PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Zelboraf®

Strength: 240 mg Vemurafenib

Pharmaceutical form: Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: vemurafenib

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

Sugar Free

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Zelboraf film coated tablets: Pinkish white to orange white, oval, biconvex film-coated tablet, with VEM engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zelboraf is indicated as monotherapy for the treatment of adult patients with BRAF V600E mutation-positive unresectable or metastatic melanoma.

4.2 Posology and method of administration

Posology

Treatment with Zelboraf should be initiated and supervised by a qualified medical practitioner experienced in the use of anticancer medicines.

Before taking Zelboraf, patients must have BRAF V600E mutation- positive tumour status confirmed by a validated test (see sections 4.4 and 5).

The recommended dose of Zelboraf is 960 mg (four tablets of 240 mg) twice daily (equivalent to a total daily dose of 1 920 mg). The first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. Each dose of Zelboraf in the morning/evening should always be taken in the same manner i.e. either at least 1 hour before or at least 2 hours after a meal.

Method of administration:

Zelboraf tablets should to be swallowed whole with water.

Zelboraf tablets should not be chewed or crushed.

Duration of treatment:

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

Missed doses:

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

Vomiting:

In case of vomiting after Zelboraf administration the patient should not take an additional dose of the medicine but the treatment should be continued as usual.

Dose adjustments:

Management of symptomatic adverse drug reactions or QTc prolongation may require a dose reduction, temporary interruption and/or treatment discontinuation. Dose adjustments resulting in a dose below 480 mg twice daily are not recommended. In the event the patient develops Cutaneous Squamous Cell Carcinoma (cuSCC), it is recommended to continue the treatment without modifying the dose of Zelboraf (see sections 4.4 and 4.8)

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

Toxicity Grade (CTC-AE) *	**Vemurafenib dose changes during current treatment period**	**Dose Modification at resumption of treatment**
Grade 1 or Grade 2 (tolerable)	No change	N/A
Grade 2 (intolerable) or Grade 3		
1st Appearance ^	Interrupt until resolved: grade 0 – 1.	Reduce dose by 240 mg twice daily.
2nd Appearance ^	Interrupt until resolved: grade 0 – 1.	Reduce dose by 240 mg twice daily.
3rd Appearance ^	Discontinue permanently.	N/A
Grade 4		
1st Appearance ^	Discontinue permanently or interrupt until resolved: grade 0 – 1.	Reduce dose to 480 mg twice daily.
2nd Appearance ^	Discontinue permanently.	N/A

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

^ Any AE where treatment interruption and dose reduction are clinically indicated and undertaken.

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 4.8).

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.

QTc value	Recommended dose modification
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. Reduce the morning and evening dose by 240 mg (total daily dose reduction 480 mg).
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 Reduce both the morning and evening dose by 240 mg daily (total daily dose reduction 480 mg) (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.

***Use in Special Populations**:*

Elderly population

No special dose adjustment is required in patients aged 65 years and older. In clinical trials, all patients received the same starting dose of Zelboraf independent of age.

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 section 4.4 and 5)

Hepatic impairment

Limited data are available in patients with hepatic impairment. As vemurafenib is cleared by the liver, patients with moderate to severe hepatic (Child-Pugh Class B & C) impairment may have increased exposure and should be closely monitored. Cases of liver injury have been reported (see sections 4.4 and 5).

Paediatric Population

The safety and efficacy of Zelboraf in patients under the age of 18 years have not been established. Zelboraf is not approved for use in patients under the age of 18 years.

Non-Caucasian patients

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

4.3 Contraindications

Patients with hypersensitivity to Vemurafenib or to any of its excipients listed in section 6.1.

History of severe hepatic impairment (Child-Pugh C).

Pregnancy. Women should not breastfeed their infants while on Zelboraf (see section 4.6).

4.4 Special warnings and precautions for use

Before taking Zelboraf, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. The efficacy and safety of Zelboraf in patients with tumours expressing BRAF V600 non-E mutations have not been convincingly established (see section 5).

Zelboraf should not be used in patients with wild-type BRAF malignant melanoma.

***Hypersensitivity reactions**:*

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with Zelboraf (see section 4.8).

Severe hypersensitivity reactions may include Stevens-Johnson syndrome, generalised rash, erythema or hypotension. In patients who experience severe hypersensitivity reactions, Zelboraf treatment should be permanently discontinued.

***Dermatological reactions**:*

Severe dermatological reactions have been reported in patients receiving Zelboraf, including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with Zelboraf (see section 4.8). In patients who experience a severe dermatological reaction, Zelboraf treatment should be permanently discontinued.

***Potentiation of Radiation Toxicity**:*

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

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

***QT Prolongation**:*

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase II study in previously treated patients with metastatic melanoma (see section 4.8).

QT prolongation may lead to an increased risk of ventricular dysrhythmias including Torsade de Pointes.

Treatment with Zelboraf is not recommended in patients with un-correctable electrolyte abnormalities (including magnesium), long QT syndrome, or who are taking medicine known to prolong the QT interval.

Electrocardiogram (ECG) and electrolytes (including magnesium) should be monitored in all patients before treatment with Zelboraf, after one month of treatment and after dose modification. Further monitoring is recommended in patients with moderate (Child-Pugh Class B) to severe (Child-Pugh Class C) hepatic impairment monthly during the first 3 months of treatment followed by every 3 months thereafter or more often as clinically indicated. Zelboraf treatment should not be initiated in patients with QTc > 500 milliseconds (ms).

If, during treatment. the QTc exceeds 500 ms (CTCAE ≥ grade 3), Zelboraf treatment should be temporarily interrupted, electrolyte abnormalities (including magnesium, calcium and potassium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure,

bradydysrhythmias) should be controlled. Re-initiation of treatment should occur once the QTc decreases below 500 ms and at a lower dose as described in Tables 2 and 3. Permanent discontinuation of Zelboraf treatment is recommended if, after correction of associated risk factors, the QTc increase meets values of both > 500 ms and > 60 ms change from pre-treatment values.

***Ophthalmological reactions**:*

Serious ophthalmological reactions, including uveitis, iritis, photophobia and retinal vein occlusion, have been reported. Patients should be monitored routinely for ophthalmological reactions and be advised to urgently seek medical attention in the event of acute onset eye pain and/or change in visual acuity.

***Concurrent administration with ipilimumab**:*

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

Malignancies:

***Cutaneous Squamous Cell Carcinoma (cuSCC)**:*

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

CuSCC usually occurred early in the course of treatment. Potential risk factors associated with cuSCC in vemurafenib clinical trials included age (≥ 65 years), prior skin cancer, and chronic sun exposure. Cases of cuSCC were typically managed with simple excision, and patients were able to continue treatment without dose adjustment.

It is recommended that all patients receive a dermatological evaluation prior to initiation of therapy and be monitored routinely while on therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per local standard of care. The prescriber should examine the patient monthly during and up to six months after treatment for cuSCC. In patients who develop cuSCC, it is recommended to continue the treatment without dose adjustment. Monitoring should continue for 6 months following discontinuation of Zelboraf or until initiation of

another anti-neoplastic therapy. Patients should be instructed to inform their medical practitioners upon the occurrence of any skin changes.

Non-Cutaneous Squamous Cell Carcinoma (non-cuSCC):

Cases of non-cuSCC of the head and neck (tongue and tonsils) 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 initiation of treatment and every 6 months during treatment. Anal examinations and pelvic examinations (for women) are recommended before and at the end of treatment or when considered clinically indicated.

Following discontinuation of Zelboraf, monitoring for non-cuSCC should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

New primary melanoma:

New primary melanomas have been reported in clinical trials.

Cases were managed with excision and patients continued treatment without dose adjustment. Monitoring for skin lesions should occur as outlined above for cutaneous squamous cell carcinoma.

Other Malignancies*:*

Zelboraf may cause progression of cancers associated with RAS mutations (see section 4.8). Zelboraf should be used with caution in patients with prior or concurrent cancer associated with RAS mutation.

Pancreatitis

Pancreatitis has been reported in Zelboraf-treated patients. It generally occurs within two weeks after initiation of Zelboraf treatment.

Unexplained abdominal pain should be promptly investigated (including measurement of amylase and lipase serum levels). Patients should be closely monitored when re-starting Zelboraf after an episode of pancreatitis.

Liver injury:

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

Liver laboratory abnormalities may occur with Zelboraf (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 section 4.2)

Creatinine:

Laboratory abnormalities have been reported, mostly cases of mild (> 1-1,5 x ULN) to moderate (> 1,5 – 3 x ULN) serum creatinine elevation. In most cases, serum creatinine elevations appear to be reversible (see section 4.8). However, acute kidney failure may occur. Serum creatinine should be measured before initiation of treatment and periodically monitored during treatment as clinically indicated. For recommended dose modifications, see section 4.2. It is thought that Zelboraf directly inhibits creatinine elimination by the kidney.

Special populations

Elderly population

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

Paediatric population

The safety and efficacy of Zelboraf in children below 18 years of age have not been established.

Gender

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

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. Safety and efficacy have not been established in patients with moderate to severe (Child-Pugh Class B & C) 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 toxicity

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

Renal impairment:

No adjustment to the starting dose is needed for patients with mild or moderate renal impairment. Safety and efficacy have not been established in patients with severe renal impairment (see section 5.2).

Zelboraf should be used with caution in patients with severe renal impairment (CrCl <30mL/min) and patients should be closely monitored.

Photosensitivity*:*

Mild to severe photosensitivity was reported in patients who were treated with Zelboraf in clinical studies (see section 4.8). All patients should be advised to avoid sun exposure while taking Zelboraf. While taking Zelboraf, patients should be advised to wear protective clothing and use a broad spectrum Ultraviolet A (UVA)/Ultraviolet B (UVB) sunscreen and lip balm (Sun Protection Factor (SPF) ≥ 30+) when outdoors to help protect against sunburn. For photosensitivity grade 2

(intolerable) or greater, adverse reactions, dose modifications are recommended (See section 4.2).

***Effects of Zelboraf on other medicines**:*

Zelboraf is a moderate CYP1A2 inhibitor and a CYP3A4 inducer.

Zelboraf may increase the plasma exposure of medicines predominantly metabolised by CYP1A2 and decrease the plasma exposure of medicines predominantly metabolised by CYP3A4. Concomitant use of Zelboraf with medicines metabolised by CYP1A2 and CYP3A4 with narrow therapeutic windows is not recommended. Dose adjustments for medicines predominantly metabolised via CYP1A2 or CYP3A4 should be considered based on their therapeutic windows before concomitantly treating with Zelboraf (see sections 4.5 and 4.6). Perform additional INR (International Normalised Ratio) monitoring when Zelboraf is used concomitantly with warfarin.

Zelboraf is an inhibitor of the efflux transporters P-glycoprotein (P-gp). 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 of the concomitant P-gp substrate medicine may be considered, if clinically indicated (see section 4.5).

***Effect of other medicines on Zelboraf**:*

Vemurafenib pharmacokinetics could be affected by medicines that inhibit or influence P-gp (e.g. verapamil, clarithromycin, ciclosporin, ritonavir, quinidine, dronedarone, amiodarone, itraconazole, ranolazine). Concomitant administration of potent inducers of P-gp glucuronidation, CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort [hypericum peforatum]) should be avoided as it might lead to a decreased exposure of vemurafenib (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 Zelboraf with strong CYP3A4/PgP inhibitors. Patients should be carefully monitored for safety and dose modifications applied if clinically indicated.

***Dupuytren's contracture and plantar fascial fibromatosis**:*

Dupuytren's contracture and plantar fascial fibromatosis have been reported with Zelboraf including severe, disabling cases (see section 4.8).

Events should be managed with dose reduction, treatment interruption, or with treatment discontinuation (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

***Effects of Zelboraf on Medicine Metabolising Enzymes**:*

Results from an *in-vivo* interaction study in metastatic melanoma patients demonstrated that vemurafenib is a moderate CYP1A2 inhibitor and a CYP3A4 inducer.

Co-administration of Zelboraf increased the AUC of caffeine (CYP1A2 substrate) 2,6-fold, while it decreased the AUC of midazolam (CYP3A4 substrate) by 39 %. In another clinical trial, Zelboraf increased AUC_{last} and AUC_{inf} of a single 2 mg dose of tizanidine (CYP1A2 substrate) approximately 4,2 and 4,7 fold, respectively. The AUC of dextromethorphan (CYP2D6 substrate) and its metabolite dextrorphan were increased by approximately 47 % indicating an effect on dextromethorphan kinetics that may not be mediated by inhibition of CYP2D6. Concomitant use of Zelboraf with medicines metabolised by CYP1A2 and CYP3A4 with narrow therapeutic windows, including oral contraceptives, is not recommended. If co-administration cannot be avoided, exercise caution, as Zelboraf may increase plasma exposure of CYP1A2 substrate medicines and decrease plasma exposure of CYP3A4 substrate medicines. Dose reduction of the concomitant CYP1A2 substrate medicine may be considered, if clinically indicated (see section 4.4 and 4.6).

Concomitant use of Zelboraf with medicines metabolised 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 metabolised by CYP3A4 used concomitantly with Zelboraf might be decreased. Dose adjustments for CYP3A4 substrates with narrow therapeutic window may be considered, if clinically indicated (see sections 4.4 and

4.6). 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 Zelboraf resulted in an 18 % increase in AUC of S-warfarin (CYP2C9 substrate) (see section 5.2). Exercise caution and consider additional INR (international normalised ratio) monitoring when Zelboraf is used concomitantly with warfarin (see section 4.4).

Zelboraf moderately inhibited CYP2C8 *in vitro*. A risk for a clinically relevant effect on concomitantly administered CYP2C8 substrates cannot be excluded.

Concomitant administration of CYP2C8 substrates with a narrow therapeutic window should be made with caution since Zelboraf may increase their concentrations such as repaglinide and paclitaxel.

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

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

***Medicines that Inhibit or Induce CYP3A4**:*

Vemurafenib is a substrate of CYP3A4, and therefore concomitant administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Coadministration of rifampicin, a strong CYP3A4 inducer, significantly decreased the plasma exposure of vemurafenib (AUC) by approximately 40 % following a single 960 mg dose of vemurafenib (see section 5 and 5.2). Coadministration of itraconazole, a strong CYP3A4 inhibitor, increased steady state vemurafenib AUC by approximately 40 %. Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) and inducers (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbitone) should be used with caution when co-administered with Zelboraf. Dose reduction of vemurafenib may be considered during coadministration with a strong CYP3A4 inhibitor, if clinically indicated.

***Radiation Treatment**:*

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

Interaction of Vemurafenib with Drug Transport Systems:

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

Clinical medicine interaction study G028394 using a P-gp substrate medicine (digoxin) demonstrated that multiple oral doses of Zelboraf (960 mg twice daily) increased the exposure of a single oral dose of digoxin, with an approximately 1,8 and 1,5 fold increase in digoxin AUC_{last} and C_{max}, respectively. Caution should be exercised when dosing Zelboraf concurrently with P-gp substrates (e.g. aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, sirolimus, sitagliptin, talinolol, topotecan). Dose reduction of the concomitant P-gp substrate medicine may be considered if clinically indicated. Consider additional drug level monitoring for P-gp substrate medicinal products with a narrow therapeutic index (NTI) (e.g. digoxin, dabigatran etexilate, aliskiren) (see section 4.4)

The effects of Zelboraf on medicines that are substrates of BCRP and the effects of Pgg or BCRP inducers and inhibitors on vemurafenib exposure are unknown. It cannot be excluded that vemurafenib may increase the exposure of medicines transported by BCRP (e.g. methotrexate, mitoxantrone, rosuvastatin). *In vitro* studies have also demonstrated that Zelboraf is an inhibitor of bile salt export pump (BSEP). The *in vivo* relevance of this finding is unknown.

Effects of concomitant medicines on Zelboraf

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 %. Zelboraf should be used with caution in combination with strong inhibitors of CYP3A4, glucuronidation and/or transport proteins (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir). Patients co-treated with such medicines should be carefully monitored for safety and dose modifications applied if clinically indicated. 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

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).

Women of childbearing potential / Contraception in males and females:

Men and women of childbearing potential have to use effective contraception during treatment and for at least 6 months after treatment. Zelboraf might decrease the efficacy of hormonal contraceptives (see section 4.5).

Pregnancy*:*

Safety in pregnancy has not been established. Zelboraf revealed no evidence of teratogenicity in preclinical studies. In animal studies, vemurafenib was found to cross the placenta. Based on its

mechanism of action, vemurafenib could cause foetal harm when administered to a pregnant woman. Zelboraf should not be administered to pregnant women (see section 4.3).

***Breastfeeding**:*

A risk to the newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with Zelboraf (see section 4.3).

4.7 Effects on ability to drive and use machines

Zelboraf has an influence on the ability to drive and use machines. Patients should be made aware of the potential fatigue, dizziness or eye problems that could be a reason for not driving. (see section 4.8).

4.8 Undesirable effects

The most common adverse medicine reactions (> 30 %) reported with Zelboraf include: arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus, diarrhoea, headache, vomiting, skin papilloma and hyperkeratosis. The most common (≥ 5 %) Grade 3 ADRs were cuSCC, keratoacanthoma, rash, arthralgia and increased Gammaglutamyl transferase (GGT). CuSCC was very commonly reported and was most commonly treated by local excision. 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 500 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). All terms included are based on the highest percentage observed among phase II and phase III clinical trials.

Within each system organ class, ADR with the same frequency are presented in order of decreasing seriousness and were reported using NCI-CTCAE v 4.0 (common toxicity criteria) for assessment of toxicity.

Table 3 is based on ADR (all grades) occurring in at least 10 % of patients in the phase II (NP22657) or the phase III study (NO25026). For completeness, the table specifies the frequency rate when these ADRs have also been reported as grade 3 - 4 ADRs.

Tabulated summary of adverse reactions

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(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, Melanocytic naevus	Basal cell carcinoma, new primary melanoma(3)	Non-cuSCC(1)(3)	Chronic myelomonocytic leukaemia(2)(4), pancreatic adeno carcinoma(5)
Blood and lymphatic		Neutropenia		

system disorders				
Immune system disorders				Sarcoidosis (1)(2)(j)
Metabolism and nutrition disorders	Decreased appetite, decreased weight			
Nervous system disorders	Headache, dysgeusia, dizziness	Facial nerve (7th nerve) paralysis, peripheral neuropathy		
Eye disorders		Uveitis,	Retinal vein occlusion, iridocyclitis	
Vascular disorders	Hypertension	Vasculitis		
Respiratory, thoracic and mediastinal disorders	Cough			
Gastrointestinal disorders	Diarrhoea, vomiting, nausea, constipation		Pancreatitis(2)	
Hepato-biliary	Increased GGT		Liver injury(1)(2)	

disorders			(g)	
Skin and subcutaneous tissue disorders	Photosensitivity reaction, actinic keratosis, rash, maculo-papular rash, pruritus, hyperkeratosis, erythema, palmar-plantar erythrodysaesthesia syndrome, alopecia, dry skin, sunburn	Papular rash, panniculitis (including erythema nodosum), keratosis pilaris	Toxic epidermal necrolysis (e), Stevens-Johnson syndrome (f)	Medicine reaction with eosinophilia and systemic symptoms(1)(2)
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, pain in extremity, musculoskeletal pain, back pain	Arthritis	Plantar fascial fibromatosis(1)(2) Dupuytren's contracture(1)(2)	
Renal and urinary disorders				Acute interstitial nephritis(1)(2) (h), acute tubular necrosis(1)(2) (h)
General disorders and administration site conditions	Fatigue, pyrexia, peripheral oedema, asthenia			

Investigations		Increased ALT[(c)], increased alkaline phosphatase (ALP) [(c)], increased AST[(c)], increased bilirubin[(c)], increased GGT[(c)], decreased weight, prolonged electrocardiogram QTc, increased blood creatinine [(1)(2) (h)]		
Injury, Poisoning, and Procedural Complications	Sunburn	Potentiation of Radiation toxicity [(1) (2) (i)]		
Cardiac Disorders		Prolonged electrocardiogram QT interval		

(1) Events originating from safety reports across all trials

(2) Events originating from post-marketing sources.

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

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

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

Description of selected adverse reactions:

Hepatic enzyme increase (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: Gamma-glutamyl transferase (GGT)
- Common: alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin
- Uncommon: aspartate aminotransferase (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 (DILI) 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 (c) *(cuSCC):*

Cases of cuSCC have been reported in patients treated with Zelboraf. The incidence of cuSCC in Zelboraf-treated patients across studies was approximately 20 %. The majority of the excised lesions reviewed by an independent central dermatopathology laboratory were classified as SCC-keratoacanthoma subtype or with mixed-keratoacanthoma features (52 %), both of which are a more benign, less invasive type of cuSCC. Most lesions classified as “other” (43 %) were benign

skin lesions e.g. verruca vulgaris, actinic 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).

In patients with ECD, the incidence of cuSCC and/or keratoacanthoma was 40,9 %. The median time to first appearance of cuSCC amongst patients with at least one occurence was 12,1 weeks.

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 (d)

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with Zelboraf. Severe hypersensitivity reactions may include Stevens-Johnson syndrome, generalised rash, rigors, erythema or hypotension. A case of hypersensitivity reaction with rash, fever, rigors and hypotension 8 days after starting vemurafenib 960 mg twice daily was reported in a clinical trial. Similar symptoms were observed upon re-initiation of treatment with a single dose of 240

mg vemurafenib. In patients who experience severe hypersensitivity reactions, Zelboraf treatment should be permanently discontinued (see section 4.4)

Dermatological Reactions (e)

Severe dermatological reactions have been reported in patients receiving Zelboraf, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. In patients who experience a severe dermatological reaction, Zelboraf 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 Zelboraf 960 mg twice daily (NP22657) showed an exposure-dependent QTc prolongation. The mean QTc effect remained stable between 12-15 ms beyond the first month of treatment, with the largest mean QTc prolongation (15,1 ms; upper 95 % CI: 17,7 ms) observed within the first 6 months (n=90 patients). Two patients (1,5 %) developed treatment-emergent absolute QTc values >500 ms (CTC Grade 3), and only one patient (0,8 %) exhibited a QTc change from baseline of >60 ms (see section 4.4).

Modeling and simulation of QT prolongation resulted in the following estimates: for the 960 mg twice-daily dose, the percentage of patients with QTcP prolongation exceeding 60 ms was predicted to be 0,05 %. This percentage was predicted to increase to 0,2 %, for obese patients with BMI of 45 kg/m^2. Percentage of patients with change from baseline in QTcP greater than 60 ms was predicted to be 0,043 % for males and 0,046 % for females. Percentage of patients with QTcP values above 500 ms was predicted to be 0,05 % for males and 1,1 % for females. Creatinine laboratory abnormalities were reported in the post marketing setting (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.

Table 6 Adverse Drug Reactions from postmarketing experience.

System Organ Class (SOC)	**Zelboraf (%)**	**Frequency**
Hepatobiliary Disorders		
Liver Injury[1]	<1	*Uncommon*
Blood and lymphatic systems disorders		

System Organ Class (SOC)	Zelboraf (%)	Frequency
Neutropenia	<1	*Uncommon*
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Chronic myelomonocytic leukemia (CMML)[1,2]	N/A	*frequency not known*
Pancreatic adenocarcinoma[1,3]	N/A	*frequency not known*
Skin and Subcutaneous Tissue Disorders		
Drug reaction with eosinophilia and systemic symptoms (DRESS)[1]	N/A	*frequency not known*
Injury, poisoning and procedural complications		
Radiation injury[1,4]	N/A	*frequency not known*
Gastrointestinal Disorders		
Pancreatitis	<1	*Uncommon*
Renal and Urinary Disorders		
Acute kidney Injury	N/A	*frequency not known*
Musculoskeletal and connective tissue disorders		
Dupuytren's contracture	N/A	*frequency not known*
Plantar fascial fibromatosis	N/A	*frequency not known*

Further information on selected side effects

Acute kidney injury:

A broad spectrum of renal cases has been reported with Zelboraf ranging from mild/moderate creatinine elevations to acute interstitial nephritis and acute tubular necrosis, some observed in the setting of dehydration events. In most cases, creatinine elevations appear to be reversible in nature.

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.

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 32.16 Others – Protein kinase inhibitors

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

Vemurafenib is a low molecular weight, inhibitor of murine sarcoma viral oncogene homolog B1 (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 7).

Table 7: Kinase inhibitory activity of vemurafenib against different BRAF kinases

Kinase	Anticipated frequency in V600 mutation-positive melanoma [(f)]	Inhibitory Concentration 50 (nm)
$BRAF^{V600E}$	87,3 %	10
$BRAF^{V600K}$	7,9 %	7
$BRAF^{V600R}$	1 %	9
$BRAF^{V600D}$	<0,2 %	7
$BRAF^{V600G}$	<0,1 %	8
$BRAF^{V600M}$	0,1 %	7
$BRAF^{V600A}$	<0,1 %	14
$BRAF^{WT}$	NA	39

[(f)] Estimated from 16 403 melanomas with annotated BRAF codon 600 mutations in the public COSMIC database, release 71 (Nov 2014). This inhibitory effect was confirmed in the ERK phosphorylation and cellular anti-proliferation assays in available melanoma cell lines expressing V600-mutant BRAF. In cellular anti-proliferation assays the inhibitory concentration (IC)50 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 European Conformity (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 analysed by sequencing, no specimen was identified as being wild-type by both Sanger and 454 sequencing.

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 pharmacokinetic (PK) analysis using pooled data from 458 patients, estimated the median of the steady-state C_{max}, C_{min} and AUC to be 62 µg/mL, 59 µg/mL and 734 µg*h/mL, respectively. The median accumulation ratio estimate for a twice-daily regimen is 7,36. The PK of vemurafenib is shown to be dose proportional between 240 and 960 mg twice daily, and population PK analysis also confirmed that the PK of vemurafenib is linear. Among these patients, 457 were Caucasians. Mean C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ were approximately 62 µg/mL, 53 µg/mL and 600 µg*h/mL.

Absorption:

The absolute bioavailability of the vemurafenib 240 mg tablet is unknown. 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 T_{max} of approximately 4 hours following a single 960 mg dose (four 240 mg tablets) taken in the fasting state. 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.

The bioavailability of vemurafenib at steady state was 57,8 % (geometric mean). 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 vemurafenib 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 occur due to differences in gastro-intestinal fluid content, volumes, pH, motility and transition time and bile composition. At steady state, reached by day 15 in 80 % of patients, 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 %).

Metabolism/Biotransformation:

The relative proportions of vemurafenib and its metabolites were characterised in a human mass balance study with a single dose of ^{14}C-labelled vemurafenib administered orally at steady state. On average, 95 % of the dose was recovered within 18 days. The majority (94 %) in faeces, with <1 % recovered in urine. 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. Coadministration of rifampicin, a strong CYP3A4 inducer, significantly decreased the plasma exposure of vemurafenib (AUC) by approximately 40 % following a single 960 mg dose of vemurafenib, suggesting that CYP3A4 pathway could be an important elimination pathway for vemurafenib. Coadministration of itraconazole, a strong CYP3A4 inhibitor, increased steady state vemurafenib AUC by approximately 40 %.

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 population:

Based on the population PK analysis, age has no statistically significant effect on vemurafenib pharmacokinetics. No data are available for Asian population.

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.

Paediatric population:

Limited pharmacokinetic data from six adolescent patients aged 15 to 17 with stage IIIC or IV BRAF V600 mutation positive melanoma suggest that vemurafenib pharmacokinetic characteristics in adolescents are generally similar to those in adults. However, no conclusion can be made due to the limited amount of data (see section 4.2).

Renal impairment:

In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, mild and moderate renal impairment did not influence the apparent clearance of vemurafenib (creatinine clearance >30 mL/min). The potential need for dose adjustment in patients with severe renal impairment (creatinine clearance <29 mL/min) cannot be determined as clinical and pharmacokinetic data were available for only one patient (see sections 4.2 and 4.4).

Hepatic impairment:

Based on preclinical data and the human mass balance study, the 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, ALT, and total bilirubin up to three times the upper limit of normal did not influence the apparent clearance of vemurafenib. The potential need for dose adjustment in patients with severe hepatic impairment cannot be determined as clinical and pharmacokinetic data are insufficient to determine the effect of metabolic or excretory hepatic impairment on vemurafenib pharmacokinetics (see sections 4.2 and 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Croscarmellose sodium, hydroxypropylcellulose, magnesium stearate, silica colloidal anhydrous

Film coating mixture: Iron oxide red (E172), macrogol 3350, polyvinyl alcohol, talc, titanium dioxide

(E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C. Protect from moisture.

Keep in carton until required for use.

This medicine should not be used after the expiry date (EXP) shown on the pack.

6.5 Nature and contents of container

Zelboraf: OPA/Alu/PVC aluminium blisters (7 blisters of 8 tablets), containing 56 film-coated tablets per pack.

6.6 Special precautions for disposal and other handling

Disposal of Unused/Expired Medicines

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road

Hertford Office Park, Building E

Vorna Valley, Midrand

Johannesburg

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

47/32.16/0247

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 26 November 2015

10. DATE OF REVISION OF THE TEXT

14 April 2022

Namibia	NS2 16/26/0129