ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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

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 trials, treatment with Erivedge was continued until disease progression or until unacceptable toxicity. Treatment interruptions of up to 4 weeks were allowed based on individual tolerability.

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

Special populations

Older people
No dose adjustment is required in patients ≥ 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.

Patients with renal and hepatic impairment
The safety and efficacy of Erivedge have not been studied in patients with impaired renal and hepatic function (see section 5.2). No specific dose recommendations for these patient populations are available. Patients with severe renal impairment or moderate to severe hepatic impairment should be carefully monitored for adverse reactions.

Paediatric population
The safety and efficacy of Erivedge in children and adolescents aged below 18 years have not been established. No data are available.
Due to safety concerns (see sections 4.4 and 5.3), Erivedge 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 contained in semen. To avoid potential foetal exposure during pregnancy, a male patient must understand that:
- Erivedge exposes a teratogenic risk to the unborn child if he engages in unprotected sexual activity with a pregnant woman,
- He must always use the recommended contraception (see the 'Contraception' section below and 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 amenorrhea during treatment with Erivedge should continue monthly pregnancy testing while on treatment.

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

Educational material
In order to assist 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
In animal species, vismodegib has been shown to cause severe irreversible changes in growing teeth (degeneration/necrosis of odontoblasts, formation of fluid-filled cysts in the dental pulp, ossification of the root canal, and haemorrhage) and closure of the epiphyseal growth plate. These findings indicate a potential risk for short stature and tooth deformities to infants and children (see sections 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, primary hypolactasia 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
Medicinal products that alter the pH of the upper gastrointestinal (GI) tract (e.g., proton pump inhibitors, H_2-receptor antagonists, and antacids) may alter the solubility of vismodegib and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of gastric pH altering agents on the systemic exposure of vismodegib. Increasing the dose of vismodegib when co-administered with such agents is not likely to compensate for the loss of exposure. When vismodegib is co-administered with a proton pump inhibitor, H_2-receptor antagonist, or antacid, systemic exposure of vismodegib may be decreased, and the effect on efficacy of vismodegib is unknown. Patients with achlorhydria would be subject to the same potential effect.

In vitro studies indicate that vismodegib is a substrate of the efflux transporter P-glycoprotein (P-gp) and the drug metabolising enzymes CYP2C9 and CYP3A4. When vismodegib is co-administered with medicinal products that inhibit P-gp (e.g. clarithromycin, erythromycin, azithromycin, verapamil, cyclosporin), CYP2C9 (amiodarone, fluconazole or miconazole), or CYP3A4 (boceprevir,

clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole), systemic exposure of vismodegib and incidence of adverse events of vismodegib may be increased. 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.

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.

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 contained in semen. To avoid potential foetal exposure during pregnancy, male patients must always use a condom (with spermicide, if available), even after a vasectomy, when having sex with a female partner while taking Erivedge and for 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
Dedicated studies to assess the potential of Erivedge to affect fertility have not been performed. However, data from studies in rats and dogs indicate that male and female fertility may be irreversibly compromised by treatment with Erivedge (see section 5.3). Additionally, amenorrhea 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.

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 (65.2 %), dysgeusia (57.2 %), weight decreased (48.6 %), fatigue (44.9 %) and nausea (34.8 %).

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

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

MedDRA SOC	Very common	Common
Investigation		Hepatic enzymes increased**
Metabolism and nutrition disorders	Decreased appetite	Dehydration Hyponatremia
Nervous system disorder	Dysgeusia Ageusia	Hypogeusia
Gastrointestinal disorders	Nausea Diarrhoea Constipation Vomiting	Dyspepsia Upper abdominal pain Abdominal pain
Skin and subcutaneous tissue disorders	Alopecia Pruritus	Rash Madarosis Abnormal hair growth
Musculoskeletal and connective tissue disorders	Muscle spasms	Arthralgia Pain in extremity Back pain Musculoskeletal chest pain Myalgia Flank pain Musculoskeletal pain
Reproductive system and breast disorders	Amenorrhea*	
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, amenorrhea was observed in 3 patients (30 %).
MedDRA = Medical Dictionary for Regulatory Activities.
**Includes preferred terms: aspartate aminotransferase increased, alkaline phosphatase increased, liver hepatic enzyme increased.

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 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 36.6 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) $\geq$ 30 % reduction in lesion size [sum of the longest diameter (SLD)], from baseline in target lesions by radiography; (2) $\geq$ 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 (21 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 %) (30.5 %, 56.0 %)	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)	14.7 (5.5, NE)	20.3# (7.4, NE)
Median Progression Free survival (months) (95 % CI)	9.5 (7.4,11.1)	9.5 (7.4, 14.8)	9.3 (7.4, 16.6)	12.9 (10.2, NE)
Median OS, (months) (95 % CI)			30.9# (18.1, NE) #	NE (NE, NE)
1-year survival rate (95 % CI)			78.0 % (63.6, 92.4)	93.1 % (86.6, 99.6)

NE = not estimable

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

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

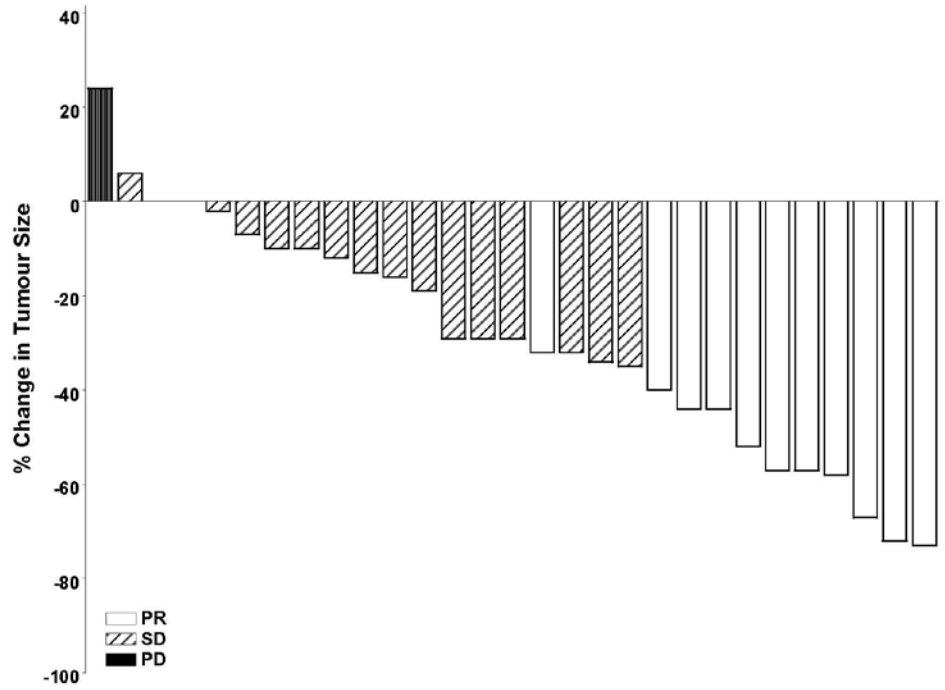
‡ Progression in laBCC cohort is defined as meeting any of the following criteria: (1) ≥ 20 % increase in the sum of the longest dimensions (SLD) from nadir in target lesions (either by radiography or by externally visible dimension), (2) New ulceration of target lesions persisting without evidence of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

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

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

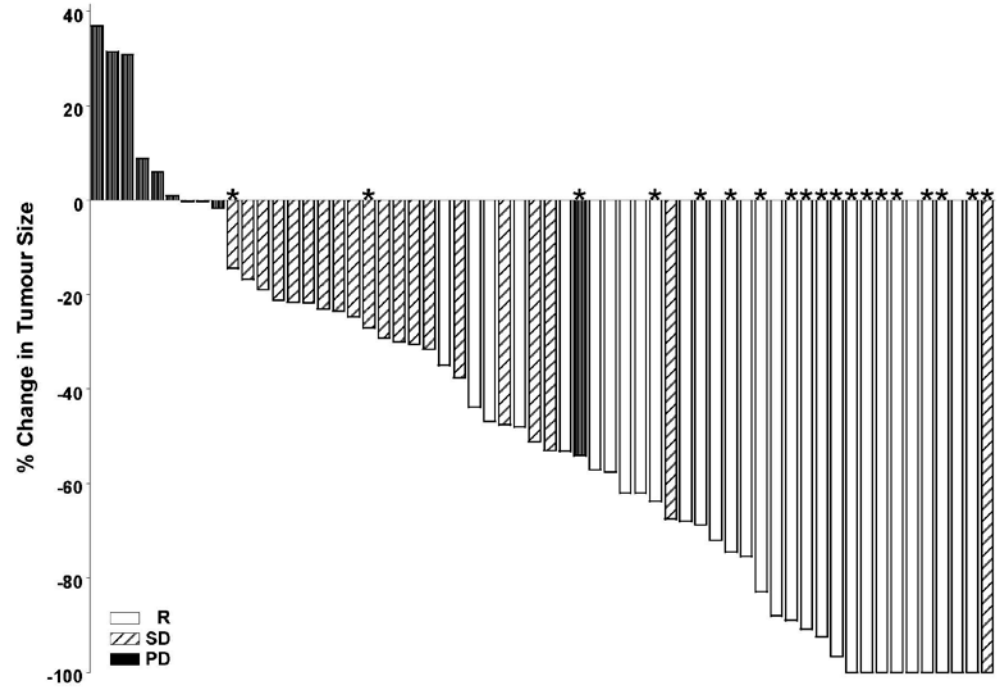
As shown in the waterfall plots in figures 1 and 2, which chart maximum reduction in target lesion(s) size for each patient, the majority of patients in both cohorts experienced tumour shrinkage as assessed by the IRF.

Figure 1 SHH4476g Metastatic BCC Cohort



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.

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).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

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. The two most abundant oxidative metabolites recovered in faeces are produced in vitro by recombinant CYP2C9 and CYP3A4/5. These enzymes may thus be major enzymes involved in the elimination.

Elimination
After oral administration of a radiolabelled dose, vismodegib is absorbed and slowly eliminated by a combination of metabolism and excretion of parent drug substance, the majority of which is recovered in the faeces (82 % of the administered dose), with 4.4 % of the administered dose recovered in urine. Vismodegib and associated metabolic products are eliminated primarily by the hepatic route.
After continuous once-daily dosing, the pharmacokinetics of vismodegib appears to be nonlinear due to saturable absorption and saturable protein binding. After a single oral dose, vismodegib has a terminal half-life of ca. 12 days.

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

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

Special populations

Older people

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

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.

Patients with renal impairment

There are currently insufficient data in patients with severe renal impairment. Therefore, an effect of severe renal impairment cannot be excluded. Based on population pharmacokinetic analysis of combined data from 5 clinical studies, renal function (creatinine clearance) did not appear to affect the pharmacokinetics of vismodegib (see section 4.2). Therefore**,** based on the low urinary excretion of vismodegib, an effect of mild to moderate renal impairment is not expected.

Patients with hepatic impairment

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

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

Dedicated nonclinical studies to evaluate the carcinogenicity of vismodegib have not been performed. However, pilomatricoma (a benign cutaneous neoplasm) was observed in the 26 week rat toxicity study. Pilomatricoma has not been reported in clinical trials with Erivedge, and the relevance of this finding to humans is therefore 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
Dedicated nonclinical studies to assess the potential of Erivedge to affect fertility have not been performed. However, data from studies in rats and dogs indicate that male and female fertility may be irreversibly compromised by treatment with Erivedge. Germ cell degeneration and hypospermia were observed in the 4 week dog toxicity study but not in longer-duration studies with older dogs. Decreased number of corpora lutea in the ovary and decreased mean percent motile sperm in the 26 week rat toxicity study were not demonstrated to be reversible by the end of the 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
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

2 years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

HDPE bottle with a child-resistant screw cap containing 28 hard capsules. 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 Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/848/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 educational material
Healthcare professional reminder card
Patient educational material
Patient reminder card

The healthcare professional educational material for Erivedge should contain the following key elements:

- Brief background on Erivedge, its licensed indication and posology
- A requirement to inform patients of the teratogenic risks associated with Erivedge and the need to avoid foetal exposure
- Description of the pregnancy prevention programme and categorisation of patients based on sex and childbearing potential
- Information on the recommended forms of contraception both for women and men
- 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 and patient reminder cards
- Safety advice for women of childbearing potential
    - The need for adequate contraceptive measures (even if the woman has amenorrhoea) during treatment and for 24 months after Erivedge treatment
    - Pregnancy test within 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
- Safety advice for men
    - The need to use condoms if his sexual partner is pregnant or a women of childbearing potential (even if the man has had a vasectomy) during treatment and for 2 months after Erivedge treatment
    - The need for the patient to report immediately to the treating healthcare professional if his partner becomes pregnant whilst he is taking Erivedge or shortly after he has stopped taking Erivedge
    - Not to donate semen during treatment and for 2 months after the final dose
- Requirements in the event of pregnancy
    - Instructions to stop Erivedge upon suspicion of pregnancy
    - The need to refer the patient to a specialist physician
    - Local contact details for reporting of any suspected pregnancy
    - Pregnancy reporting form
- Inform patients that they should not donate blood during treatment with Erivedge and for 24 months after their final dose
- Check list for healthcare professional ensuring that patients receive the appropriate counselling
- The need to ensure all patients complete and sign the Erivedge Verification of Counselling Form which is to be present in the healthcare professional educational material
- Adverse event reporting forms
- Information on the methodology, agreed with the National Competent Authority, to collect information on the use of Erivedge and the compliance with the pregnancy pharmacovigilance programme and its effectiveness.

The patient educational material 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
- Description of the patient reminder card
- 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 medication
- 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 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

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

- 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

The patient reminder card should contain the following key elements:

- Information for patients of the teratogenic risks associated with Erivedge and the need to avoid foetal exposure
- Not to donate blood during treatment and for 24 months after the final dose
- Information for women of childbearing potential
    - The need for monthly pregnancy tests
    - The need for adequate contraceptive measures
    - The need to contact the healthcare professional immediately if a pregnancy is suspected during treatment or in the 24 months following treatment

- Information for men
    - The need to use condoms when having sex with a female partner
    - Not to donate semen during treatment and for 2 months after the final dose
    - The need to contact the healthcare professional if the female partner suspects that she is pregnant while the patient is treated with Erivedge or in the 2 months following treatment
- To return unused capsules at the end of the treatment (disposal will depend on local requirements)
- Emergency contact phone numbers

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
The applicant should provide a safety update of the pooled safety population, a final SHH4476g (pivotal study) and an interims analysis of study MO25616 of 500 patients with a potential one year follow up.	June 2014
The applicant should provide further data on safety and data on efficacy in patients with symptomatic metastatic BCC from the final analysis of MO25616.	June 2015

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 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

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

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

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6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/848/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

erivedge

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 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

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

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

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EU/1/13/848/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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.

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 and 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 and reminder card 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.
- Your doctor will check your skin regularly for a type of cancer called "cutaneous squamous cell carcinoma' (SCC). It is not known if SCC is related to treatment with Erivedge. Usually this type of lesion appears on sun-damaged skin, remains local and can be cured. Tell your doctor in case you notice any changes in your skin.
- 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. 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 includes prescription and 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:

- ketoconazole (except in shampoo), fluconazole, itraconazole, miconazole, posaconazole, voriconazole – used for fungal infections,
- clarithromycin, telithromycin, rifampicin, erythromycin, azithromycin – used for bacterial infections,
- amiodarone, verapamil – used for certain heart disorders,
- cyclosporine – used in organ transplantation to prevent rejection,
- carbamazepine, phenytoin – used for epilepsy,
- indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, boceprevir – used for viral infections,
- atorvastatin, rosuvastatin, simvastatin – used for high cholesterol,
- 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, breast-feeding and fertility

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 your ability to have children, which applies to both men and women. 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:
- at least 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.

Important information about some of the ingredients of Erivedge

Erivedge capsules contain a type of sugar called lactose. If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.
Erivedge contains less than 1 mmol sodium (23 mg) per capsule, i.e. it is 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 sections "Do not take Erivedge" and "Pregnancy, breast-feeding and fertility").

Other side effects are presented in order of severity and frequency:

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),
- a change in the way things taste or the complete loss of taste,
- constipation,
- vomiting or feeling like you want to vomit (nausea),
- joint pain,

- itchiness.

Common (may affect up to 1 in 10 people):
- pain (in general) or pain in your arms, legs, chest, back or side,
- lack of energy or weakness (asthenia),
- loss of water from the body (dehydration),
- muscle, tendon, ligament, bone pain,
- stomach pain, upset stomach or indigestion,
- rash,
- loss of taste,
- abnormal hair growth,
- eyelashes falling out (madarosis)
- changes in blood tests, which include increased values in liver tests or decreased values in sodium.

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.
- 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, sodium starch glycolate (Type A).
- Capsule shell: iron oxide red (E172), iron oxide black (E172), titanium dioxide, 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 screw cap containing 28 capsules. Each pack contains one bottle.

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Welwyn Garden City
AL7 1TW
United Kingdom

Manufacturer
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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

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

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
- Patient Reminder Card

Please refer to these documents for further information.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION AND PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorization**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.