Erivedge PI version 5

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Erivedge®

Vismodegib

Capsules 150 mg

1. NAME OF THE MEDICINAL PRODUCT

Erivedge 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 150 mg of vismodegib.

Excipient with known effect:
Each hard capsule contains 71.5 mg lactose monohydrate per capsule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Pink coloured opaque body marked “150 mg” and a grey opaque cap marked “VISMO” with black ink. The size of the capsule is ‘Size 1’ (dimensions 19.0 x 6.6 mm).

4. CLINICAL PARTICULARS

Educational material
In order to assist health care providers and patients to avoid embryonic and foetal exposure to Erivedge the Marketing Authorisation Holder will provide educational materials (Erivedge Pregnancy Prevention Programme) to reinforce the potential risks associated with the use of Erivedge:

HCP (Health Care Provider) Information Card and Brochure
This product is marketed with HCP information card and HCP brochure providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

Patient Information Card and Brochure
This product is marketed with patient safety information materials (patient information card and patient brochure). Please explain to the patient the implications of this treatment including the need for compliance. Please also explain the signs of important adverse reactions and instruct the patient when to seek medical care.

4.1 Therapeutic indication

Erivedge is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

4.2 Posology and method of administration

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

Posology
The recommended dose is one 150 mg capsule taken once daily.

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

Elderly
No dose adjustment is required in patients ≥ 65years of age (see section 5.2). Of a total number of 138 patients in 4 clinical trials of Erivedge in advanced basal cell carcinoma, approximately 40 % of patients were ≥ 65 years old and no overall differences in safety and efficacy were observed between these patients and younger patients.

Renal impairment
Mild and moderate renal impairment is not expected to impact the elimination of vismodegib and no dose adjustment is needed. Very limited data is available in patients with severe renal impairment. Patients with severe renal impairment should be carefully monitored for adverse reactions.

Hepatic impairment
No dose adjustment is required in patients with mild, moderate or severe hepatic impairment defined based on National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG)- criteria for hepatic impairment:

- mild:total bilirubin (TB) ≤ upper limit of normal (ULN), aspartate aminotransferase (AST)>ULN or ULN<TB≤1.5xULN, AST any
- moderate: 1.5 x ULN < TB < 3 x ULN, AST any
- severe: 3 x ULN < TB < 10 x ULN, AST any

(see section 5.2)

Paediatric population
The safety and efficacy of Erivedge in children and adolescents aged below 18 years have not been established.
Due to safety concerns (see sections 4.4 and 5.3), this medicinal product should not be used in children and adolescents aged below 18 years.

Method of administration
Erivedge is for oral use.The capsules must be swallowed whole with water, with or without food (see section 5.2). The capsules must not be opened, to avoid unintended exposure to patients and health care providers.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Women who are pregnant or breast-feeding (see sections 4.4 and 4.6).
- Women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme (see sections 4.4 and 4.6).
- Coadministration of St John's wort (*Hypericum perforatum)* (see section 4.5).

4.4 Special warnings and precautions for use

Embryo-foetal death or severe birth defects

Erivedge may cause embryo-foetal death or severe birth defects when administered to a pregnant woman (see section 4.6). Hedgehog pathway inhibitors, (see section 5.1) 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 (see section 5.3). 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, or who 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 4.6) 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 breast-feed while taking Erivedge and for 24 months after the final dose.

For men

Vismodegib is present 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 section 4.6),

- He will tell his healthcare provider if his female partner becomes pregnant while he is taking Erivedge or during the 2 months after his final dose.

For health care providers (HCP)
HCPs must educate the patients so they understand and acknowledge all the conditions of the Erivedge Pregnancy Prevention Programme.

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 4.6).

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 2 months after the final dose (see section 4.6).

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 tests should have a minimum sensitivity of 25 mIU/mL as per local availability. 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 a maximum of 7 days of a negative pregnancy test (day of pregnancy test = day 1). Prescriptions of Erivedge should be limited to 28 days of treatment and continuation of treatment requires a new prescription.

Effects on post-natal development
Premature fusion of the epiphyses and precocious puberty have been reported in paediatric patients exposed to Erivedge. Due to the long drug elimination half-life, these events may occur or progress after drug discontinuation. 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. The findings of premature fusion of the epiphyses indicate a potential risk for short stature and tooth deformities to infants and children (see section 5.3).

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 2 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 section 4.5).

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.

Additional precautions
Patients should be instructed never to give this medicinal product 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 physician).

Excipients
Erivedge capsules contain lactose monohydrate. Patients with a rare hereditary problem of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of concomitant medicinal products on vismodegib

Clinically significant PK interactions between vismodegib and pH elevating agents are not expected. Results from a clinical study demonstrated a 33% decrease in vismodegib unbound drug concentrations after 7 days co-treatment with 20 mg rabeprazole (a proton pump inhibitor) given 2 h before each vismodegib administration. This interaction is not expected to be clinically significant.

Clinically significant PK interactions between vismodegib and CYP450 inhibitors are not expected. Results from a clinical study demonstrated a 57% increase in vismodegib unbound drug concentrations on day 7 after co-treatment with 400 mg fluconazole (a moderate CYP2C9 inhibitor) daily, but this interaction is not expected to be clinically significant. Itraconazole (a strong CYP3A4 inhibitor) 200 mg daily did not influence vismodegib AUC0-24h after 7 days co-treament in healthy volunteers.

Clinically significant PK interactions between vismodegib and P-gp inhibitors are not expected. Results from a clinical study demonstrated no clinically significant PK interaction between vismodegib and itraconazole (a strong P-glycoprotein inhibitor) in healthy volunteers.

When vismodegib is administered with CYP inducers (rifampicin, carbamazepine, phenytoin, St. John´s wort), exposure to vismodegib may be decreased (see sections 4.3 and 4.4).

Effects of vismodegib on concomitant medicinal products

Contraceptive steroids
Results of a drug-drug interaction study conducted in cancer patients demonstrated that the systemic exposure of ethinyl estradiol and norethindrone is not altered when co-administered with vismodegib. However, the interaction study was of only 7 days duration and it cannot be excluded that vismodegib upon longer treatment is an inducer of enzymes which metabolise contraceptive steroids**.** Induction could lead to decreases in systemic exposure of the contraceptive steroid**s** and thereby reduced contraceptive efficacy.

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

Clinically significant PK interactions between vismodegib and CYP450 substrates are not expected. *In vitro*, CYP2C8 was the most sensitive CYP isoform for vismodegib inhibition. However, results of a drug-drug interaction study conducted in cancer patients demonstrated that the systemic exposure of rosiglitazone (a CYP2C8 substrate) is not altered when co-administered with vismodegib. Thus inhibition of CYP enzymes by vismodegib *in vivo* may be excluded.

In vitro, vismodegib is an inhibitor of OATP1B1. It cannot be excluded that vismodegib may increase the exposure to substrates of OATP1B1, e.g. bosentan, ezetimibe, glibenclamide, repaglinide, valsartan and statins. In particular, caution should be exercised if vismodegib is administered in combination with any statin.

4.6 Fertility, 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 4.3 and 4.4).
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 physician 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
Vismodegib is present 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 2 months after the final dose.

The following are recommended forms of highly effective methods:
- 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 may cause embryo-foetal death or severe birth defects when administered to a pregnant woman (see section 4.4). Hedgehog pathway inhibitors (see section 5.1) 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 (see section 5.3). In case of pregnancy in a woman treated with Erivedge, treatment must be stopped immediately.

Breast-feeding
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 breast-feed while taking Erivedge and for 24 months after the final dose (see sections 4.3 and 5.3).

Fertility
Human female fertility may be compromised by treatment with Erivedge (see section 5.3). Reversibility of fertility impairment is unknown. Additionally, amenorrhoea has been observed in clinical trials in WCBP (see section 4.8). Fertility preservation strategies should be discussed with WCBP prior to starting treatment with Erivedge.

Fertility impairment in human males is not expected (see Section 5.3).

4.7 Effects on ability to drive and use machines

Erivedge has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse drug reactions (ADR) occurring in ≥ 30 % of patients, were muscle spasms (74.6 %), alopecia (65.9%), dysgeusia (58.7%), weight decreased (50.0%), fatigue (47.1%), nausea (34.8 %) and diarrhea (33.3%).

Tabulated list of adverse reactions
ADRs are presented in table 1 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)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data).
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 four open label phase 1 and 2 clinical trials patients were treated with at least one dose of Erivedge monotherapy at doses ≥ 150 mg. Doses > 150 mg did not result in higher plasma concentrations in clinical trials and patients on doses > 150 mg have been included in the analysis. Additionally, safety was assessed in a post approval study that included 1215 aBCC patients evaluable for safety and treated with 150 mg. In general the safety profile observed was consistent in both mBCC and laBCC patients and across studies as described below.

Table 1 ADRs occurring in patients treated with Erivedge in clinical trials

MedDRA SOC	Very common	Common	Frequency not known
Metabolism and nutrition disorders	Decreased appetite	Dehydration	
Nervous system disorder	Dysgeusia Ageusia	Hypogeusia	
Gastrointestinal disorders	Nausea Diarrhoea Constipation Vomiting Dyspepsia	Abdominal pain upper Abdominal pain	
Hepatobiliary disorders		Hepatic enzymes increased**	Drug induced liver injury*****
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 Blood creatine phosphokinase increased***	Epiphyses premature fusion****
Endocrine disorders			Precocious puberty****
Reproductive system and breast disorders	Amenorrhoea*		
General disorders and administration site conditions	Weight decreased 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, amenorrhoea was observed in 3 patients (30 %).
MedDRA = Medical Dictionary for Regulatory Activities.
**Includes preferred terms: liver function test abnormal, blood bilirubin increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, alkaline phosphatase increased, liver hepatic enzyme increased.
*** Observed in patients during a post-approval study with 1215 safety evaluable patients.
****Individual cases have been reported in patients with medulloblastoma during post-marketing use (see section 4.4)
***** Cases of drug induced liver injury have been reported in patients during post-marketing use.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX43.

Mechanism of action
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 proliferation, survival, and differentiation. Vismodegib binds to and inhibits the SMO protein thereby blocking Hedgehog signal transduction.

Clinical efficacy and safety
The pivotal trial, ERIVANCE BCC (SHH4476g), was an international, single-arm, multi-centre, 2-cohort study. Metastatic BCC 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. 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 aBCC lesion and met inclusion criteria were eligible to participate in the study. Patients were treated with oral daily dosing of Erivedge at 150 mg.

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, 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 47.8 months).

The primary endpoint was objective response rate (ORR) as assessed by an independent review facility (IRF) as summarised in Table 2. 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 2:

Table 2 SHH4476g Erivedge Efficacy Results (IRF 21 months and Investigator assessed 39 months follow-up after last patient enrolled): efficacy-evaluable patients*,†

	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 %) (35.5 %, 60.6 %)	16 (48.5 %) (30.8%, 66.2 %)	38 (60.3 %) (47.2 %, 71.7 %)
Complete Response	0	14 (22.2 %)	0	20 (31.7 %)
Partial Response	11 (33.3 %)	16 (25.4 %)	16 (48.5 %)	18 (28.6 %)
Stable disease	20	22	14	15
Progressive disease ‡	1	8	2	6
Median Duration of Response (months) (95 % CI)	7.6 (5.5, 9.4)	9.5 (7.4, 21.4)	14.8 (5.6, 17.0)	26.2 (9.0, 37.6)
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, 28.0)
Median OS, (months) (95 % CI)			33.4 (18.1, NE)	NE (NE, NE)
1-year survival rate (95 % CI)			78.7 % (64.7, 92.7)	93.2 % (86.8, 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.

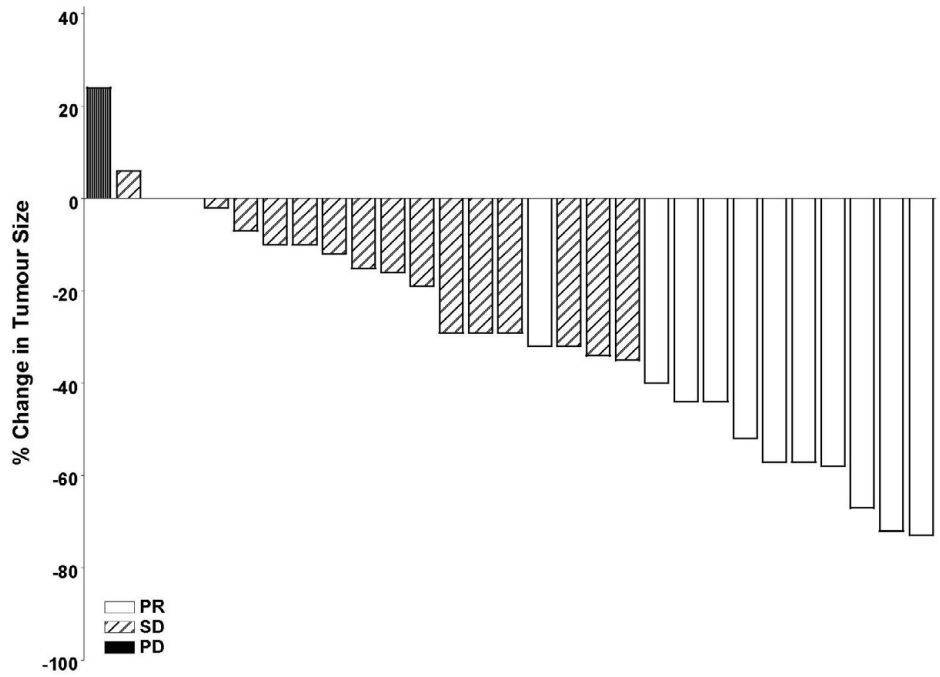
† Unevaluable/missing data included 1 mBCC and 4 laBCC patients.

‡ 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.

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

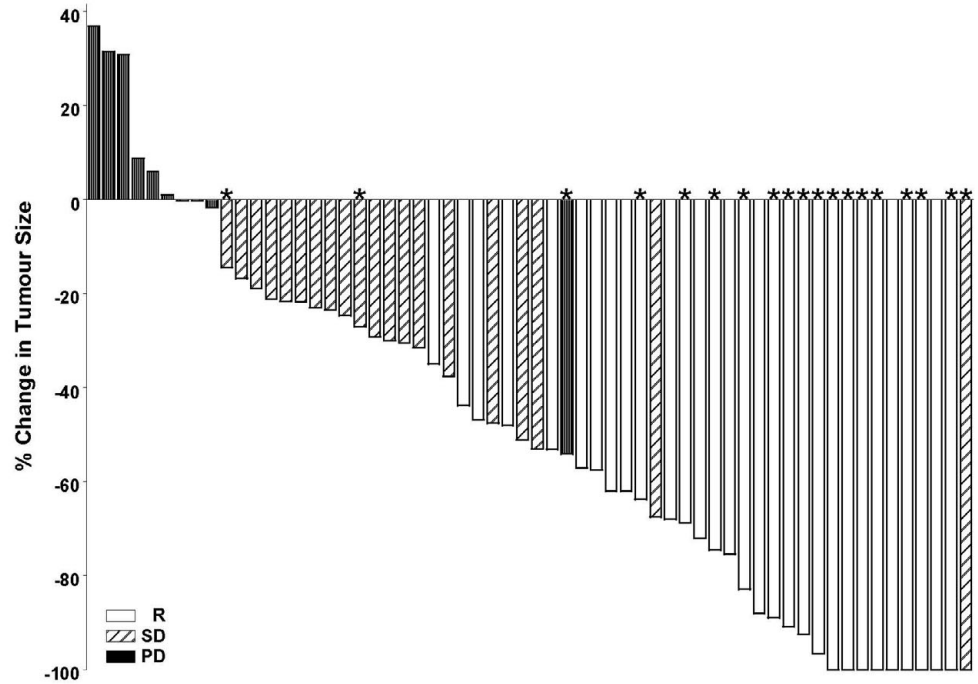
As shown in the waterfall plots in figures 1 and 2, which chart maximum reduction in target lesion(s) size for each patient, the majority of patients in both cohorts experienced tumour shrinkage as assessed by the IRF.

Figure 1 SHH4476g Metastatic BCC Cohort



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



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 thorough QTc study in 60 healthy subjects, there was no effect of therapeutic doses of Erivedge on the QTc interval.

Post approval study results
A post-approval, open-label, non-comparative, multicenter, phase II clinical trial (MO25616) was conducted in 1232 patients with advanced BCC, of whom 1215 patients were evaluable for efficacy and safety with laBCC (n = 1119) or mBCC (n = 96). LaBCC was defined as cutaneous lesions that were inappropriate for surgery (inoperable, or for whom surgery would result in substantial deformity) and for which radiotherapy was unsuccessful or contraindicated. Metastatic BCC was defined as histologically confirmed distant metastasis. Prior to study enrollment, diagnosis of BCC was confirmed by histology. Patients were treated with oral daily dosing of Erivedge at 150mg.
The median age for all patients was 72 years. The majority of patients were male (57%); 8% had mBCC whereas 92% had laBCC. For the metastatic cohort, the majority of patients had prior therapies, including surgery (91%), radiotherapy (62%) and systemic therapy (16%). For the locally advanced cohort, the majority of patients had prior therapies, including surgery (85%), radiotherapy (28%) and systemic therapy (7%). The median duration of treatment for all patients was 8.6 months (range 0 to 44.1).
Among patients in the efficacy-evaluable population with measurable and histologically confirmed disease, 68.5% and 36.9% responded to treatment in the laBCC and mBCC cohorts, respectively, by RECIST v1.1. Of patients who had a confirmed response (partial or complete), the median Duration of Response was 23.0 months (95% CI: 20.4, 26.7) in the laBCC cohort and 13.9 months (95% CI: 9.2, NE) in the mBCC cohort. Complete response was achieved in 4.8% patients in the mBCC cohort and 33.4% in the laBCC cohort. Partial response was achieved in 32.1% patients in the mBCC cohort and 35.1% in the laBCC cohort.

5.2 Pharmacokinetic properties

Absorption
Erivedge is a highly permeable compound with low aqueous solubility (BCS Class 2). The single dose mean (CV %) absolute bioavailability of Erivedge 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 Erivedge. Under clinically relevant conditions (steady state), the PK of vismodegib is not affected by food. Therefore, Erivedge may be taken without regard to meals.

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.

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. CYP2C9 appears to contribute in part to vismodegib metabolism *in vivo*.

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
Elderly
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.

Gender
Based on population pharmacokinetic analysis of combined data from 121 males and 104 females, gender did not appear to affect the pharmacokinetics of vismodegib.

Race
There are 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.

Renal impairment
Renal excretion of orally administered vismodegib is low. Therefore, mild and moderate renal impairment is unlikely to have a clinically significant effect on the pharmacokinetics of vismodegib. Based on a population PK analysis in patients with mild (BSA-indexed CrCl 50 to 80 mL/min, n=58) and moderate (BSA-indexed CrCl 30 to 50 mL/min, n=16) renal impairment, mild and moderate impaired renal function had no clinically significant effect on the pharmacokinetics of vismodegib (see section 4.2). Very limited data is available in patients with severe renal impairments.

Hepatic impairment
The major elimination pathways of vismodegib involve hepatic metabolism and biliary/intestinal secretion. In a clinical study in patients with hepatic impairment (degree of impairment based on subject's AST and total bilirubin levels) following multiple doses of vismodegib, it was shown that in patients with mild (NCI-ODWG criteria, n=8), moderate (NCI-ODWG criteria, n=6), and severe (NCI-ODWG criteria, n=3) hepatic impairment, the pharmacokinetic profile of vismodegib was comparable to that of subjects with normal hepatic function (n=9) (see section 4.2).

Paediatric population
There are insufficient pharmacokinetic data in paediatric patients.

5.3 Preclinical safety data

The preclinical safety profile of Erivedge was assessed in mice, rats, and dogs.

Repeat-dose toxicity
In general, the tolerability of Erivedge in repeat-dose toxicity studies in rats and dogs was limited by nonspecific manifestations of toxicity including decreased body weight gain and food consumption. Additional findings at clinically relevant exposures included faecal changes; skeletal muscle twitching

or tremors; alopecia; swelling, follicular hyperkeratosis, and inflammation in paw pads; and increased LDL and HDL cholesterol. Decreased haematocrit or platelet count were observed in some dogs at clinically relevant exposures; however, there was no evidence of a primary effect on bone marrow in affected animals.

Carcinogenicity
Carcinogenicity studies were performed in mice and rats. Carcinogenic potential was identified in rats only and was limited to benign hair follicle tumors, including pilomatricomas and keratoacanthomas respectively at ≥ 0.1-fold and ≥0.6-fold of the steady-state AUC(0-24h) of the recommended human dose. No malignant tumors were identified in either species tested. Benign hair follicle tumors have not been reported in clinical trials with Erivedge, and the relevance of this finding to humans is uncertain.

Mutagenicity
There was no evidence of genotoxicity in *in vitro* assays (reverse bacterial mutagenesis [Ames] and human lymphocyte chromosome aberration assays) or in the *in vivo* rat bone marrow micronucleus assay.

Fertility
In the dedicated 26-week vismodegib rat fertility study, significantly increased absolute weights of seminal vesicles and reduced absolute weights of prostate were observed. In addition, the ratio of organ weight to terminal body weight was significantly increased for epididymis, cauda epididymis, testes and seminal vesicles. In the same study there were no histopathological findings in male reproductive organs and no effects on male fertility endpoints, including percent motile sperm, observed at 100 mg/kg/day at the end of dosing or recovery phase (corresponding to 1.3-fold of the steady-state AUC0-24h at the recommended human dose). In addition, in the vismodegib general toxicity studies up to 26-week in sexually mature rats and dogs, no effects on male reproductive organs were observed. Increased number of degenerating germ cells and hypospermia in sexually immature dogs observed at ≥ 50 mg/kg/day in the 4-week general toxicity study was of undetermined relationship to vismodegib.

In the dedicated 26-week vismodegib rat fertility study, vismodegib-related effects on female reproductive organs were observed at 100 mg/kg/day immediately after treatment discontinuation, including decreased implantations, increased percent preimplantation loss, and decreased number of dams with viable embryos. Similar findings were not observed after a 16 week recovery period. No correlative histopathologic changes were observed. The exposure in female rats at 100 mg/kg corresponds to 1.2-fold of the steady-state AUC0-24h at the recommended human dose. In addition, in the vismodegib general 26-week toxicity study, decreased number of corpora lutea was observed at 100 mg/kg/day; the effect was not reversed by the end of an 8 week recovery period.

Teratogenicity
In an embryo-foetal development study in which pregnant rats were administered vismodegib daily during organogenesis, vismodegib crossed the placenta and was severely toxic to the conceptus. Malformations, including craniofacial anomalies, open perineum, and absent and/or fused digits, were observed in foetuses of dams at a dose which corresponded to 20 % of the typical steady-state exposure in patients, and a 100 % incidence of embryolethality was observed at higher doses.

Post-natal development
Dedicated studies to assess the potential of vismodegib to affect post-natal development have not been performed. However, irreversible defects in growing teeth and premature closure of the femoral epiphyseal plate, observed in rat toxicity studies at clinically relevant exposures, represent risks to post-natal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Microcrystalline cellulose PH101
Lactose monohydrate
Sodium starch glycolate
Povidone K29/32
Sodium lauril sulfate
Talc
Magnesium stearate (non-bovine)

Capsule shell
Iron oxide black (E172)
Iron oxide red (E172)
Titanium dioxide
Gelatine

Printing ink
Shellac glaze
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life after first openning: 12 months or expiry date which ever comes first

6.4 Special precautions for storage

Do not store above 30°C.
Keep the bottle tightly closed in order to protect from moisture

6.5 Nature and contents of container

HDPE bottle with a child-resistant closure containing 28 hard capsules. Each pack contains one bottle. The bottle cap material is Polypropylene. The cap liner is aluminum foil-lined waxed pulp board.

6.6 Special precautions for disposal

Any unused medicinal product at the end of treatment must immediately be disposed of by the patient in accordance with local requirements (if applicable, e.g. by returning the capsules to the pharmacist or physician).

7. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd., P.O. B. 6391, Hod Hasharon 4524079

8. MARKETING AUTHORISATION NUMBER(S)

149.22.33688.00

9. MANUFACTURER

F. Hoffmann-La Roche Ltd., Basel, Switzerland

Medicine: keep out of reach of children