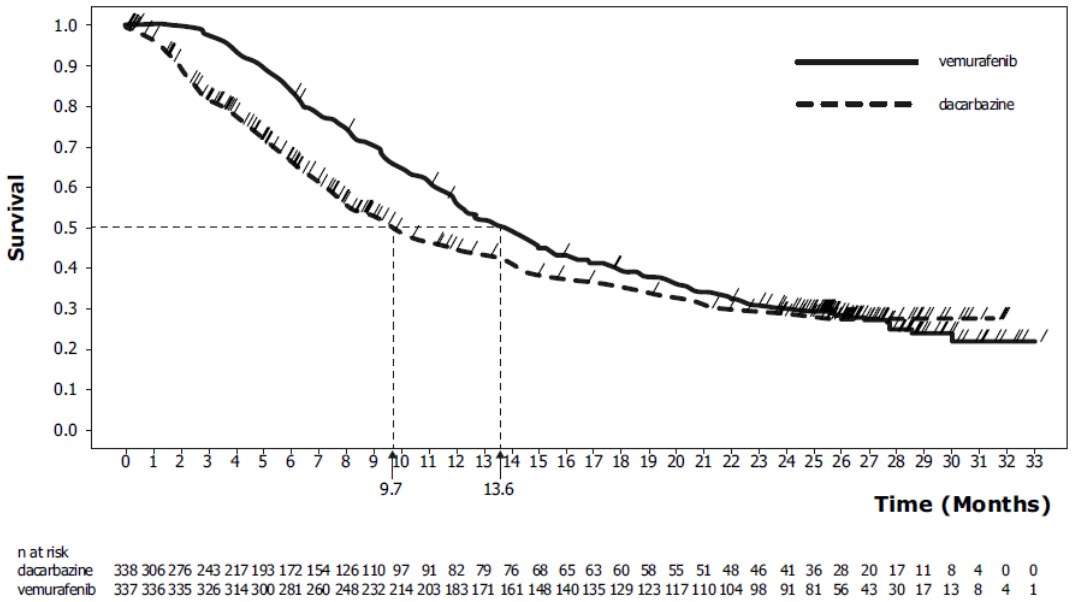

Table 8 shows the treatment effect for all pre-specified stratification variables which are established as prognostic factors.

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

	vemurafenib	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) (95% CI)	6.87 (6.14, 6.97)	1.64 (1.58, 2.07)	

[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 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-centre, 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 vemurafenib 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 vemurafenib 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 vemurafenib 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

Paediatric population

Results from the phase I study (NO25390) in paediatric patients

A phase I dose-escalation study evaluating the use of vemurafenib in six adolescent patients with stage IIIC or IV BRAF V600 mutation positive melanoma was conducted. All patients treated were at least 15 years of age and weighed at least 45 kg. Three patients were treated with vemurafenib 720 mg twice daily, and three patients were treated with vemurafenib 960 mg twice daily. The maximum tolerated dose could not be determined. Although transient tumour regressions were seen, the best overall response rate (BORR) was 0% (95% CI: 0%, 46%) based on confirmed responses. The study was terminated due to low enrollment. See section 4.2 for information on paediatric use.

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 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.

Vemurafenib is absorbed with a median Tmax of approximately 4 hours following a single 960 mg dose (four 240 mg tablets). Vemurafenib exhibits high inter-patient variability. In the phase II study, $AUC_{0\text{-}8h}$ 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 $AUC_{0\text{-}8h}$ 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 2.5 and 4.6 to 5.1 fold, respectively. The median T_{max} was increased from 4 to 7.5 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 characterised 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. Renal elimination does not appear to be of importance for vemurafenib elimiation, whereas biliary excretion of unchanged compound may be an important route of elimination.. 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
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 vemurafenib 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 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-haematopoietic 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

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 Shelf life

3 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 GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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
Date of latest renewal: 22 September 2016

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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 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 GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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 GmbH.

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. See section 4.

What is in this leaflet

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.

Previous history of cancer

- **Tell your doctor if you have had a different type of cancer than melanoma**, as Zelboraf may cause progression of certain types of cancers.

Radiation therapy reactions

- **Tell your doctor if you have had, or are going to have radiotherapy**, as Zelboraf may worsen radiation treatment side effects.

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.

Musculoskeletal/Connective Tissue disorder

- **Tell your doctor if you observe any unusual thickening of the palms of your hands** accompanied by tightening of the fingers inward or any unusual thickening of the soles of your feet which may be painful.

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 check your liver and kidney functions before you start taking Zelboraf and during treatment.

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 or BCRP (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole, gefitinib).
- Medicines that could be influenced by a protein called P-gp (e.g. aliskiren, colchicine, digoxin, everolimus, fexofenadine) or a protein called BCRP (e.g. methotrexate, mitoxantrone, rosuvastatin).
- 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)
- Medicines that strongly inhibit the metabolising protein called CYP3A4 (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir)
- A medicine used to prevent blood clots called warfarin
- A medicine called 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
Zelboraf has side effects that can affect your ability to drive or to operate machines. Beware of fatigue or eye problems that could be a reason for not driving.

Important information about some of the ingredients of Zelboraf
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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. Do not chew or crush the tablets.

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.

Worsening of radiation treatment side effects can occur in patients who are treated with radiation before, during, or after Zelboraf treatment. This can occur on the area that was treated with radiation, such as the skin, esophagus, bladder, liver, rectum, and lungs.
Tell your doctor immediately if you experience any of the following symptoms:

- Skin rash, blistering, peeling or discoloration of the skin
- Shortness of breath, which may be accompanied by a cough, fever or chills (pneumonitis)
- Difficulty or pain when swallowing, chest pain, heartburn or acid reflux (esophagitis).

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)
- Palmar plantar syndrome (i.e. redness, skin peeling or blisters on hands and feet)
- 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)
- Dizziness
- Fever
- Swelling usually in the legs (peripheral oedema)
- Cough.

Common (may affect up to 1 in 10 people):

- Types of skin cancers (basal cell carcinoma, new primary melanoma)
- Thickening of tissues underneath the palm of the hand which may cause tightening of the fingers inward; it can be disabling if severe
- 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
- Inflammation of blood vessels
- Problem with the nerves that can produce pain, loss of sensation and/or muscle weakness (neuropathy peripheral)
- Change in liver tests results (ALT, alkaline phosphatase and bilirubin increase)
- Changes in electrical activity of the heart (QT prolongation)
- Inflammation of the fatty tissue under the skin
- Abnormal kidney blood test results (creatinine increased)
- Change in liver tests results (GGT increase)
- Decreased white blood cells (neutropenia)
- Low blood platelet count (thrombocytopenia)
- Sore mouth or mouth ulcers, inflammation of mucous membranes (stomatitis)

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)

- Inflammation of the pancreas
- Change in liver laboratory tests results or liver injury, including severe liver injury where liver is injured to the extent that it is not able to fully perform its function
- A type of cancer (non-cutaneous squamous cell carcinoma**)**
- Thickening of deep tissues underneath the sole of the feet that may be disabling if severe

Rare (may affect up to 1 in 1,000 people)
- Progression of a type of pre-existing cancers with RAS mutations (Chronic Myelomonocytic Leukaemia, Pancreatic adenocarcinoma)
- A type of severe skin reaction characterised by rash accompanied by fever and inflammation of internal organs such as liver and kidney
- Inflammatory disease mainly affecting the skin, lung and eye (sarcoidosis)
- Types of kidney injury characterized by inflammation (acute interstitial nephritis) or damage to the tubules of the kidney (acute tubular necrosis).

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

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 that 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:
  - Tablet core: colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl cellulose and magnesium stearate
  - Film-coating: 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.

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