ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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.

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

4.1 Therapeutic indication

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 (see section 5.1).

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 studies, 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 studies 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 (see section 5.2):

- 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

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 (see section 4.3).

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 heath 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.

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.

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).

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs) including cases of Stevens-Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening, have been reported during post-marketing use (see section 4.8). If the patient has developed any of these reactions with the use of vismodegib, treatment with vismodegib must not be restarted in this patient at any time.

Excipients
Erivedge capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total 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, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of concomitant medicinal products on vismodegib

Clinically significant pharmacokinetic (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 hours 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 studies 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 studies 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 studies 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 studies 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

MedDRA SOC	Very common	Common	Frequency not known
Endocrine disorders			precocious puberty****
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	Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP)******
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****
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.
******Cases of SCAR (including SJS/TEN, DRESS and AGEP) 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. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 studies.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents,
ATC code: L01XJ01

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.

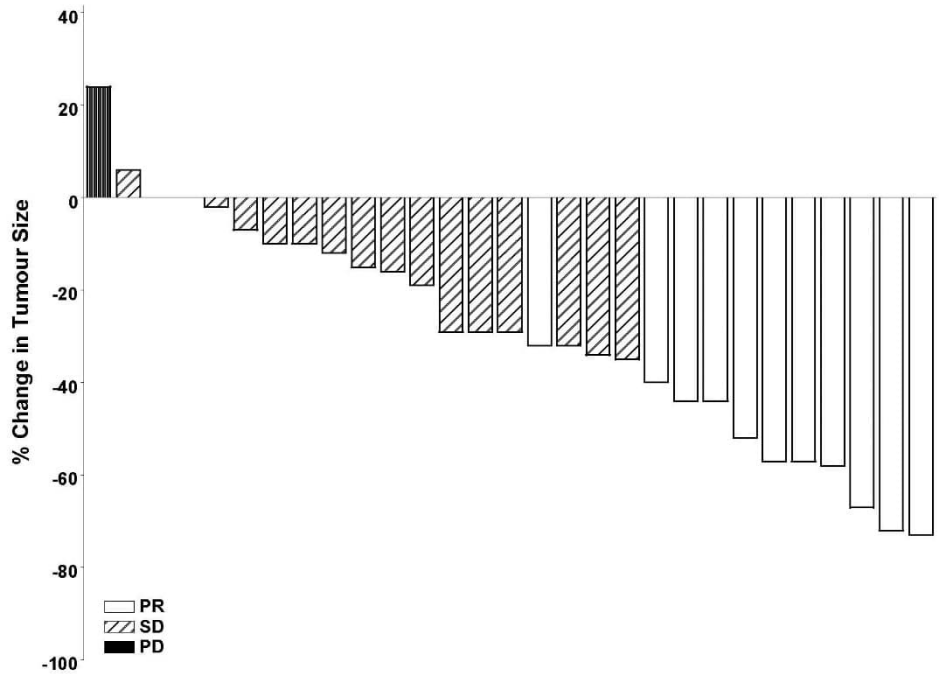
† Unevaluable/missing data included 1 mBCC and 4 laBCC patients.

‡ 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.

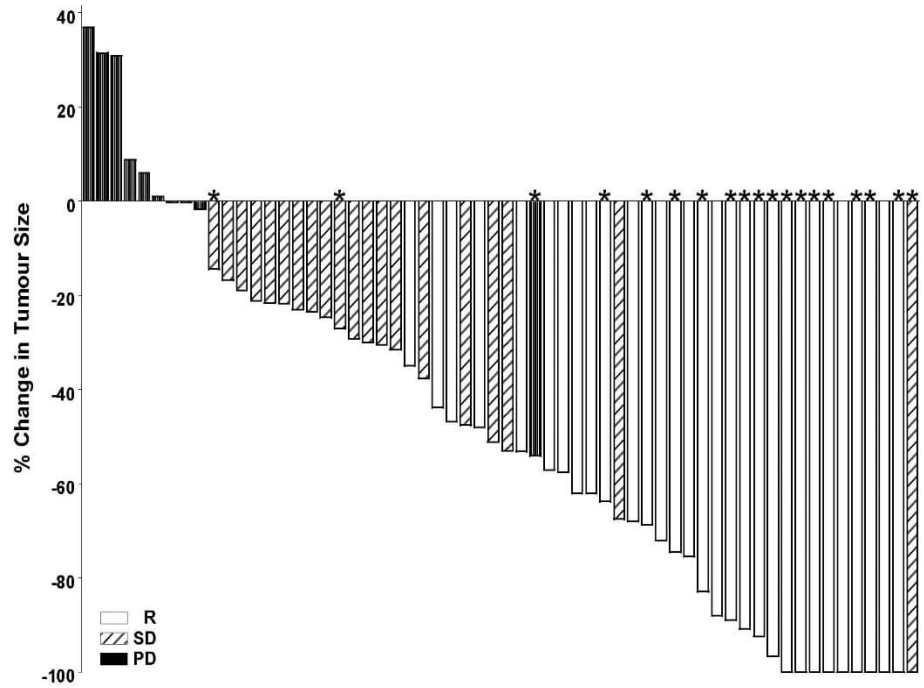
As shown in the waterfall plots in figures 1 and 2, which chart maximum reduction in target lesion(s) size for each patient, the majority of patients in both cohorts experienced tumour shrinkage as assessed by the IRF.

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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Erivedge in all subsets of the paediatric population with basal cell carcinoma (see section 4.2 for information on paediatric use).

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 studies 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
Lactose monohydrate
Sodium lauril sulfate
Povidone (K29/32)
Sodium starch glycolate (Type A)
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)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

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. The bottle cap material is polypropylene. The cap liner is aluminum foil-lined waxed pulp board.
Each pack contains one bottle.

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/848/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 July 2013
Date of latest renewal: 01 July 2021

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- Risk management plan (RMP)

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

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State, the Marketing Authorisation Holder (MAH) shall agree the following with the National Competent Authority:

- The national part of the DHPC
- Methodology to collect information on the use of Erivedge and the compliance with the pregnancy pharmacovigilance programme and its effectiveness
- The format and content of the Healthcare professional and patient material

The MAH shall distribute a Direct Healthcare Professional Communication letter at launch of the product, which should contain the following:

- A core text as agreed by the Rapporteur
- National specific requirements as agreed with the National Competent Authority regarding:
    - Distribution of the product
    - Measures to ensure that all appropriate actions have been performed prior to Erivedge being prescribed and dispensed

The MAH shall continuously ensure that all physicians who are expected to prescribe Erivedge are provided with the following:
Product information
Healthcare professional reminder card
Patient educational material i.e. Brochure
Patient Counselling Guideline

The healthcare professional's reminder card should contain the following key elements

- Obligations of the health care professional in relation to the prescribing of Erivedge
    - The need to provide comprehensive advice and counselling to patients
    - To ensure that patients are capable of complying with the requirements for the safe use of Erivedge
    - The need to provide patients with the patient educational material
- Information for women of childbearing potential
    - The need for monthly pregnancy tests even if the patient has amenorrhoea
    - The need for adequate contraceptive measures during treatment and for 24 months after Erivedge treatment
    - Not to breastfeed during treatment and for 24 months after Erivedge treatment
- Information for men
    - The need to use condoms when having sex with a female partner during treatment and for 2 months after Erivedge treatment
    - Not to donate semen during treatment and for 2 months after the final dose
- The need to tell patients to report immediately to the treating healthcare professional if pregnancy is suspected in a female patient, or in a female partner of a male patient
    - The healthcare professional should assess the pregnancy status, counsel the patient on teratogenicity risk and refer the patient to a specialised physician for counselling
    - The healthcare professional should report confirmed pregnancies to the MAH
- Remind patients to return unused capsules at the end of the treatment (disposal will depend on local requirements)
- Remind patients not to donate blood during treatment and for 24 months after the final dose

Patient Counselling Guideline

- The Patient Counselling Guideline can be used as guidance for physicians to inform and educate the patient about the teratogenic risks of Erivedge

The patient educational material i.e. Brochure for Erivedge should contain the following key elements

- Information for patients on the teratogenic risks associated with Erivedge and the need to avoid foetal exposure
- The need for adequate contraception and definition of adequate contraception
- National or other applicable specific arrangements for a prescription for Erivedge to be dispensed
- Not to give Erivedge to any other person
- Information on the disposal of unwanted medicinal product
- The need to keep Erivedge capsules out of sight and reach of children
- That the patient should not donate blood during treatment and for 24 months after their final dose
- That the patient should not breastfeed during treatment and for 24 months after their final dose
- That the patient should tell the healthcare professional about any adverse event
- Information for women of childbearing potential
    - Description of the pregnancy prevention programme
    - The need for adequate contraceptive measures during treatment and for 24 months after Erivedge treatment
    - Pregnancy test within a maximum of 7 days prior to treatment initiation, and monthly medically supervised pregnancy tests during treatment
    - The need to stop Erivedge immediately upon suspicion of pregnancy
    - The need for the patient to report a suspected pregnancy immediately to the treating healthcare professional
- Information for men
    - The need to use condoms (even if the man has had a vasectomy) if his sexual partner is pregnant or a women of childbearing potential during treatment and for 2 months after Erivedge treatment
    - That if his partner becomes pregnant he should inform the treating healthcare professional immediately
    - Not to donate semen during treatment and for 2 months after the final dose

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Erivedge 150 mg hard capsules
vismodegib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg of vismodegib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not crush, open or chew the capsule
Read the package leaflet before use
Oral use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Risk of severe birth defects
Do not use while pregnant or breast-feeding
You must follow the Erivedge Pregnancy Prevention Programme

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

Unused capsules should be returned at the end of treatment

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/848/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

erivedge

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Erivedge 150 mg hard capsules
vismodegib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 150 mg of vismodegib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not crush, open or chew the capsule
Read the package leaflet before use
Oral use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Risk of severe birth defects
Do not use while pregnant or breast-feeding
You must follow the Erivedge Pregnancy Prevention Programme

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

Unused capsules should be returned at the end of treatment

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
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Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/848/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Erivedge 150 mg hard capsules
vismodegib

Erivedge may cause severe birth defects. It may lead to the death of a baby before it is born or shortly after being born. You must not become pregnant while taking this medicine. You must follow the contraception advice described in this leaflet.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Erivedge is and what it is used for

What Erivedge is
Erivedge is an anti-cancer medicine that contains the active substance vismodegib.

What Erivedge is used for
Erivedge is used to treat adults with a type of skin cancer called advanced basal cell carcinoma. It is used when the cancer:

- has spread to other parts of the body (called “metastatic” basal cell carcinoma)
- has spread to areas nearby (called “locally advanced” basal cell carcinoma) and your doctor decides that treatment with surgery or radiation is inappropriate

How Erivedge works
Basal cell carcinoma develops when DNA in normal skin cells becomes damaged and the body cannot repair the damage. This damage can change how certain proteins in these cells work and the damaged cells become cancerous and begin to grow and divide. Erivedge is an anti-cancer medicine that works by controlling one of the key proteins involved in basal cell carcinoma. This may slow down or stop the growth of the cancer cells, or may kill them. As a result, your skin cancer may shrink.

2. What you need to know before you take Erivedge

Read the specific instructions given to you by your doctor, particularly on the effects of Erivedge on unborn babies.

Read carefully and follow the instructions of the patient brochure given to you by your doctor.

Do not take Erivedge

- if you are **allergic** to vismodegib or any of the other ingredients of this medicine (listed in section 6).
- if you are **pregnant**, think you may be pregnant, or are planning to become pregnant during the course of treatment or during the 24 months after your final dose of this medicine. This is because Erivedge may harm or cause the death of your unborn baby.
- if you are **breast-feeding** or plan to breast-feed during the course of treatment or during the 24 months after your final dose of this medicine. This is because it is unknown whether Erivedge can pass into your milk and cause harm to your baby.
- if you are able to become pregnant but are unable or unwilling to follow the necessary pregnancy prevention measures that are listed in the **Erivedge Pregnancy Prevention Programme**.
- if you are also taking St John's wort (*Hypericum perforatum*) – a herbal medicine used for depression (see "Other medicines and Erivedge").

More information on the issues above is found in the sections "Pregnancy", "Breast-feeding" and "Fertility" and "Contraception – for men and women".

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Erivedge.

Warnings and precautions
Talk to your doctor or pharmacist before taking Erivedge if you have questions on the information in this section:

- You should not donate blood at any time during treatment and for 24 months after your final dose of this medicine.
- If you are male, you should not donate semen at any time during treatment and for 2 months after the final dose.
- Serious skin reactions have been reported in association with Erivedge treatment. Stop using Erivedge and seek medical attention immediately if you notice any of the symptoms described in section 4.
- Never give this medicine to anyone else. You should return unused capsules at the end of your treatment. Talk to your doctor or pharmacist regarding where to return the capsules.

Children and adolescents
The use of Erivedge in children and adolescents under the age of 18 years is not recommended. This is because it is not known if it is safe or effective in this age group. Erivedge can cause bones to stop growing and lead to premature onset of puberty (before age 8 years in girls or age 9 years in boys). This can happen even after stopping Erivedge. Problems with growing teeth and bones were seen in animal studies with this medicine.

Other medicines and Erivedge
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This also includes non-prescription medicines, vitamins and herbal medicines.

Some medicines may affect how Erivedge works, or make it more likely that you will have side effects. Erivedge can also affect how some other medicines work.
In particular, tell your doctor if you take any of the following medicines:

- rifampicin – used for bacterial infections
- carbamazepine, phenytoin – used for epilepsy
- ezetimibe and statins , such as atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin – used for high cholesterol
- bosentan, glibenclamide, repaglinide, valsartan
- topotecan – used for certain types of cancer
- sulfasalazine – used for certain inflammatory disorders, and especially
- St. John's wort (*Hypericum perforatum*) – a herbal medicine used for depression, since you must not use it at the same time as Erivedge

Pregnancy
Do not take Erivedge if you are pregnant, think you may be pregnant, or are planning to become pregnant during the course of treatment or during the 24 months after your final dose of this medicine.

You must stop treatment and inform your doctor straight away if: you miss or think you have missed a period, or you have unusual menstrual bleeding, or suspect you are pregnant. If you do become pregnant during the treatment with Erivedge, you must stop the treatment and inform your doctor immediately.

Erivedge may cause severe birth defects. It may also lead to the death of the unborn baby. Specific instructions (the Erivedge Pregnancy Prevention Programme), given to you by your doctor contain information particularly on the effects of Erivedge on unborn babies.

Breast-feeding
Do not breast-feed during your treatment and for 24 months after your final dose of this medicine. It is not known if Erivedge can pass into your breast milk and harm your baby.

Fertility
Erivedge may affect a woman's ability to have children. Some women taking Erivedge have stopped having periods. If this happens to you, it is not known if your periods will come back. Talk to your doctor if you wish to have children in the future.

Contraception – for men and women
For **women** taking Erivedge
Before starting the treatment, ask your doctor if you are able to become pregnant. Even if your periods have stopped, it is essential to ask your doctor if there is any risk that you could become pregnant.

If you are able to become pregnant:

- you must take precautions so that you do not become pregnant while taking Erivedge
- use 2 methods of contraception, one highly effective method and one barrier method (please see the examples below)
- you need to continue contraception for 24 months after your final dose of this medicine – because Erivedge may remain in your body for up to 24 months after your final dose

Method of recommended contraception: Talk to your doctor about the best two contraception methods for you.

Use one highly effective method, such as:
- a contraceptive depot injection
- an intra-uterine device ("the coil" or IUD)
- surgical sterilisation

You must also use one barrier method, such as:
- a condom (with spermicide, if available)
- a diaphragm (with spermicide, if available)

Your doctor will make sure to test you for pregnancy:
- within a maximum of 7 days before starting treatment – to make sure that you are not already pregnant
- every month during treatment

You must tell your doctor immediately during the course of treatment or during the 24 months after your final dose of this medicine if:
- you think your contraception has failed for any reason
- your periods stop
- you stop using contraception
- you need to change contraception

For **men** taking Erivedge
Erivedge can pass into semen. Always use a condom (with spermicide, if available) even after a vasectomy, when you have sex with a female partner. Do this during treatment and for 2 months after your final dose of this medicine.

You should not donate semen at any time during treatment and for 2 months after your final dose of this medicine.

Driving and using machines
Erivedge is unlikely to affect your ability to drive, use any tools or machines. Talk to your doctor if you are not sure.

Erivedge contains lactose and sodium
Erivedge contains a type of sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium free'.

3. How to take Erivedge

Always take Erivedge exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Taking this medicine
The recommended dose is one capsule each day.
- Swallow the capsule whole with a drink of water.
- Do not crush, open or chew the capsule, to avoid unintended exposure to the capsule contents.
- Erivedge can be taken with or without food.

If you take more Erivedge than you should
If you take more Erivedge than you should, talk to your doctor.

If you forget to take Erivedge
Do not take a double dose to make up for a forgotten dose, but resume with the next scheduled dose.

If you stop taking Erivedge
Do not stop taking this medicine without talking to your doctor first as this could make your treatment less effective.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Erivedge may cause severe birth defects. It may also lead to the death of a baby before it is born or shortly after being born. You must not become pregnant while taking this medicine (see section 2, "Do not take Erivedge" and "Pregnancy", "Breast-feeding" and "Fertility").

Other side effects are presented in order of severity and frequency
If any of these side effects become severe, tell your doctor or pharmacist.

Very common (may affect more than 1 in 10 people):
- loss of monthly periods in women of childbearing age
- loss of appetite and weight loss
- feeling tired
- muscle spasm
- diarrhoea
- hair loss (alopecia)
- rash
- a change in the way things taste or the complete loss of taste
- constipation
- vomiting or feeling like you want to vomit (nausea)
- upset stomach or indigestion
- joint pain
- pain (in general) or pain in your arms, legs
- itchiness

Common (may affect up to 1 in 10 people):
- pain in your chest, back or side
- lack of energy or weakness (asthenia)
- loss of water from the body (dehydration)
- muscle, tendon, ligament, bone pain
- stomach pain
- loss of taste
- abnormal hair growth
- eyelashes falling out (madarosis)
- changes in blood tests, which include increased values in liver tests or increased values in creatine phosphokinase (a protein mainly from muscle)

Frequency not known
- Bones stop growing (epiphyses premature fusion)
- Premature puberty (precocious puberty)

- Liver injury
- Serious skin reactions:
    - reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. The skin reactions are often preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis)
    - widespread rash, fever, and enlarged lymph nodes (DRESS-syndrome or drug hypersensitivity syndrome)
    - red, scaly widespread rash with bumps under the skin and blisters accompanied by fever at the initiation of treatment (acute generalised exanthematous pustulosis)

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

5. How to store Erivedge

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which is stated on the bottle and carton after EXP. The expiry date refers to the last day of that month.
- Do not store above 30 °C.
- Keep the bottle tightly closed in order to protect from moisture.
- Do not throw away any medicines via wastewater or household waste.
- At the end of your treatment you should return all unused capsules. This will prevent misuse and help to protect the environment. Talk to your pharmacist or doctor regarding where to return the medicine.

6. Contents of the pack and other information

What Erivedge contains
- The active substance is vismodegib. Each hard capsule contains 150 mg of vismodegib.
- The other ingredients are:
    - Capsule contents: microcrystalline cellulose, lactose monohydrate, sodium lauril sulfate, povidone (K29/32), sodium starch glycolate (Type A), talc and magnesium stearate (see section 2 “Erivedge contains lactose and sodium”)
    - Capsule shell: iron oxide red (E172), iron oxide black (E172), titanium dioxide and gelatine
    - Printing ink: shellac glaze and iron oxide black (E172)

What Erivedge looks like and contents of the pack
The capsules have a pink opaque coloured body marked “150 mg” and a grey cap marked "VISMO” in black edible ink. They are available in bottles with a child-resistant closure containing 28 capsules. Each pack contains one bottle.

Marketing Authorisation Holder
Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
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Manufacturer
Roche Pharma AG
Emil-Barell-Strasse 1
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Germany

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

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This leaflet was last revised in

Other sources of information

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

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

As part of the Erivedge Pregnancy Prevention Programme, all patients will receive a Patient Brochure.

Please refer to this document for further information.