SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

Erivedge® Hard gelatin capsules

WARNING: EMBRYO-FOETAL DEATH AND SEVERE BIRTH DEFECTS

Erivedge (vismodegib) capsule can result in embryo-foetal death or severe birth defects.

Erivedge is embryotoxic and teratogenic in animals. Teratogenic effects included severe midline defects, missing digits, and other irreversible malformations.

Verify pregnancy status prior to the initiation of Erivedge. Advise male and female patients of these risks. Advise female patients of the need for contraception and advise male patients of the potential risk of Erivedge exposure through semen (see WARNINGS AND SPECIAL PRECAUTIONS for use in specific populations).

COMPOSITION

Each hard gelatin capsule contains 150 mg of vismodegib.

Excipients: Microcrystalline cellulose, lactose monohydrate, sodium lauryl sulphate, povidone, sodium starch glycolate, talc, magnesium stearate.

Capsule Shell: Iron oxide black (E172), iron oxide red (E172), titanium dioxide (E171), gelatine.

Printing ink: Shellac glaze, iron oxide black (E172).

Contains sugar: Lactose.

PHARMACOLOGICAL CLASSIFICATION

A 32.16 Others – Antineoplastic agent

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Vismodegib is an orally available small-molecule inhibitor of the Hedgehog pathway. Hedgehog pathway signalling through the smoothened transmembrane protein (SMO) leads to the activation and nuclear localisation of glioma-associated oncogene (GLI) transcription factors and induction of Hedgehog target genes. Many of these genes are involved in cellular proliferation, survival, and organ differentiation. Vismodegib binds to and inhibits the SMO protein thereby blocking Hedgehog signal transduction.

Pharmacokinetic properties:

Absorption: Vismodegib is a highly permeable compound with low aqueous solubility (BCS Class 2). The single dose mean (CV %) absolute bioavailability of vismodegib is 31,8 (14,5) %. Absorption is saturable as evidenced by the lack of dose proportional increase in exposure after a single dose of 270 mg and 540 mg vismodegib. Under clinically relevant conditions (steady state), the PK of vismodegib is not affected by food.

Distribution: The volume of distribution for vismodegib is low, ranging from 16,4 to 26,6 ℓ. *In vitro* binding of vismodegib to human plasma proteins is high (97 %) at clinically relevant concentrations. Vismodegib binds to both human serum albumin and alpha-1-acid glycoprotein (AAG). *In vitro* binding to AAG is saturable at clinically relevant concentrations. *Ex vivo* plasma protein binding in human patients is > 99 %. Vismodegib concentrations are strongly correlated with AAG levels, showing parallel fluctuations of AAG and total vismodegib over time and consistently low unbound vismodegib levels.

In vitro binding of vismodegib to human serum albumin (HAS) is dependent on HAS concentration and independent of vismodegib concentration.

Biotransformation: Vismodegib is slowly eliminated by a combination of metabolism and excretion of parent drug substance. Vismodegib is predominant in plasma, with concentrations representing greater than 98% of the total circulating concentrations (including associated metabolites). Metabolic pathways of vismodegib in humans include oxidation, glucuronidation, and an uncommon pyridine ring cleavage. The two most abundant oxidative metabolites recovered in faeces are produced *in vitro* by recombinant CYP2C9 and CYP3A4/5. These enzymes may thus be major enzymes involved in the elimination.

Elimination: After oral administration of a radiolabelled dose, vismodegib is absorbed and slowly eliminated by a combination of metabolism and excretion of parent drug substance, the majority of which is recovered in the faeces (82 % of the administered dose), with 4,4 % of the administered dose recovered in urine. Vismodegib and associated metabolic products are eliminated primarily by the hepatic route.

After continuous once-daily dosing, the pharmacokinetics of vismodegib appears to be nonlinear due to saturable absorption and saturable protein binding. After a single oral dose, vismodegib has a terminal half-life of ca. 12 days.

The apparent half-life of vismodegib at steady-state is estimated to be 4 days with continuous daily dosing. Upon continuous daily dosing, there is a 3 fold accumulation of vismodegib total plasma concentrations.

Vismodegib inhibits UGT2B7 *in vitro* and it may not be excluded that inhibition can take place *in vivo* in the intestine.

Special populations

Older people: There are limited data in older people. In clinical trials with aBCC, approximately 40 % of patients were of geriatric age (≥ 65 years). Population pharmacokinetic analyses suggest that age did not have a clinically significant impact on steady-state concentration of vismodegib.

Race: There are very limited data in non-Caucasian patients. Since the number of subjects who were not Caucasian comprised only < 3 % of the total population (6 Black, 219 Caucasian), race was not evaluated as a covariate in the population pharmacokinetic analysis.

Patients with renal impairment: There are currently insufficient data in patients with severe renal impairment. Therefore, an effect of severe renal impairment cannot be excluded. Based on population pharmacokinetic analysis of combined data from 5 clinical studies, renal function (creatinine clearance) did not appear to affect the pharmacokinetics of vismodegib (see section DOSAGE AND DIRECTIONS FOR USE). Therefore, based on the low urinary excretion of vismodegib, an effect of mild to moderate renal impairment is not expected.

Patients with hepatic impairment: Limited data indicate that exposure of vismodegib is not relevantly increased in patients with mild hepatic impairment. Data in moderate and severe hepatic impairment are too limited to recommend treatment.

Paediatric population: There are insufficient pharmacokinetic data in paediatric patients.

Clinical efficacy and safety

The pivotal trial was an international, uncontrolled, non-comparative, multi-centre, 2-cohort study. Metastatic basal cell carcinoma (mBCC) was defined as BCC that had spread beyond the skin to other parts of the body, including the lymph nodes, lung, bones and/or internal organs. Locally advanced BCC (laBCC) patients had cutaneous lesions that were inappropriate for surgery (inoperable, multiply recurrent where curative resection deemed to be unlikely or for whom surgery would result in substantial deformity or morbidity) and for which radiotherapy was unsuccessful or contraindicated or inappropriate. Prior to study enrolment, diagnosis of BCC was confirmed by histology. Patients with Gorlin syndrome who had at least one advanced BCC (aBCC) lesion and met inclusion criteria were eligible to participate in the study. Patients were treated with oral daily dosing of vismodegib at 150 mg.

The pivotal study was conducted in 104 patients with advanced basal cell carcinoma (BCC), including metastatic BCC (n = 33) and locally advanced BCC (n = 71).

The median age of the efficacy evaluable population was 62 years (46 % were at least 65 years old), 61 % male and 100 % White. For the mBCC cohort (n = 33), 97 % of patients had prior therapy including surgery (97 %), radiotherapy (58 %), and systemic therapies (30 %). For the laBCC cohort (n = 63), 94 % of patients had prior therapies including surgery (89 %), radiotherapy (27 %), and systemic/topical therapies (11 %). The median duration of treatment was 12,9 months (range 0,7 to 36,6 months).

The primary endpoint was objective response rate (ORR) as assessed by an independent review facility (IRF). Objective response was defined as a complete or partial response determined on two consecutive assessments separated by at least 4 weeks. In the mBCC cohort, tumour response was assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0. In the laBCC cohort, tumour response was assessed based on visual assessment of external tumour and ulceration, tumour imaging (where appropriate), and tumour biopsy. A patient was considered a responder in the laBCC cohort if at least one of the following criteria was met and the patient did not experience progression: (1) ≥ 30 % reduction in lesion size [sum of the longest diameter (SLD)], from baseline in target lesions by radiography; (2) ≥ 30 % reduction in SLD from baseline in externally visible dimension of target lesions; (3) Complete resolution of ulceration in all target lesions. Key data are summarised in Table 1:

Table 1: SHH4476g Erivedge Efficacy Results (21 months follow-up after last patient enrolled): efficacy-evaluable patients*,†

SHH4476g Erivedge Efficacy Results	IRF-Assessed		Investigator-Assessed	
	mBCC (n = 33)	laBCC** (n = 63)	mBCC (n = 33)	laBCC** (n = 63)
Responders 95 % CI for overall response	11 (33,3 %) (19,2 %; 51,8 %)	30 (47,6 %) (30,5 %; 56,0 %)	16 (48,5 %) (30,8 %; 66,2 %)	38 (60,3 %) (47,2 %; 71,7 %)
Complete Response Partial Response Stable disease Progressive disease‡	0 11 (33,3 %) 20 1	14 (22,2 %) 16 (25,4 %) 22 8	0 16 (48,5 %) 14 2	20 (31,7 %) 18 (28,6 %) 15 6
Median Duration of Response (months) (95 % CI)	7,6 (5,5; 9,4)	9,5 (7,4; 21,4)	14,7 (5,5; NE)	20,3# (7,4; NE)
Median Progression Free Survival (months) (95 % CI)	9,5 (7,4; 11,1)	9,5 (7,4; 14,8)	9,3 (7,4; 16,6)	12,9 (10,2; NE)
Median OS, (months) (95 % CI)			30,9# (18,1; NE)#	NE (NE; NE)
1-year survival rate (95 % CI)			78,0 % (63,6; 92,4)	93,1 % (86,6; 99,6)

NE = not estimable

* Efficacy-evaluable patient population is defined as all enrolled patients who received any amount of Erivedge and for whom the independent pathologist's interpretation of archival tissue or baseline biopsy was consistent with BCC.

† Unevaluable/missing data included 1 mBCC and 4 laBCC patients.

‡ Progression in laBCC cohort is defined as meeting any of the following criteria: (1) ≥ 20 % increase in the sum of the longest dimensions (SLD) from nadir in target lesions (either by radiography or by externally visible dimension), (2) New ulceration of target lesions persisting without evidence of healing for at least 2 weeks, (3) New lesions by radiography or physical examination, (4) Progression of non-target lesions by RECIST.

Estimate from 27 month follow-up after last patient enrolled.

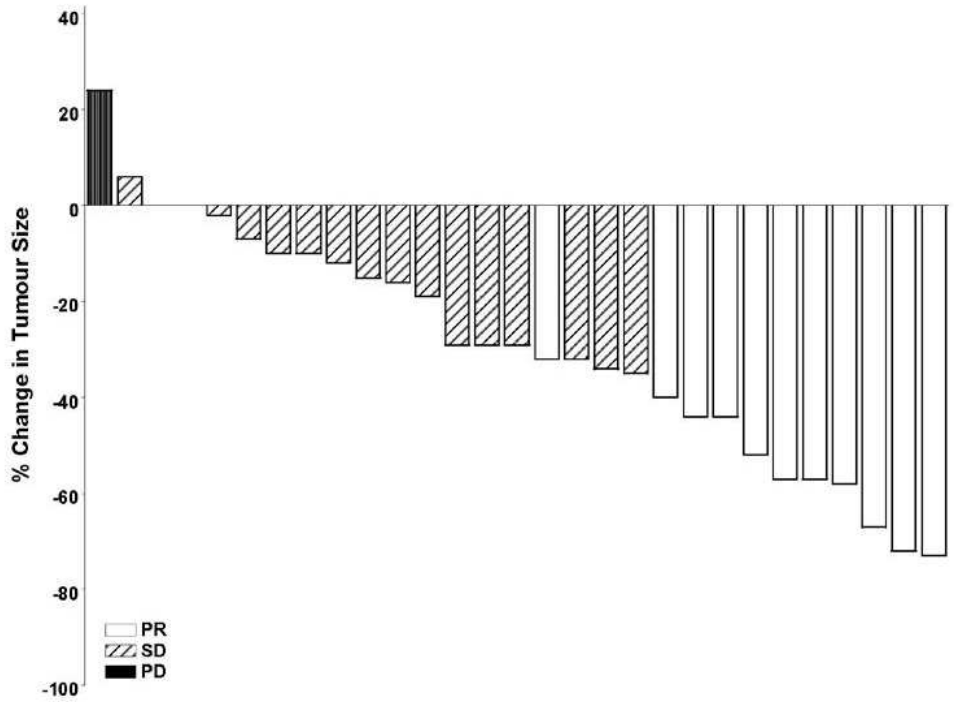
**54 % of laBCC patients had no histopathologic evidence of BCC at 24 weeks.

As shown in the waterfall plots in figures 1 and 2, which chart maximum reduction in target lesion(s) size for each patient, the majority of patients in both cohorts experienced tumour shrinkage as assessed by the IRF.

Figure 1: SHH4476g Metastatic BCC Cohort

(% Change in Tumour Size vs Individual Patient Response)

Each bar represents one patient

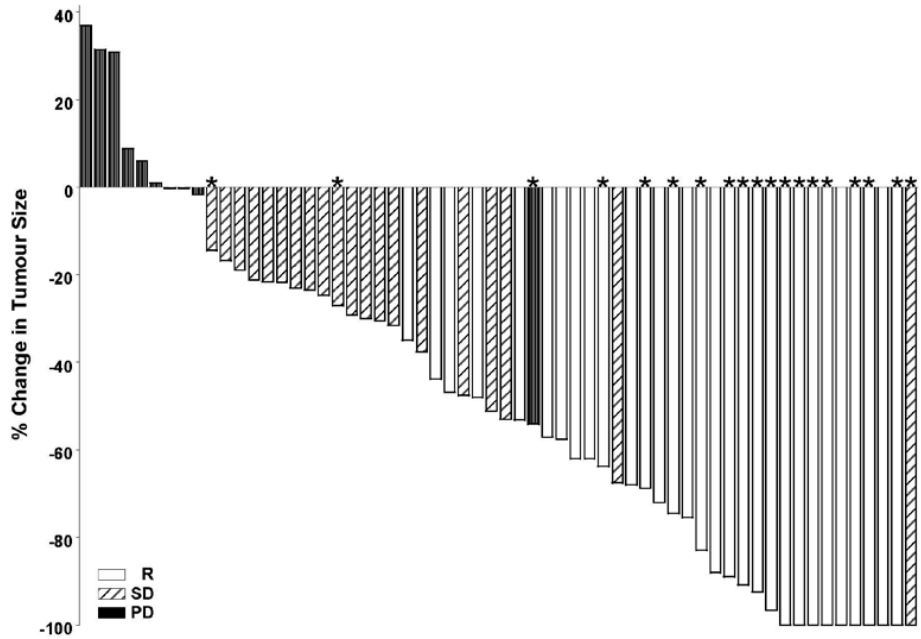


Note: Tumour size is based on sum of longest dimensions of target lesions. PD = progressive disease, SD = stable disease, PR = partial response. 3 patients had a best percent change in tumour size of 0; these are represented by minimal positive bars in the figure. Four patients were excluded from the figure: 3 patients with stable disease were assessed by non-target lesions only and 1 patient was unevaluable.

Figure 2: SHH4476g Locally Advanced BCC Cohort

(% Change in Tumour Size vs Individual Patient Response)

Each bar represents one patient



Note: Tumour size is based on sum of longest dimensions of target lesions. PD = progressive disease, SD = stable disease, R = response, * = complete resolution of ulceration(s). Response assessment was based on a composite endpoint defined as above. Four patients did not have lesion measurements and were not included in the plot.

Time to maximum tumour reduction: Among patients who achieved tumour reduction, the median time to maximum tumour reduction occurred in 5,6 and 5,5 months for laBCC and mBCC patients respectively, based on the IRF assessment. According to investigator assessment, the median time to maximum tumour reduction occurred in 6,7 and 5,5 months for laBCC and mBCC patients respectively.

Cardiac electrophysiology: In a QTc study in 60 healthy subjects, there was no effect of therapeutic doses of vismodegib on the QTc interval.

INDICATIONS

Erivedge is indicated for the treatment of adult patients with:

- symptomatic metastatic basal cell carcinoma
- locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

CONTRAINDICATIONS

- Hypersensitivity to vismodegib or to any of the excipients of Erivedge.
- Women who are pregnant or breastfeeding (see WARNINGS AND SPECIAL PRECAUTIONS).
- Women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme (see sections WARNINGS AND SPECIAL PRECAUTIONS and PREGNANCY AND LACTATION).
- Co-administration of St. John's wort (*Hypericum perforatum)* (see INTERACTIONS).

WARNINGS AND SPECIAL PRECAUTIONS

Embryo-foetal death or severe birth defects

Erivedge may cause embryo-foetal death or severe birth defects when administered to a pregnant woman (see PREGNANCY AND LACTATION). Hedgehog pathway inhibitors, (see PHARMACOLOGICAL ACTION) such as vismodegib, have been demonstrated to be embryotoxic and/or teratogenic in multiple animal species and can cause severe malformations, including craniofacial anomalies, midline defects and limb defects. Erivedge must not be used during pregnancy.

Criteria for a woman of childbearing potential (WCBP)

A WCBP is defined in the Erivedge Pregnancy Prevention Programme as:

- a sexually mature female who
  - has menstruated at any time during the previous 12 consecutive months,
  - has not undergone a hysterectomy or a bilateral oophorectomy,
  - does not have medically confirmed permanent premature ovarian failure,
  - does not have a XY genotype, Turner’s syndrome, or uterine agenesis,
  - becomes amenorrhoeic following cancer therapy, including treatment with Erivedge.

Counselling

For a WCBP

Erivedge is contraindicated in a WCBP who does not comply with the Erivedge Pregnancy Prevention Programme.

A WCBP must understand that:

- Erivedge exposes a teratogenic risk to the unborn child,
- She must not take Erivedge if she is pregnant or plans to become pregnant,
- She must have a negative pregnancy test, conducted by a health care provider within 7 days before starting Erivedge treatment,
- She must have a negative pregnancy test monthly during treatment, even if she has become amenorrhoeic,
- She must not become pregnant while taking Erivedge and for 24 months after her final dose,
- She must be able to comply with effective contraceptive measures,
- She must use 2 methods of recommended contraception (see the ‘Contraception' section below and section PREGNANCY AND LACTATION) while she is taking Erivedge, unless she commits to not having sexual intercourse (abstinence),
- She must tell her healthcare provider if any of the following occur during treatment and for 24 months after her final dose:
  - If she becomes pregnant or think for any reason that she may be pregnant,
  - If she misses her expected menstrual period,
  - If she stops using contraception unless she commits to not having sexual intercourse (abstinence),
  - If she needs to change contraception during treatment.
- She must not breastfeed while taking Erivedge and for 24 months after the final dose.

For men

Vismodegib is contained in semen. To avoid potential foetal exposure during pregnancy, a male patient must understand that:

- Erivedge exposes a teratogenic risk to the unborn child if he engages in unprotected sexual activity with a pregnant woman,
- He must always use the recommended contraception (see the 'Contraception' section below and PREGNANCY AND LACTATION),
- He will tell his healthcare provider if his female partner becomes pregnant while he is taking Erivedge or during the 6 months after his final dose.

For healthcare providers (HCP)

HCPs must educate the patients so they understand and acknowledge all the conditions of the Erivedge Pregnancy Prevention Programme. This includes that all patients, male and female, sign the Verification of Counselling form. The patient's spouse/partner should sign the Verification of Counselling form as well.

Contraception: *WCBP:* Female patients must use two methods of recommended contraception including one highly effective method and a barrier method during Erivedge therapy and for 24 months after the final dose (see section PREGNANCY AND LACTATION).

Men: Male patients must always use a condom (with spermicide, if available), even after a vasectomy, when having sex with a female partner while taking Erivedge and for 6 months after the final dose (see section PREGNANCY AND LACTATION).

Pregnancy testing: In a WCBP, a medically supervised pregnancy test, conducted by a health care provider, should be performed within 7 days prior to initiating treatment and monthly during treatment. Pregnancy should be excluded by a subsequent pregnancy test. Patients who present with amenorrhoea during treatment with Erivedge should continue monthly pregnancy testing while on treatment.

Prescribing and dispensing restrictions for WCBP: The initial prescription and dispensing of Erivedge should occur within 7 days of a negative pregnancy test. Prescriptions of Erivedge should be limited to 28 days of treatment and continuation of treatment requires a new prescription.

Educational material: In order to assist healthcare providers and patients to avoid embryonic and foetal exposure to Erivedge the Registration Holder will provide educational materials (Erivedge Pregnancy Prevention Programme) for patients and their partners, to reinforce the potential risks associated with the use of Erivedge.

Effects on post-natal development: Premature fusion of the epiphyses has been reported in patients exposed to Erivedge. In some cases, fusion progressed after discontinuation of Erivedge. In animal species, vismodegib has been shown to cause severe irreversible changes in growing teeth (degeneration/necrosis of odontoblasts, formation of fluid-filled cysts in the dental pulp, ossification of the root canal, and haemorrhage) and closure of the epiphyseal growth plate. These findings indicate a potential risk for short stature and tooth deformities to infants and children.

Blood donation: Patients should not donate blood while taking Erivedge and for 24 months after the final dose.

Semen donation: Male patients should not donate semen while taking Erivedge and for 6 months after the final dose.

Interactions: Concomitant treatment with strong CYP inducers (e.g. rifampicin, carbamazepine or phenytoin) should be avoided, as a risk for decreased plasma concentrations and decreased efficacy of vismodegib cannot be excluded (see also INTERACTIONS).

Cutaneous squamous cell carcinoma (cuSCC): Patients with advanced BCC have an increased risk of developing cuSCC. Cases of cuSCC have been reported in advanced BCC patients treated with Erivedge. It has not been determined whether cuSCC is related to Erivedge treatment. Therefore, all patients should be monitored routinely while taking Erivedge, and cuSCC should be treated according to the standard of care.

Patients should be instructed never to give Erivedge to another person.

Any unused capsules at the end of treatment should immediately be disposed of by the patient in accordance with local requirements (if applicable, e.g. by returning the capsules to their pharmacist or treating doctor).

Effects on ability to drive and use machines

Erivedge may cause fatigue and muscle pain that may influence the ability to drive and use machines.

Excipients: Erivedge capsules contain lactose monohydrate. Patients with a rare hereditary problem of galactose intolerance, galactosaemia, primary hypolactasia or glucose-galactose malabsorption should not take Erivedge.

Erivedge contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium free'.

INTERACTIONS

Effects of concomitant medicinal products on vismodegib

Medicines that alter the pH of the upper gastrointestinal (GI) tract (e.g., proton pump inhibitors, H_2-receptor antagonists, and antacids) may alter the solubility of vismodegib and reduce its bioavailability. Patients with achlorhydria would be subject to the same potential effect.

In vitro studies indicate that Erivedge is a substrate of the efflux transporter P-glycoprotein (P-gp) and the drug metabolising enzymes CYP2C9 and CYP3A4. When Erivedge is co-administered with medicines that inhibit P-gp (e.g. clarithromycin, erythromycin, azithromycin, verapamil, cyclosporin), CYP2C9 (amiodarone, fluconazole or miconazole), or CYP3A4 (boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole), systemic exposure of Erivedge and incidence of adverse events of Erivedge may be increased. When Erivedge is administered with

CYP inducers (rifampicin, carbamazepine, phenytoin, St. John´s wort), exposure to Erivedge may be decreased (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

Effects on specific enzymes and transporters: In vitro studies indicate that Erivedge has the potential to act as an inhibitor of breast cancer resistance protein (BCRP). *In vivo* interaction data are not available. It may not be excluded that Erivedge may give rise to increased exposure of medicines transported by this protein, such as rosuvastatin, topotecan, and sulfasalazin. Concomitant administration should be performed with caution and a dose adjustment may be necessary.

In vitro, CYP2C8 was the most sensitive CYP isoform for Erivedge inhibition. However, results of an interaction study conducted in cancer patients demonstrated that the systemic exposure of rosiglitazone (a CYP2C8 substrate) is not altered when co-administered with Erivedge. Thus inhibition of CYP enzymes by Erivedge *in vivo* may be excluded.

PREGNANCY AND LACTATION

Women of childbearing potential (WCBP)

Due to the risk of embryo-foetal death or severe birth defects caused by vismodegib, women taking Erivedge must not be pregnant or become pregnant during treatment and for 24 months after the final dose (see sections CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS). Erivedge is contraindicated in WCBP who do not comply with the Erivedge Pregnancy Prevention Programme.

In case of pregnancy or missed menstrual periods

If the patient does become pregnant, misses a menstrual period, or suspects for any reason that she may be pregnant, she must notify her treating doctor immediately. Persistent lack of menses

during treatment with Erivedge should be assumed to indicate pregnancy until medical evaluation and confirmation.

Contraception in males and females

Women of childbearing potential (*WCBP*): WCBP must be able to comply with effective contraceptive measures. She must use two methods of recommended contraception including one highly effective method and a barrier method during Erivedge therapy and for 24 months after the final dose. WCBP, whose periods are irregular or stopped, must follow all the advice on effective contraception.

Men: Erivedge is contained in semen. To avoid potential foetal exposure during pregnancy, male patients must always use a condom (with spermicide, if available), even after a vasectomy, when having sex with a female partner while taking Erivedge and for 6 months after the final dose.

The following are recommended forms of highly effective methods:

- Oral contraceptives,
- Hormonal depot injection,
- Tubal sterilisation,
- Vasectomy,
- Intrauterine device (IUD).

The following are recommended forms of barrier methods:

- Any male condom (with spermicide, if available),
- Diaphragm (with spermicide, if available).

Pregnancy

Erivedge is contraindicated in pregnant women. Erivedge may cause embryo-foetal death or severe birth defects when administered to a pregnant woman (see WARNINGS AND SPECIAL PRECAUTIONS). Hedgehog pathway inhibitors (see PHARMACOLOGICAL ACTION -

Pharmacodynamic Properties) such as vismodegib, have been demonstrated to be embryotoxic and/or teratogenic in multiple animal species and can cause severe malformations, including craniofacial anomalies, midline defects and limb defects. In case of pregnancy in a woman treated with Erivedge, treatment must be stopped immediately.

Breastfeeding

The extent to which vismodegib is excreted in breast milk is not known. Due to its potential to cause serious developmental defects women must not breastfeed while taking Erivedge and for 24 months after the final dose (see CONTRAINDICATIONS).

Fertility

Data from studies in rats and dogs indicate that male and female fertility may be irreversibly compromised by treatment with Erivedge (see SIDE EFFECTS). Additionally, amenorrhoea has been observed in clinical trials in WCBP (see SIDE EFFECTS). Fertility preservation strategies should be discussed with WCBP prior to starting treatment with Erivedge.

DOSAGE AND DIRECTIONS FOR USE

Erivedge should only be prescribed by or under the supervision of a specialist healthcare professional experienced in the management of the approved indication.

Standard dose: Erivedge is for oral use. The recommended dose is one 150 mg capsule taken once daily, with or without food. The capsules must be swallowed whole with water and must not be opened or crushed under any circumstances.

Erivedge should be continued until disease progression or until unacceptable toxicity.

Missed doses: If a dose is missed, patients should be instructed not to take the missed dose but to resume with the next scheduled dose.

Duration of treatment: In clinical trials, treatment with Erivedge was continued until disease progression or until unacceptable toxicity. Treatment interruptions of up to 4 weeks were allowed

based on individual tolerability. Benefit of continued treatment should be regularly assessed, with the optimal duration of therapy varying for each individual patient.

Special populations

Older people: No dose adjustment is required in patients ≥ 65 years of age.

Patients with renal and hepatic impairment: The safety and efficacy of Erivedge have not been studied in patients with impaired renal and hepatic function (see PHARMACOLOGICAL ACTION – Pharmacokinetic properties). No specific dose recommendations for these patient populations are available. Patients with severe renal impairment or moderate to severe hepatic impairment should be carefully monitored for adverse reactions.

Paediatric population: The safety and efficacy of Erivedge in children and adolescents aged below 18 years have not been established. Premature fusion of the epiphyses has been reported in paediatric patients exposed to Erivedge. Erivedge should not be used in children and adolescents aged below 18 years, (see WARNINGS AND SPECIAL PRECAUTIONS).

SIDE EFFECTS

The most common adverse drug reactions (ADR), were muscle spasms (74,6 %), alopecia (65,2 %), dysgeusia (57,2 %), weight decreased (48,6 %), fatigue (44,9 %) and nausea (34,8 %).

ADRs are presented in Table 2 below by system organ class (SOC) and absolute frequency.

Frequencies are defined as: 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) and Very rare (< 1/10 000).

Within each frequency grouping, ADRs are presented in the order of decreasing seriousness.

The safety of Erivedge has been evaluated in clinical trials with 138 patients treated for advanced basal cell carcinoma (aBCC), which includes both metastatic BCC (mBCC) and locally advanced

BCC (laBCC). In general the safety profile observed was consistent in both mBCC and laBCC patients as described below.

Table 2: ADRs occurring in patients treated with Erivedge in clinical trials

MedDRA SOC	Very common	Common
Investigation		Increased** hepatic enzymes; Increased blood creatine phosphokinase
Metabolism and nutrition disorders	Decreased appetite	Dehydration Hyponatraemia
Nervous system disorder	Dysgeusia Ageusia	Hypogeusia
Gastrointestinal disorders	Nausea Diarrhoea Constipation Vomiting	Dyspepsia Upper abdominal pain Abdominal pain
Skin and subcutaneous tissue disorders	Alopecia Pruritus	Rash Madarosis Abnormal hair growth
Musculoskeletal and connective tissue disorders	Muscle spasms	Arthralgia Pain in extremity Back pain Musculoskeletal chest pain Myalgia Flank pain Musculoskeletal pain
Reproductive system and breast disorders	Amenorrhoea*	
General disorders and administration site conditions	Decreased Weight Fatigue	Pain Asthenia

All reporting is based on ADRs of all grades using National Cancer Institute - Common Terminology Criteria for Adverse Events v 3,0 except where noted.
*Of the 138 patients with advanced BCC, 10 were WCBP. Amongst these women, amenorrhea was observed in 3 patients (30 %).
**Includes preferred terms: aspartate aminotransferase increased, alkaline phosphatase increased, liver hepatic enzyme increased.
MedDRA = Medical Dictionary for Regulatory Activities.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of Erivedge is important. It allows continued monitoring of the benefit/risk balance of Erivedge. Healthcare professionals are asked to report any suspected adverse reactions via the Roche Ethical Assistance Line listed at the end of this package insert.

Post Marketing

The following adverse drug reactions have been identified during post-approval use of Erivedge:
Musculoskeletal and connective tissue disorders: Epiphyses premature fusion (see WARNINGS AND SPECIAL PRECAUTIONS and DOSAGE AND DIRECTIONS FOR USE - use in special populations).
Renal impairment and renal failure have been reported. Cases of myositis and muscle weakness have occurred and trismus has been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Erivedge has been administered at doses 3,6 times higher than the recommended 150 mg daily dose. No increases in plasma vismodegib levels or toxicity were observed during these clinical trials.

IDENTIFICATION

The capsule (size 1) has a pink opaque body marked “150 mg” and a grey opaque cap marked with “VISMO” in black ink.

PRESENTATION

Each carton contains a white square HDPE bottle with a white child-resistant screw cap containing 28 hard capsules.

STORAGE INSTRUCTIONS

Store at or below 30°C. Store in outer carton until required for use.

Keep the bottle tightly closed in order to protect from moisture.

Store out of reach of children.

REGISTRATION NUMBER

48/32.16/0658

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road

Hertford Office Park

Building E

Vorna Valley

Midrand

South Africa

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

DATE OF PUBLICATION OF THIS PACKAGE INSERT

Registration: 22 May 2022