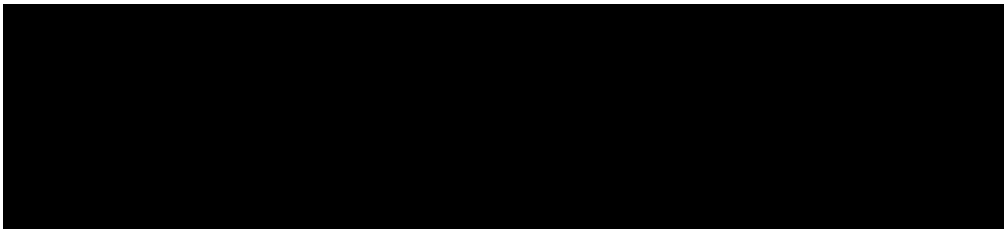
EU RISK MANAGEMENT PLAN FOR ERIVEDGE®/VISMODEGIB

RMP version to be assessed as part of this application:

RMP Version number: 14.1

Data lock point for this RMP: 31/1/2019

Date of final sign off: See latest date in date stamps below



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Rationale for submitting an updated Risk Management Plan (RMP): The Erivedge EU RMP Version 14.1 is updated in response to the variation assessment report issued by the Pharmacovigilance Risk Assessment Committee (PRAC) for procedure EMEA/H/C/002602/II/0046 requesting to provide additional information on the HCP reminder card. The EU RMP version 14.0 was submitted as part of the Type II variation.

Summary of significant changes in this RMP:

- Annex 6 is updated with the inclusion of information to the HCP reminder card, previously presented in the HCP Brochure.
- Annex 8 (Summary of changes to the risk management plan over time) is updated with summary of changes related to EU RMP version 14.1.

Other RMP versions under evaluation:

There are currently no other versions of the vismodegib EU RMP under evaluation by the EMA.

RMP Version number: None

Submitted on: None applicable

Procedure number: None applicable

Details of Currently Approved RMP:

RMP Version number: 13.0

Approved with procedure: EMEA/H/C/002602/II/0039

Date of approval (opinion date): 12 July 2018

See page 1 for signature and date

Dr. Birgitt Gellert (QPPV)/ [redacted]	Date

See page 1 for signature and date

[redacted]	Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance (INN or common name)	Vismodegib
Pharmacotherapeutic group (ATC Code)	L01XX43
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH.
Medicinal products to which this Risk Minimization Plan (RMP) refers	One
Invented name(s) in the European Economic Area (EEA)	Erivedge®
Marketing authorization procedure	Centrally authorized procedure
Brief description of the product including:	Chemical Class 2-chloro-N-(4-chloro-3-[pyridin-2-yl]-phenyl)-4-(methylsulfonyl) benzamide.
	Summary of mode of action Vismodegib is a low molecular weight, orally available inhibitor of the Hedgehog pathway. Vismodegib binds to and inhibits the Smoothened transmembrane protein thereby preventing Hedgehog signal transduction.
	Important information about its composition The 150-mg vismodegib drug product is a hard gelatin capsule formulation for oral administration. The capsule fill consists of vismodegib and the following excipients: microcrystalline cellulose PH101, lactose monohydrate, sodium lauryl sulfate, povidone K29/32, sodium starch glycolate, talc, magnesium stearate, and purified water. All of these excipients are compendial (USP/NF-EP) grade. The capsule shell consists of gelatin, red iron oxide, black iron oxide, and titanium dioxide.
Hyperlink to the Product Information	
Indication(s) in the EEA	Current: 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
	Proposed: Not applicable

Dosage in the EEA	Current: 150 mg per day
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Hard capsule. Each hard capsules contains 150 mg of vismodegib
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the EU?	No

EEA = European Economic Area; EU = European Union

ABBREVIATIONS

aBCC	advanced basal cell carcinoma
ADRs	adverse drug reactions
AUC	area under the curve
BCC	basal cell carcinoma
DLP	data lock point
EU	European Union
GATCF	Genentech Access to Care Foundation
HCP	healthcare provider
Hh	Hedgehog
laBCC	locally advanced basal cell carcinoma
MAH	Market Authorization Holder
mBCC	metastatic basal cell carcinoma
NCI	National Cancer Institute
NMSC	non-melanoma skin cancer
PBRER	Periodic Benefit-Risk Evaluation Report
PPP	Pregnancy Prevention Programme
PSUR	Periodic Safety Update Report
SCC	squamous cell carcinoma
SHH	Sonic hedgehog
SmPC	Summary of Product Characteristics
NCI CTCAE Definitions	
Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe
Grade 4	Life- threatening consequences
Grade 5	Death related to adverse event

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Data on incidence, prevalence, mortality, and comorbidities in the target population of advanced basal cell carcinoma (aBCC) were not available in the literature; therefore, information on surrogate populations was described instead, when available. These populations included:

- Other advanced or metastatic skin cancers (i.e., melanoma and squamous cell carcinoma [SCC])
- Metastatic SCC of the head and neck, and
- The general cancer patient population.

The metastatic skin cancer populations reflect the disease severity of the target aBCC population, especially the metastatic basal cell carcinoma (mBCC) patients, in contrast to the general population of patients with skin cancer (BCC, SCC or melanoma), which is primarily composed of patients with treatable early stage disease, who are expected to be healthier than patients with metastatic cancer.

Although there are some differences in treatment, prognosis, and risk factors, the majority of patients with aBCC who have inoperable disease tend to have tumors located in the head and neck region. For this reason, a population of patients with metastatic squamous cell head and neck cancer (although not limited to patients with cutaneous tumors) was also thought to be a relevant surrogate population.

In some cases below where data from the cancer populations described above were not available in the literature, data from the general population have been provided.

SI.1 Locally advanced basal cell carcinoma

- Incidence

No data are available for locally advanced basal cell carcinoma (laBCC).

Basal cell carcinoma is the most common malignancy worldwide, particularly among Caucasians. It is difficult to estimate the number of patients with BCC because cases typically have been designated as non-melanoma skin cancers (NMSCs), which include basal cell and squamous cell carcinomas, and these cases are not required to be reported to cancer registries. While the exact number of patients with BCC is difficult to obtain, estimates suggest an annual BCC incidence ranging from 88 to 239 per 100,000 persons in Europe. The estimated crude incidence rate for BCC per 100,000 persons is 239 in France (Bernard et al. 2008), 154 in the UK (Bath-Hextall et al. 2007), 148 in Spain (Revenga Arranz et al. 2004), 96 in Germany (Katalinic et al. 2003) and 88 in Italy (Boi et al. 2003). In the U.S., it was estimated that more than 2.1 million new patients

were treated for NMSC in 2006 (Rogers et al. 2010). Updated data revised the number to over 2.4 million (Rogers et al. 2015). Approximately 80% of NMSC is BCC.

- Prevalence

Not available

- Risk factors for the disease

The disease is caused largely by sun exposure, with people of fair complexion at highest risk. The lifetime risk for development of BCC in Caucasian Americans is 30% (Fantini et al. 2008). The risk of localized BCC is similar between men and women although more men than women have been reported in literature reviews and case series of metastatic BCC (von Domarus and Stevens 1984; Lo et al. 1991).

Patients who develop locally advanced disease may have received prior radiation or surgical treatments for BCC but have particularly aggressive BCCs that recur and progress despite standard treatment. Alternatively, some patients with locally advanced disease may have waited to seek medical treatment until their BCC had become significantly physically destructive.

- Natural history of the indicated condition in the (untreated) population:

  Morbidity:

Locally advanced BCC occurs in a small subset of patients with BCC when tumors enlarge and/or invade local subcutaneous structures, resulting in significant morbidity and disfigurement (Cohen et al. 2000; Kovarik et al. 2005).

- Important co-morbidities:

Main comorbidities in the laBCC population in study MO28682 (RONNIE) included hypertension (44.4%), cardiovascular disease (32.5%), and diabetes (9.4%) (n= 117) (John Lear et al, “Final Results of RONNIE, a Retrospective Chart Review to Describe Treatment Patterns and Outcomes in Advanced Basal Cell Carcinoma Before Availability of Hedgehog Pathway Inhibitors,” presented at EADO Congress, 7-10 May, 2014).

SI.2 Metastatic Basal Cell Carcinoma

- Incidence

Metastatic BCC is extremely rare, with a reported metastasis rate ranging from 0.0028% to 0.55%; however, most believe the true metastasis rate to be significantly less than 0.1% (Wadhera et al. 2006).

- Prevalence

Not available

- Demographics:

Metastatic disease typically occurs in middle-aged men with a history of recalcitrant BCC that has been refractory to conventional methods of treatment.

The male to female ratio of the incidence of BCC metastasis is 2:1 (Seo et al.2011; von Domarus and Stevens 1984).

Median age at onset of the primary BCC is about 45 years (~43.5 in men, 51 in women), while the median age at first sign of metastasis was 59 years (60 in men, 57.5 in women), (von Domarus and Stevens 1984). The median time from onset of BCC to diagnosis of metastatic disease is approximately 9 years (11 in men, 8 in women), although this interval ranged from 0 to 45 years (von Domarus and Stevens 1984).

- Risk factors for the disease

Risk factors for mBCC, and relevant to laBCC, include long-standing lesions, head and neck localization, size of primary tumor (>10 cm in diameter), depth of the tumor, resistance to radiation therapy, incomplete surgical resection, and aggressive histologic subtypes (Wadhera et al. 2006; Ozbek et al. 2004). Additional predictors of aggressive behavior include defects in cellular immunity, multiple lesions, recurrences, age at presentation, and infiltrative histologic pattern (Snow et al. 1994).

Risk factors for the development of metastasis are lack of treatment over many years, perineural invasion, size over 10 cm^2, and basosquamous and morphoeic subtypes (Samarasinghe et al. 2011).

- Natural history of the indicated condition in the (untreated) population:

  Mortality:

Historically, estimated median survival after diagnosis of mBCC is 8-14 months (Wysong et al. 2013; Raszewski and Guyuron 1990). However, recent reports found that patients treated at a tertiary cancer center, as well as patients with regional metastases or disease confined to regional lymph nodes have median overall survival in excess of 7 years (McCusker et al. 2014; Danial et al. 2013).

Discussion of the possible stages of disease progression to be treated:

Due to its rarity and lack of approved or effective treatments, there is little information in the published literature regarding metastatic disease. Recurrence of primary tumor after treatment accounts for 80% of metastatic basal cell carcinoma (mBCC) cases and 66% –85% of cases arise from primary lesions in the head and neck region, with the ear being the most common location (Snow et al. 1994). Higher rates of metastases also occur from primary lesions on the scalp and genitalia (Snow et al. 1994). In one study, the most commonly reported sites of metastasis were skeletal and pulmonary (Samarasinghe et al. 2011). Another study of sites of metastases reported the most common sites as: the regional lymph nodes (40%–83%); lung (35%–53%); bone (20%–28%); skin (10%–17%); and liver (9%) (Fantini et al. 2008).

- Important co-morbidities:

Important comorbidities in the relevant population metastatic melanoma (among patients ≥ 65 years at time of diagnosis) include diabetes (14.9%), chronic obstructive pulmonary disease (10.2%), congestive heart failure (8.2%), cerebrovascular disease (5.8%), diabetes with sequelae (4.0%), peripheral vascular disease (3.8%), rheumatologic disease (2.5%), and chronic renal failure (2.3%).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

1. TERATOGENICITY

Hedgehog (Hh) pathway inhibitors such as vismodegib have been demonstrated to be embryotoxic and/or teratogenic in multiple species and can cause major craniofacial malformations or other severe midline defects, limb defects, and other irreversible malformations in the developing fetus (Binns et al.1963; Binns et al.1965; Binns et al. 1972; Chiang et al.1996; Keeler 1990; Lipinski et al. 2008; Lipinski et al. 2010)

The embryotoxicity and teratogenicity of vismodegib were confirmed in an embryo–fetal development study in which pregnant rats were administered vismodegib daily during organogenesis. Malformations consistent with deficient Hh pathway signalling were observed in fetuses of dams administered a dose of 10 mg/kg/day, which corresponded to an area under the concentration–time curve ($AUC_{0\text{-}24hr}$) exposure approximately 20% of that observed at steady-state at the recommended human dose. The observed malformations included multiple craniofacial anomalies, open perineum (gap between genital and presumed location of anus), and absent and/or fused digits. The incidence of fetal retardations or variations (such as dilated renal pelvis or dilated ureter) and incompletely-ossified or unossified sternal elements, centra of cervical vertebrae, or proximal phalanges and claws, was increased at 10 mg/kg/day. Vismodegib was embryolethal when administered at 60 mg/kg/day, which corresponded to an $AUC_{0\text{-}24hr}$ exposure 2.8-fold that observed at steady-state at the recommended human dose.

Relevance to human usage: Yes

Discussion:
Vismodegib may cause embryo-fetal death or severe birth defects when administered to a pregnant woman. The conditions of the vismodegib Pregnancy Prevention Programme (PPP), including educational components and appropriate contraception measures, should be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Vismodegib is contraindicated in:

- Women who are pregnant or breastfeeding
- Women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme

Vismodegib is contained in semen. To avoid potential fetal exposure during pregnancy, a male patient must understand Erivedge exposure represents a teratogenic risk to the unborn child if he engages in unprotected sexual activity with a pregnant woman, and that he must always use a condom (with spermicide, where available), even after a vasectomy, when having sex with a female partner while taking Erivedge and for two months after the final dose. He will tell his healthcare provider (HCP) if his female partner becomes pregnant while he is taking Erivedge or during the two months after his final dose. Additionally a male patient should not donate semen during this time.

Roche operates a Pregnancy Prevention Programme that includes comprehensive education. The Erivedge Pregnancy Prevention Programme is described in Annex 6 of this document.

Teratogenicity is considered an important identified risk in humans (SVII3).

2. EFFECTS ON POST-NATAL DEVELOPMENT

Insufficient Hh pathway signaling has been associated with irreversible post-natal developmental defects, including irreversible effects on growing teeth and bones. Adverse effects on growing teeth, including degradation of dentin with scattered sequestrae, degeneration/necrosis of odontoblasts, formation of fluid-filled cysts in the dental pulp, ossification of the root canal, and hemorrhage were observed in repeat-dose rat toxicity studies with vismodegib at a dose ≥15 mg/kg/day (corresponding to an $AUC_{0\text{-}24h}$ exposure approximately 34% of that observed at steady-state at the recommended human dose). In the six-month rat toxicity study with vismodegib, closure of the epiphyseal growth plate was observed at a dose ≥ 50 mg/kg/day (corresponding to an $AUC_{0\text{-}24h}$ exposure approximately 58% of that observed in patients at steady-state). The effects on bone and tooth development were not reversible and have the potential to result in permanent defects in bone and tooth development.

The effects of vismodegib on teeth and growth plates are consistent with previously published literature describing an essential role of Hh pathway signaling in the development and maintenance of these tissues in mice (Kimura et al. 2008; Gritli-Linde et al. 2002).

Relevance to human usage: Yes

Discussion:
Vismodegib may adversely affect the development and maintenance of teeth, bones, or growth plates in a pediatric patient population either directly via vismodegib treatment or as a result of lactational exposure to vismodegib.

Nonclinical experimental data indicate that oral Hh pathway inhibitors pose a substantial risk of developmental defects. 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.

The safety and efficacy of Erivedge in children and adolescents aged below 18 years have not been established. Premature fusion of the epiphyses and precocious puberty have been reported in patients exposed to Erivedge. Due to the long drug elimination half-life, fusion of the epiphyses may occur or progress after drug discontinuation. Due to safety concerns, Erivedge should not be used in children and adolescents aged below 18 years.

3. CARCINOGENICITY

In the 26-week rat toxicity study (GLP Study 07-1224), pilomatricoma (a benign cutaneous neoplasm) was observed during recovery period in 2 rats administered vismodegib for six months at the highest dose tested (100 mg/kg), which corresponded to 1.1-fold of the estimated steady-state exposure ($AUC_{0\text{-}24h}$) at the recommended human dose.

In a 26-week carcinogenicity study in RasH2 transgenic mice (GLP Study 13-0322), vismodegib administration at doses up to 100 mg/kg/day had no carcinogenic effects.

In a 2-year rat carcinogenicity study (GLP Study 13-0323), vismodegib was administered daily at 3, 10, or 30 mg/kg/day for at least 88 weeks, or for 52 weeks in the recovery groups. Vismodegib-related carcinogenic effects were limited to benign hair follicle tumors, including keratoacanthomas in recovery males administered 30 mg/kg/day (0.6-fold of the steady-state exposure AUC_{0-24h} of the recommended human dose) and pilomatricomas at the end of dosing and in recovery males administered ≥ 3 mg/kg/day (≥ 0.1-fold of the steady-state exposure AUC_{0-24h} of the recommended human dose).

Relevance to human usage: Uncertain

Discussion:
Benign hair follicle tumors have not been reported in clinical trials with vismodegib, and the relevance of this finding in rats to humans is uncertain.

4. IMPAIRMENT OF 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 $AUC_{0\text{-}24h}$ 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. However, in sexually immature dogs, increased number of degenerating germ cells and hypospermia observed at $\geq$ 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 (GLP Study 12-2793), 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 $AUC_{0\text{-}24h}$ at the recommended human dose. In addition, in the vismodegib general 26-week rat 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.

Relevance to human usage: Yes

Discussion:
Fertility impairment in human males is not expected. Human female fertility may be compromised by treatment with vismodegib. Reversibility of fertility impairment is unknown. Additionally, amenorrhea has been observed in clinical trials in women of childbearing potential. Fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment with vismodegib.

5. NEUROLOGICAL EFFECTS

Neurologic effects characterized as twitching and limb or body tremors were observed in repeat-dose rat studies with vismodegib. These effects completely resolved upon discontinuation of dosing and were not associated with histologic findings. It was not

determined if these effects were centrally or peripherally mediated; however, in a rat whole-body autoradiography study the penetration of vismodegib into central nervous system tissues was low. No similar clinical signs were observed in dogs treated daily with vismodegib for up to six months.

Relevance to human usage: Yes

Discussion:
It is possible that twitching and limb or body tremors that were observed in rats are related to the muscle spasms and musculoskeletal pain that were reported by patients in clinical trials with vismodegib, and that were described in the prescribing information.

6. EFFECTS OF VISMODEGIB ON CONCOMITANT MEDICINAL PRODUCTS

A nonclinical Study12-1797 was to investigate the ability of vismodegib to inhibit human uptake transporters OATP1B1 and OATP1B3 and to determine if vismodegib is a substrate of these transporters, which would affect the metabolism of co-administered drugs.

The accumulation of the test article was measured in HEK293 cells expressing OATP1B1, OATP1B3 and control cells. Vismodegib was evaluated as an inhibitor of OATP1B1 and OATP1B3 by measuring the effect of vismodegib on the accumulation of a probe substrate ([3H]-estradiol-17β- glucuronide) in transporter-expressing and control HEK293 cells. Known inhibitors were included as positive controls in all experiments. Vismodegib inhibited OATP1B1 with an IC50 of 2.01 μM and inhibited OATP1B3 with an IC50 of 14.8 μM. Vismodegib was not actively taken up into OATP1B1 or OATP1B3 cells to a greater extent than it was taken up into control cells.

While vismodegib was not a substrate of OATP1B1 or OATP1B3, there was some evidence of inhibition of both transporters. However, the IC50 associated with this in vitro effect was at least 10-fold greater than the typical unbound concentration of vismodegib in patients.

Relevance to human usage: Yes

Discussion:
OATP1B1 and OATP1B3 are expressed on the sinusoidal membrane of hepatocytes and facilitate the uptake of endogenous and xenobiotic compounds into hepatocytes.

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, glibenclamide, repaglinide, valsartan and statins). In particular, caution should be exercised if vismodegib is administered in combination with any statin.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE
EXPOSURE IN ROCHE-SPONSORED STUDIES CONDUCTED IN THE ADVANCED BASAL CELL CARCINOMA POPULATION

As of the submission of the initial Marketing Authorization Application, the clinical efficacy and safety of vismodegib in the treatment of aBCC had been evaluated in the pivotal clinical trial SHH4476g. Overall, a total of 138 aBCC patients from the studies SHH4476g (n = 104, 75.4%), SHH3925g (n = 33, 23.9%; 12 of 33 patients subsequently enrolled in SHH4437g), and SHH4610g (n = 1, 0.7%; the patients subsequently enrolled in SHH4437g) were pooled (unless otherwise indicated) to provide a more complete characterization of the safety profile in vismodegib-treated aBCC patients. Data from patients who received at least one dose of study drug in these four company-sponsored clinical studies formed the basis for the use of vismodegib in the treatment of advanced BCC patients and will be referred to in the rest of this document as the pooled safety population.

Studies of relevance to the use of vismodegib in BCC also include the global safety Study MO25616 (STEVIE) and the U.S. Expanded Access Study, SHH4811g. Study MO25616 is a Phase II open-label, single-arm, multicenter study (conducted in Europe, Canada, South-America and Asia-Pacific) of vismodegib in patients with locally advanced or metastatic BCC who are otherwise without satisfactory treatment options.

Detailed exposure data reported in this RMP are derived from the pooled safety population, MO25616, and SHH4811g. Exposure data for clinical pharmacology studies are provided only in terms of number of patients exposed.

The clinical safety data presented in the RMP are from the pooled safety population and MO25616. Both populations include a larger number of patients followed for a longer period of time and are therefore more representative of the patient experience for adverse events.

EXPOSURE TO VISMODEGIB IN POOLED SAFETY POPULATION

Exposure in the pooled safety population (SHH 4476g, SHH 3925, SHH4610g and the extension study, SHH4437g) is described in Table 2– Table 7 and have been updated to the data lock point (DLP) of 30 May 2013.

Although patients with several different types of solid tumors were enrolled into SHH3925g, SHH4610g, and SHH4437g, only those patients with aBCC are referenced in the tables below.

Table 7 reports clinical trial exposure to vismodegib in the pooled aBCC safety population. In the pooled safety population, the median duration on study treatment was 12.7 months (range: 0.7 – 65.9 months). The median cumulative dose of vismodegib received by patients in the aBCC pooled safety population was 60.9 g.

Table 2 Duration of Exposure to Vismodegib as Monotherapy

Vismodegib exposure in patients with aBCC Exposed for:	Patients n (%) (n=138)	Person-Years
≥ 1 month	137 (99.3)	201.54
≥ 3 months	125 (90.6)	199.58
≥ 6 months	112 (81.2)	194.67
≥ 12 months	72 (52.2)	165.02
≥ 24 months	37 (26.8)	115.22
≥ 36 months	19 (13.8)	70.87
≥ 48 months	3 (2.2)	15.41
Total	**138 (100)**	**201.60**

aBCC = advanced basal cell carcinoma

Studies included SHH3925g, SHH4437g, SHH4476g and SHH4610g.

Source: Biostatistics([redacted]) pgm(/onco/shh/hpi_iss/final_30m/programs/t_rmp_table1_durexp)

Database (OPEN) Datasets (adsl)

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Table 3 Exposure to Vismodegib as a Monotherapy by Dose

Vismodegib daily exposure in patients with aBCC (mg) (Daily Dose)	Pooled Safety Population n=138 (%)	Person-Years
150	122 (88.4)	172.32
270	15 (10.9)	29.17
540	1 (0.7)	0.11
Total	**138 (100)**	**201.60**

aBCC = advanced basal cell carcinoma

Studies included SHH3925g, SHH4476g and SHH4610g.

The expected dose level is reported

Person−years is the total number of years from first to last administration of vismodegib, including treatment in SHH4437G for patients who crossed over.

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Table 4 Exposure to Vismodegib as Monotherapy by Age Group and Gender

Age Group (years)*	Patients n (%)		Person-Years	
	Male (n=89)	Female (n=49)	Male (n=89)	Female (n=49)
<75	75 (84.3)	40 (81.6)	122.08	57.53
>=75	14 (15.7)	9 (18.4)	12.94	9.04
<65	55 (61.8)	29 (59.2)	97.49	45.39
>=65	34 (38.2)	20 (40.8)	37.53	21.18
Total	**89 (100.0)**	**49 (100.0)**	**135.02**	**66.57**

Studies included SHH3925g, SHH4437g, SHH4476g and SHH4610g.

* Age at enrollment

Person−years is the total number of years from first to last administration of vismodegib, including treatment in SHH4437G for patients who crossed over.

Source: Biostatistics([redacted]) pgm(/onco/shh/hpi_iss/final_30m/programs/t_rmp_table5_ageandsex)

Database (OPEN) Datasets (adsl)

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Table 5 Exposure to Vismodegib as a Monotherapy by Ethnic or Racial Origin

Race	Patients n (%)	Person-Years
White	138 (100.0)	201.60

Source: Marketing Application: Vismodegib-F. Hoffmann-La Roche Limited Safety Update for Pooled Population (Advanced Basal Cell Carcinoma): 5-3-5-3

Table 6 Exposure to Vismodegib as a Monotherapy by Baseline Disease Stage

Vismodegib Exposure in Patients with aBCC [1]	Patients n (%)	Person-Years
Gorlin Patient	26 (18.8)	61.01
non-Gorlin Patient	112 (81.2)	140.59
Total	**138 (100)**	**201.60**

[1] Based on medical history.

aBCC = advanced basal cell carcinoma

Studies included SHH3925g, SHH4476g, SHH4437G and SHH4610g. Person−years is the total number of years from first to last administration of vismodegib.

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Database (OPEN) Datasets (adsl)

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Table 7 Pooled Safety Population: Exposure to Vismodegib

	All aBCC Patients (n = 138)
Total cumulative dose (g)	
N	138
Mean (SD)	81.8 (73.5)
Median	60.9
Range	2.9–463.6
Months on study treatment	
N	138
Mean (SD)	17.5 (14.0)
Median	12.7
Range	0.7–65.9
Number of non-missing vismodegib doses [a]	
N	138
Mean (SD)	503.3 (403.8)
Median	369.0
Range	19.0–1970.0
Dose intensity (%) [b]	
N	138
Mean (SD)	94.9 (14.5)
Median	97.4
Range	58.5–234.9 [c]

aBCC = advanced basal cell carcinoma; SD = standard deviation.

[a] Total number of doses received by a patient.

[b] Dose intensity is defined as total dose taken divided by the expected total dose.

[c] For Patient [redacted] (Study SHH4610g/SHH4437g), the dose intensity was calculated as 234.9% due to data entry error.

Source: Marketing Application: Vismodegib-F. Hoffmann-La Roche Limited Safety Update for Pooled Population (Advanced Basal Cell Carcinoma): 5-3-5-3

Exposure to Vismodegib in Study MO25616 (STEVIE)

Of the total 1232 patients enrolled in Study MO25616, 17 were excluded from the safety and efficacy analysis populations because they had no documented exposure based on return of drug dispensed. Exposure in Study MO25616 is described in Table 8 to Table 13 (data cutoff date 14 June 2017).

Table 8 Duration of Exposure to Vismodegib as Monotherapy

Vismodegib exposure	Safety Population (N=1215) n (%)	Person-Years
≥ 1 month	1165 (95.9)	1094.00
≥ 3 months	1019 (83.9)	1069.00
≥ 6 months	801 (65.9)	986.15
≥ 12 months	427 (35.1)	714.77
≥ 24 months	99 (8.1)	234.56
≥ 36 months	11 (0.9)	35.68

Person-years is the total number of years from first to last administration of vismodegib.

Patients with less than 1 month exposure to vismodegib are not included.

Program: /opt/BIOSTAT/prod/cdpt3616/mo25616/t_ex_dur_bymon.sas

Output: /opt/BIOSTAT/prod/cdpt3616/i25616f/reports/t_ex_dur_bymon_SE.out

21AUG2015 20:32

Source: Primary Clinical Study Report MO25616

Table 9 Exposure to Vismodegib as a Monotherapy by Dose

Vismodegib daily exposure (mg)	Safety Population (N=1215) n (%)	Person-Years
150	1215 (100.0)	1096.96
Total	**1215 (100.0)**	**1096.96**

Person-years is the total number of years from first to last administration of vismodegib.

Program: /opt/BIOSTAT/prod/cdpt3616/mo25616/t_ex_bydose.sas /

Output: /opt/BIOSTAT/prod/cdpt3616/i25616f/reports/t_ex_bydose_SE.out

21AUG2015 20:33

Source: Primary Clinical Study Report MO25616

Table 10 Exposure to Vismodegib as Monotherapy by Age Group and Gender

Age Group (years)*	Patients n (%)		Person-Years	
	Male (n=694)	Female (n=521)	Male (n=694)	Female (n=521)
<75	414 (59.7)	262 (50.3)	451.81	269.52
>=75	280 (40.3)	259 (49.7)	192.10	184.52
<65	252 (36.3)	173 (33.2)	291.54	190.41
>=65	442 (63.7)	348 (66.9)	352.38	262.63

* Age at enrollment.

Person−years is the total number of years from first to last administration of vismodegib.

Program: /opt/BIOSTAT/prod/cdpt3616/mo25616/t_ex_byage_bysex.sas

Output: /opt/BIOSTAT/prod/cdpt3616/i25616f/reports/t_ex_byage_bysex_SE.out 21AUG2015 20:33

Source: Primary Clinical Study Report MO25616

Table 11 Exposure to Vismodegib as a Monotherapy by Ethnic or Racial Origin

Race	Safety Population (N=1215) n (%)	Person-Years
White	879 (72.3)	815.36
Not Applicable[1]	317 (26.1)	258.65
Other	15 (1.2)	19.19
Black or African American	2 (0.2)	2.63
Asian	1 (0.1)	0.08

[1] Race data for patients in France are not collected.

Person-years is the total number of years from first to last administration of vismodegib.

n = the number of patients with collected race information. Patients with missing race information not included.

Program: /opt/BIOSTAT/prod/cdpt3616/mo25616/t_ex_byrace.sas /

Output: /opt/BIOSTAT/prod/cdpt3616/i25616f/reports/t_ex_byrace_SE.out

21AUG2015 20:33

Source: Primary Clinical Study Report MO25616

Table 12 Exposure to Vismodegib as a Monotherapy by Baseline Disease Stage

Disease Status		Safety Population (N=1215) n (%)	Patient-years
Locally Advanced (n=1113)	Gorlin Syndrome	214 (17.6)	256.79
	non-Gorlin Syndrome	899 (74.0)	742.44
Metastatic (n=96)	Gorlin Syndrome	5 (0.4)	5.92
	non-Gorlin Syndrome	91 (7.5)	86.04

laBCC = Locally advanced basal cell cancer; mBCC = Metastatic basal cell cancer.

Person-years is the total number of years from first to last administration of vismodegib.

n = the number of patients with collected Gorlin Syndrome

Program: /opt/BIOSTAT/prod/cdpt3616/mo25616/t_ex_bygorlin.sas

Output: /opt/BIOSTAT/prod/cdpt3616/i25616f/reports/t_ex_bygorlin_SE.out

21AUG2015 20:34

Source: Primary Clinical Study Report MO25616

Table 13 Study MO25616 – Summary of Exposure to Vismodegib

	Total (n = 1215)
Total cumulative dose (mg)	
N	1215
Mean (SD)	53114.0 (50325.3)
Median	36750.0
Range	372 – 272400
Duration on treatment (days) [a]	
N	1215
Mean (SD)	379.7 (357.4)
Median	263.0
Range	2 – 1932
Dose intensity (%) [b]	
N	1215
Mean (SD)	93.83 (8.46)
Median	97.71
Range	38.4 - 100.0

SD = standard deviation

[a] Duration on treatment is calculated as (Date of last dose - Date of first dose) + 1.

[b] Dose intensity is calculated as (Total number of doses received / Total doses expected) * 100. Total doses expected is equal to a patients duration from cycle 1 day 1 up to the end of treatment visit as patients are expected to take one capsule of Vismodegib per day.

Program: /opt/BIOSTAT/prod/cdpt3616/mo25616/t_ex.sas /

Output:/opt/BIOSTAT/prod/cdpt3616/i25616l/reports/t_ex_SE.out

23AUG2017 12:52

Source: Final Clinical Study Report MO25616; Report Number 1081025

Exposure to Vismodegib in United States Expanded Access Study SHH4811g

SHH4811g was an open-label, non-comparative, multicenter, expanded access study of vismodegib in patients with laBCC or mBCC who were otherwise without satisfactory treatment options in the U.S.

Enrolled patients received once-daily oral vismodegib at a dosage of 150 mg per administration. One cycle of therapy is defined as 28 days of treatment. All patients received study drug until investigator-assessed disease progression, unmanageable toxicities most probably attributable to vismodegib, patient request for discontinuation, or study termination by Roche. Dose reduction of vismodegib was not permitted, as there was only a 150-mg capsule strength available. Temporary discontinuation of drug for up to 8 weeks was allowed. Temporary discontinuation longer than 8 weeks was allowed following discussion with the medical monitor.

A total of 121 patients were enrolled. The final number receiving at least one dose of study medication was 120 at 11 study sites in the U.S. over about two years. This study was completed on 23 April 2012; therefore, the data included in this document for this study have a data cutoff date of 9 August 2012.

Table 14 presents the exposure data in SHH4811g (database lock 9 August 2012), in which 119 patients were treated, with a median dose intensity of 98.2% and a median duration of treatment of 5.5 months.

Table 14 United States Expanded Access Study SHH4811g: Exposure to Vismodegib

	All Subjects (N = 119)	Locally Advanced (N = 62)	Metastatic (N = 57)
Total number of vismodegib capsules taken in all cycles			
Mean (SD)	200.1 (136.1)	207.0 (134.0)	192.7 (139.2)
Median (min – max)	162.0 (13 – 585)	164.5 (32 – 553)	162.0 (13 – 585)
Total vismodegib dose received (mg) [1]			
Mean (SD)	30,020.2 (20,419.2)	31,047.6 (20,096.8)	28,902.6 (20,884.9)
Median (min – max)	24,300.0 (1950 – 87,750)	24,675.0 (4800 – 82,950)	24,300.0 (1950 – 87,750)
Dose Intensity (%) [2]			
Mean (SD)	95.7 (8.3)	94.9 (9.6)	96.6 (6.6)
Median (min – max)	98.2 (55 – 117)	98.2 (55 – 110)	98.8 (65 – 117)
Number of Treatment Cycles Received, n			
Mean (SD)	7.2 (4.9)	7.5 (4.8)	6.9 (5.0)
Median (min – max)	6.0 (1 – 21)	6.0 (1 – 21)	6.0 (1 – 21)
Treatment Duration (months)[3]			
Mean (SD)	6.9 (4.6)	7.2 (4.6)	6.6 (4.7)
Median (min – max)	5.5 (0.4 – 19.6)	5.6 (1.1 – 19.6)	5.4 (0.4 – 19.3)

	All Subjects (N = 119)	Locally Advanced (N = 62)	Metastatic (N = 57)
Average Vismodegib Dose Received per Cycle (mg/cycle)[4]			
Mean (SD)	4135.8 (365.6)	4088.8 (322.5)	4186.9 (404.1)
Median	4178.6 (1950 – 4800)	4125.0 (2875 – 4800)	4200.0 (1950 – 4800)

SD = standard deviation.

Receiving a partial dose of a cycle (any number of capsules > 0) was counted as a full cycle.

[1] Total number of capsules taken summed across all cycles multiplied by 150 mg.

[2] Dose intensity = (total dose actually received divided by total dose should have been taken on study) multiplied by 100%.

[3] Treatment duration (months) = (date of last vismodegib dose – date of first vismodegib dose + 1) / 30.4375.

[4] Average vismodegib dose received (mg/cycle) = cumulative dose of vismodegib received divided by the number of treatment cycles received, rounded to the nearest 10th of a decimal point.

Receiving partial dose of a cycle is counted as a cycle.

Source: CSR SHH4811g 12 February 2013 (Study period 28 July 2010 to 23 April 2012)

Exposure to vismodegib in the clinical pharmacology studies

A summary of exposure to vismodegib in the pharmacology studies is presented in Table 15.

Table 15 Exposure to vismodegib in the clinical pharmacology studies

	Single-dose	Multiple-dose
Healthy subjects (n=179)		
SHH4433g (n=3)	3	0
SHH4683g (n=23)[1]	12	12
SHH4871g (n=61)[2]	0	21
GP28465 (n=92)	0	92
Cancer patients (n=319)		
SHH3925g (n=68)	0	68
SHH4610g (n=63)	0	63
SHH4318 (n=1)	0	1
SHH4476g (n=104)	0	104
SHH4593 (n=52)	0	52
GP27839 (n=31)[3]	0	31

[1] Study SHH4683g: PK-evaluable subjects included 23 subjects with one subject participating in both single-dose and multiple-dose treatments.

[2] Study SHH4871g included 61 healthy women of nonchildbearing potential, of which 21 were exposed to vismodegib and 40 were on moxifloxacin/placebo.

[3] Study GP27839 included 22 patients with various degrees of hepatic impairment and 9 patients in a control cohort with normal renal and normal hepatic function.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 16 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Pregnant Women	Vismodegib has been identified as a teratogen in nonclinical studies. Vismodegib can cause severe birth defects or death to an unborn fetus/embryo if taken during pregnancy.	No	Teratogenicity is an important identified risk for vismodegib. Vismodegib must not be used during pregnancy
Lactating women	The excretion of vismodegib in milk has not been studied in animals. It is possible that vismodegib may adversely affect the development and maintenance of teeth, bones, or growth plates in a pediatric patient population.	No	Vismodegib is contraindicated in breast-feeding women.
Women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme	Vismodegib has been identified as a teratogen in nonclinical studies. Vismodegib can cause severe birth defects or death to an unborn fetus/embryo if taken during pregnancy.	No	Vismodegib is contraindicated in women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme
Coadministration of St John's wort (Hypericum perforatum)	St John's wort (Hypericum perforatum), a herbal medicine used for depression, may decrease vismodegib concentration if taken concurrently.	No	Vismodegib is contraindicated in patients taking St John's wort concomitantly
Hypersensitivity to the active substance or to any of the excipients	Patients with hypersensitivity to the active substance or to any of the excipients cannot receive treatment.	No	Vismodegib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients
Male patients who would not comply with pregnancy prevention	Vismodegib has been identified as a teratogen in nonclinical studies. Vismodegib is present in semen. There is data to indicate its presence in semen and a	No	Instruction of pregnancy prevention has been included in the SmPC. In addition, a pregnancy prevention

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
measures	theoretical risk of transvaginal absorption that may have adverse effects in a developing fetus/embryo.		programme has been implemented which includes an educational program for men that focuses on the use of condoms and prevention of exposure of women partners of male patients.
Children and adolescents < 18 years	Vismodegib may adversely affect the development and maintenance of teeth and bones in a pediatric patient population either directly via vismodegib treatment or as a result of lactational exposure to vismodegib.	No	The use of Vismodegib in children and adolescents under the age of 18 years is not recommended.

SmPC = Summary of product characteristics

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 17 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
Patients with hepatic impairment	22 patients with various degrees of hepatic impairment were exposed to vismodegib in Study GP27839 (total person years: 1.86).
Patients with renal impairment	Not included in the clinical development program
Patients with cardiac impairment	Patients with cardiac impairment were not excluded from clinical trials. However, an analysis of exposure for a population with specific cardiac function abnormalities is not possible as the necessary data were not collected.
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program
Sub Populations with Genetic Polymorphism (Gorlin Syndrome)	Studies SHH3925g , SHH4476g and SHH4437g: • 26 patients (61.01 Person-Years) Study MO25616: • 219 patients (262.71 Person-Years)
Other	
Elderly	Of the total of 2356 patients who have been exposed to vismodegib in interventional clinical trials sponsored by Roche as of 29 July 2015, approximately 50% of patients were ≥ 65 years old.
Children	Study SHH4318g: One pediatric patient with refractory medulloblastoma.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 METHOD USED TO CALCULATE EXPOSURE

The number of patients exposed to Erivedge was estimated based on the volume of capsules sold and the estimated total amount taken per patient. The volume sold by Roche is sourced from Roche supply chain and financial systems (COntrolling Profitability Analysis [COPA]). The sales data are provided on a monthly basis; therefore, the exposure is available from the IBD to the nearest point of DLP (i.e., 31 January 2019).

The estimated total amount taken per patient is the product of the defined daily dose (DDD) and the estimated treatment duration. The recommended daily dose for the approved label aBCC is one 150-mg capsule per day. The label for aBCC covers both the laBCC and mBCC populations. Vismodegib is approved only in this indication and available only in the mentioned formulation and dose.

The average net treatment duration for the approved indication is 5.5 months in the US and 7 months in the RoW which is based on market research in the U.S. and EU5 (France, Germany, Italy, Spain and the United Kingdom). Adjustment factors for compliance (90%) and treatment persistence (85%) were applied. The patient exposure estimate was further adjusted for the additional 18% of patients who are receiving Erivedge through the Genentech Access to Care Foundation (GATCF) in the U.S.

No information is available about the gender and age of the patient populations.

SV.1.2 Exposure

Since the IBD, an estimated cumulative total of 37,715 patients have received Erivedge 150 mg capsule from marketing experience (Table 18).

Table 18 Cumulative Exposure from Marketing Experience as of 31 January 2019

Region	Estimated no. of patients exposed
European Economic Area	8,697
United States	24,792
Rest of World	4,225
Total	**37,715**

Note: Rounding errors may be introduced in the total figure

This output includes Genentech Access to Care Foundation patients.

Post-authorization use in populations not studied in clinical trials

As of 31 January 2019, there are 13 pregnancy cases recorded in the Roche Global Safety Database. These included seven paternal exposure cases (with one corresponding child case) and six cases of maternal exposure from non-interventional program (NIP)/ non-interventional studies (NIS) sources (N=7), followed by spontaneous reports (N=5) and a clinical study (N=1) (Study MO28295).

For the seven paternal exposure cases, the outcomes were reported as:

- normal birth outcome in two cases,
- lost to follow up in two cases,
- miscarriage and abortion in one case each where fetal birth defects were not reported.
- In the remaining case (with a corresponding child case), the father stopped vismodegib 8 months prior to conception, which is in alignment with the recommendation provided in the EU SmPC advising to use of condoms for 2 months after final dose. The child was born with epidermolysis bullosa.

Of the six maternal exposure cases, five cases were lost to follow-up. In the remaining case, the female patient was pregnant before starting therapy with vismodegib. The treatment with vismodegib was discontinued and she delivered a normal baby.

Considering the current estimated total exposure of 40,095 patients to vismodegib (market and clinical trial experience), there have been a total of 13 pregnancy cases reported. In three of them, normal newborns were delivered and there were no teratogenic effects reported in any of the remaining cases. These figures underline that the risk of teratogenicity associated with Erivedge is adequately mitigated by the risk minimization measures currently in place.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The risk of abuse or misuse of vismodegib based on its pharmacological properties is low.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Not applicable.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns have been identified since this module of the RMP was last submitted.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Information on important identified risks

Teratogenicity

MedDRA terms:

MedDRA SMQs:

Congenital, familial and genetic disorders, Fetal disorders, Neonatal disorders, and Termination of pregnancy and risk of abortion

Preferred terms (PTs):

Pregnancy, pregnancy of partner, pregnancy test positive, drug exposure during pregnancy, blood human chorionic gonadotropin positive.

Potential mechanisms:

Hh pathway signaling is an important developmental pathway that regulates embryonic patterning in many structures such as neural crest, brain, skeleton, and limbs. Inhibition of the Hh pathway by vismodegib is anticipated to interfere with this essential patterning function and may cause fetal malformations or death of the conceptus.

Evidence source(s) and strength of evidence:

Nonclinical study results and literature.

Characterization of the risk:

Frequency:

Incidence in BCC patients: Data are not available

Incidence in the general population: In the general population the incidence of major congenital malformations is approximately 3% of all births and the incidence of minor malformations may be as high as 9% (depending on the definition of minor malformations), (Gwyn 2005; Kalter and Warkany 1983a; Kalter and Warkany 1983b). Examples of incidence rates (per 100,000 live births) for specific types of congenital anomalies reported in the U.S. in 2008 were 13.8 for anencephaly, 14.9 for

meningomyelocele or spina bifida, and 45.5 for cyanotic congenital heart disease (Osterman et al. 2008).

Incidence in cancer patients receiving chemotherapy: In a review of the literature on pregnancy and cancer, Doll et al. 1989 reported that the incidence of fetal malformations with first trimester chemotherapy exposure with a variety of agents ranged from 14%-19%. However, exposure in the second and third trimester was associated with an incidence of fetal malformations of 1.3% (Doll et al. 1989; Gwyn 2005). Similar findings were reported by Cardonick et al. (2004) in their review of 376 fetuses exposed to chemotherapy in utero, the majority of which were exposed after organogenesis. Nine of the 11 reported malformations occurred in patients receiving chemotherapy in the first trimester (Cardonick and Iacobucci 2004).

Prevalence: Not available

Severity*:*

Mice deficient in Sonic hedgehog (SHH) expression exhibited reduced growth and severe craniofacial defects (Chiang et al. 1996), and severe defects in bone growth occurred in Indian hedgehog (IHH)-deficient mice (St-Jacques et al 1999). Treatment or exposure of animals of many species (including rats, mice, lambs, chicks, and others) with small-molecule inhibitors of the Hh signaling pathway resulted in similar phenotypes.

Vismodegib can cause severe birth defects or death of an unborn baby if taken during pregnancy. Hh pathway inhibitors such as vismodegib can cause severe craniofacial defects, missing digits, and other irreversible malformations in the developing fetus.

Pregnant rats were administered vismodegib daily during organogenesis. Malformations consistent with deficient Hh pathway signalling were observed in 21 of 70 fetuses of five pregnant dams administered a dose of 10 mg/kg/day.

Observed malformations among this group included multiple craniofacial anomalies (1/70), open perineum (1/70), and absent and/or fused digits (16/70 fetuses). Additionally, the incidence of fetal retardations, or variations such as dilated renal pelvis or dilated ureter, and incompletely- or un-ossified sternal elements, centra of cervical vertebrae, or proximal phalanges and claws was increased at 10 mg/kg/day.

Vismodegib was embryolethal when administered at 60 mg/kg/day or 300 mg/kg/day (100% post-implantation loss).

Evidence in literature is conclusive as to the teratogenicity of Hh pathway inhibitors in the offspring of treated animals (Binns et al. 1963; Binns et al. 1965; Chiang et al. 1996; Keeler 1990; Lipinski et al. 2008; Lipinski et al. 2010). A rat embryo-fetal development study demonstrated malformations consistent with deficient Hh pathway signalling in

fetuses of dams administered a dose of 10 mg/kg/day, which corresponded to an AUC0-24hr exposure approximately 20% of that observed at steady-state at the recommended human dose. Vismodegib was embryolethal when administered at 60 mg/kg/day, which corresponded to an AUC0-24hr exposure 2.8-fold that observed at steady-state at the recommended human dose. [GLP Study 3036R09: RO5450815-000: Dose-Range Finding Study with Oral Administration for Effects on Embryo-Fetal Development in the Rat].

Risk factors and risk groups:
The 'at risk' group for experiencing vismodegib-related teratogenicity comprises female patients of child-bearing potential or female partners of male patients treated with vismodegib.

Risk factor in cancer patients receiving chemotherapy:
Treatment with chemotherapy in the first trimester, during organogenesis, substantially increases the risk of fetal malformation compared to exposure to chemotherapy in the second and third trimesters of pregnancy (Gwyn 2005).

Preventability:
To avoid risk of fetal exposure, vismodegib is contraindicated in women who are pregnant and in women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme. In addition, male patients must always use a condom (with spermicide, where available) when having sex with a female partner while taking Erivedge and for 2 months after the final dose. Additionally, male patients should not donate semen during this time.

If pregnancy does occur during treatment, a patient should consult with a physician immediately.

Impact on the benefit-risk balance of the product:

The impact of teratogenic effects was anticipated to result in embryo-fetal death or congenital defects of high impact in terms of morbidity and quality of life. To address this risk, the EU SmPC details the risk of teratogenicity in the sections contraindications, warnings and precautions sections, including specific measures for women of child bearing potential exposed to vismodegib.

Additionally, pregnancy pharmacovigilance plan as routine PV measure was put in place to ensure that there is a consistent global approach for capturing all relevant pregnancy-related information, the same principles for obtaining initial and follow-up data on pregnancies are also part of the routine PV measure. Regular monitoring of implementation of vismodegib Pregnancy Prevention Programme (PPP) on a country-specific basis in accordance with the local legal framework has been performed as an

additional pharmacovigilance activity assessing the effectiveness of the additional risk minimization measure.

Three EU HCP surveys of PPP have been conducted in the UK, Germany, France, Austria and Hungary in 2015, 2016, and 2018, respectively. The results have shown a very high awareness of the risk of teratogenicity and a very high degree of implementation of risk minimization measures that have improved over time. The awareness about existence of the PPP is high as well.

Ongoing program and results are presented in Periodic Benefit Risk Evaluation Reports/Periodic Safety Update Reports (PBRERs/PSURs). The fact that very few pregnancy cases have been reported (13/ 40,095 [current estimated total exposure of vismodegib]) and so far no human cases of teratogenicity have been reported in offsprings of patients/ partners of patients exposed to vismodegib points towards the effectiveness of the pregnancy prevention programme.

In conclusion, the risk of teratogenicity associated with Erivedge is considered adequately mitigated by the risk minimization measures currently in place. The surveys have demonstrated consistently high knowledge regarding the risk of teratogenicity and related risk minimization actions over three years.

Public health impact:
With the Erivedge PPP being in place and with understanding typical population treated with Erivedge, being normally elderly patients, the impact on public health is considered to be very low. The Erivedge PPP aims to prevent the exposure to vismodegib of a child in utero.

Information on important potential risks

Not applicable.

SVII.3.2. Presentation of the Missing Information

Information on Missing information:

Not applicable

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 19 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Teratogenicity
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for the important identified risk of Teratogenicity:

- Roche Standard Pregnancy Follow-up Process

It is managed internally by the Roche Drug Safety organization through the company's Global Safety Database. To ensure that there is a consistent global approach for capturing all relevant pregnancy-related information, the same principles for obtaining initial and follow-up data on pregnancies will be utilized globally. Roche will follow up extensively on pregnancies that occur in patients or in the female partners of male patients who have been exposed to vismodegib, until the outcome of the pregnancy is known.

The objectives of the routine pregnancy follow-up are to:

- Collect vismodegib pregnancy reports according to Roche standard procedure.
- Determine timing of vismodegib exposure for each reported pregnancy
- Collect outcome of pregnancy including fetal outcome
- Obtain pregnancy documentation to assist in the evaluation and Root Cause Analysis of each pregnancy
- Detect any changes of the benefit/risk profile
- Provide pregnancy data to worldwide Regulatory Authorities where the product is marketed or investigated as per local regulations and guidelines
- Pregnancy Reports:

Reports of pregnancies may be received from the following sources:

- Directly or indirectly from Regulatory Authorities
- Contracted clinical research organizations (CROs)
- Ongoing local and global clinical trials
- Directly from patients, female partners of male patients, pharmacists, and healthcare providers (HCPs)
- Internal review of publications in the literature
- All Roche employees and contractors who may become aware of a pregnancy report, as mandated by company policy.

Descriptive statistics (for e.g. subject's age, duration of vismodegib treatment, and weeks of gestational age at exposure) will be the primary approach for summarizing data from the reported pregnancies. Data on gender, indication for vismodegib use, concomitant medication, type of delivery, pregnancy outcome, obstetric history, adverse events during pregnancy, fetal outcome, infant status, and genetic abnormalities will be summarized with descriptive statistics for categorical data as appropriate. Separate analyses will be provided for maternal and paternal pregnancy case and new child case.

The Root Cause Analysis of all pregnancy cases will be presented in the annual PBRER/PSUR document.

A status report of pregnancies in patients exposed to vismodegib or in female partners of male patients exposed to vismodegib will be provided in each PBRER/PSUR. Each PBRER/PSUR will include a comprehensive analysis of case reports including the reason for the occurrence of pregnancy.

Other forms of routine pharmacovigilance activities for the important identified risk of Teratogenicity:

- Expedited reporting of all pregnancies as a serious event.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no planned or ongoing additional pharmacovigilance activities with Erivedge.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no planned or ongoing additional pharmacovigilance activities with Erivedge.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing post-authorization imposed efficacy studies with Erivedge that are conditions of the marketing authorization or that are specific obligations.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 20 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Teratogenicity	**Routine risk communication**: Text in SmPC: • Section 4.3 (Contraindications) • Section 4.4 (Special warnings and precautions for use) • Section 4.6 (Fertility, pregnancy and lactation) **Routine risk minimization activities recommending specific clinical measures to address the risk**: • Women of childbearing potential (WCBP) must have a negative pregnancy test prior to initiating treatment and during treatment is included in SmPC section 4.4 • Women of childbearing potential must use two methods of recommended contraception during Erivedge therapy and after the final dose is included in SmPC section 4.4 and 4.6 • Contraception recommendation for men while taking Erivedge and for 2 months after the final dose is included in SmPC section 4.4 and 4.6 **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Erivedge is subject to restricted medical prescription

SmPC = Summary of Product Characteristics; WCBP= woman of childbearing potential

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

Table 21 Additional Risk Minimization Measures for Teratogenicity

Additional Risk Minimisation Measure	**Erivedge Pregnancy Prevention Programme**: I. For Health Care Providers • Health Care Provider Reminder Card • Patient Counselling Guideline II. For Patients • Patient Brochure
Objectives	**Prevent Erivedge exposure in pregnant women** • Inform patients and HCPs of the teratogenic risks to the fetus that are associated with vismodegib use • Communicate the requirement for pregnancy testing and contraception • Provide guidelines for prescription of Erivedge • Assist the physician to counsel and educate the patient regarding the teratogenic risk
Rationale for the additional risk minimization activity	The Erivedge PPP is designed to minimize the risk of teratogenicity outcomes in offspring through pregnancy prevention and provides education on the risk of teratogenicity and the recommended contraceptive measures to prevent fetal exposure.
Target audience and planned distribution path	**Communication Plan** Objective and justification of why needed The following steps will be taken to communicate information on the Erivedge PPP, and instructions to access materials will be provided to both HCPs and patients. Proposed actions/components and rationale • Distribution of a Dear HCP letter to relevant HCP specialties for country specific launch. • Distribution of the Erivedge PPP educational materials including HCP Reminder Card • Distribution of patient education material: Patient Information Leaflet and Patient Educational Brochure • The educational materials are translated into local language and may be reviewed by the National/Local Competent Authority prior to use in each Member State, based on applicable legislation. Materials may be customized for each Member State based upon their Erivedge PPP implementation requirements, and program assessment methods. The key messages will remain consistent throughout the EU.

Table 21 Additional Risk Minimization Measures for Teratogenicity (cont.)

Plans for evaluating the effectiveness of the interventions and criteria for success	Primary Indicator: Pregnancy Exposures • Reports of pregnancy exposure to be reviewed on an ongoing basis and summarized at the time of the PBRER/PSUR • Overall, by country and by indication also in relation to the overall patient exposure • Root causes for pregnancy exposure as per Roche Standard Pregnancy Follow-up Process • Compliance with specific elements of Erivedge Pregnancy Prevention Programme as reflected in Roche Standard Pregnancy Follow-up Process Outcome of pregnancy • Management of the event by the HCP

EU = European Union; HCPs = Health care providers; NCA = National Competent Authority; PBRER/PSUR = Periodic benefit Risk Evaluation Report/ Periodic Safety Update Report; PPP = Pregnancy Prevention Programme

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 22 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Teratogenicity	**Routine risk minimization measures**: • SmPC section 4.3 Contraindications • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk**: • Women of childbearing potential must have a negative pregnancy test prior to initiating treatment and during treatment is included in SmPC section 4.4 • Women of childbearing potential must use two methods of recommended contraception during Erivedge therapy and after the final dose is included in SmPC section 4.4 • Contraception recommendation for men while taking Erivedge and after the final dose is included in SmPC section 4.4 **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Erivedge is subject to restricted medical prescription **Additional risk minimization measures**: Erivedge Pregnancy Prevention Programme I. For Health Care Providers • Health Care Provider Reminder Card • Patient Counselling Guideline II. For Patients • Patient Brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: • Routine Pregnancy Follow-up Process **Additional pharmacovigilance activities**: None

PBRER/PSUR = Periodic benefit Risk Evaluation Report/ Periodic Safety Update Report; SmPC = Summary of Product Characteristics

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ERIVEDGE (VISMODEGIB)

This is a summary of the risk management plan (RMP) for Erivedge. The RMP details important risks of Erivedge, how these risks can be minimized, and how more information will be obtained about Erivedge risks and uncertainties (missing information).

Erivedge summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Erivedge should be used.

This summary of the RMP for Erivedge should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Erivedge RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Erivedge is authorized for metastatic breast cancer and locally advanced basal cell carcinoma mBCC and laBCC (see SmPC for the full indication). It contains vismodegib as the active substance and it is given by mouth.

Further information about the evaluation of Erivedge benefits can be found in Erivedge EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Erivedge, together with measures to minimize such risks and the proposed studies for learning more about Erivedge risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization measures*.

In the case of Erivedge, these measures are supplemented with *additional risk minimization measures* mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Erivedge are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Erivedge. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Teratogenicity
Important potential risks	None
Missing information	None

II.B SUMMARY OF IMPORTANT RISKS

Important identified risk of Teratogenicity	
Evidence for linking the risk to the medicine	Nonclinical study results and literature.
Risk factors and risk groups	The 'at risk' group for experiencing vismodegib-related teratogenicity comprises female patients of child-bearing potential or female partners of male patients treated with vismodegib. *Risk factor in cancer patients receiving chemotherapy:* Treatment with chemotherapy in the first trimester, during organogenesis, substantially increases the risk of fetal malformation compared to exposure to chemotherapy in the second and third trimesters of pregnancy.
Risk minimization measures	**Routine risk communication**: Text in SmPC: • Section 4.3 (Contraindications) • Section 4.4 (Special warnings and precautions for use) • Section 4.6 (Fertility, pregnancy and lactation) **Routine risk minimization activities recommending specific clinical measures to address the risk**: • Women of childbearing potential must have a negative pregnancy test prior to initiating treatment and during treatment is included in SmPC section 4.4 • Women of childbearing potential must use two methods of recommended contraception during Erivedge therapy and after the final dose is included in SmPC section 4.4 • Contraception recommendation for men while taking Erivedge and after the final dose is included in SmPC section 4.4 **Other risk minimization measures beyond the Product Information**: Medicine's legal status: Erivedge is subject to restricted medical prescription **Additional risk minimization measures**: Erivedge Pregnancy Prevention Programme : I. For Health Care Providers • Health Care Provider Card • Patient Counselling Guideline II. For Patients • Patient Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: None See section II.C of this summary for an overview of the post-authorization development plan.

SmPC = Summary of product characteristics

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorization

Not applicable.

II.C.2 Other studies in post-authorization development plan

Not Applicable.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Specific adverse reactions follow-up forms/questionnaires

There are no specific adverse event follow-up forms in use for this product.

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

TABLE OF CONTENTS

1. HEALTHCARE PROFESSIONALS (HCP)

1.1 OBJECTIVE OF EDUCATIONAL MATERIAL FOR HEALTHCARE PROFESSIONALs

- Educate the HCPs on the risk of teratogenicity and mandated contraceptive measures to prevent foetal exposure.
- Provide contraceptive counselling to patients or ensure they receive counselling by an appropriate specialist.

1.2 HEALTHCARE PROFESSIONALS TRAINING MATERIAL

1.2.1 HCP Reminder Card

Prescriber's role in the Erivedge® Pregnancy Prevention Programme (PPP):

- Provide comprehensive advice and counselling to patients; especially provide contraceptive counselling to the patients or ensure they receive counselling by an appropriate specialist.
- Ensure that patients are capable of complying with the requirements for the safe use of Erivedge®.
- Advice patients that Erivedge® is contraindicated for women who are pregnant or breastfeeding and for women of childbearing potential who do not comply with the Erivedge® PPP.
- Assess pregnancy status, and educate patients about the risks of teratogenicity associated with exposure to Erivedge® during pregnancy.
- Ensure that patients who are women of childbearing potential have a negative medically supervised pregnancy test within a maximum of 7 days prior to initiating treatment (day of pregnancy test = Day 1).
- Monitor patient's pregnancy status monthly during therapy with a medically supervised pregnancy test conducted by a HCP, even if she is and/or becomes amenorrhoeic.
- Ensure that patients who are woman of childbearing potential are able of complying with contraceptive measures during Erivedge® treatment and for 24 months after their final dose. Remind patients of the importance of mandated contraception, and adherence to the terms of the Erivedge®PPP, during treatment and for 24 months after their final dose.
- Ensure that for patients who are women of childbearing potential, prescriptions of Erivedge should be limited to 28 days of treatment and continuation of treatment requires a new prescription.
- Report all confirmed pregnancies to Roche. Refer the patient to a specialist physician in the event of pregnancy.
- Since Erivedge® is present in semen, every male patient must understand the risks to the unborn child. Inform the male patients that they must always use a condom (with spermicide, if available), even if he has had a vasectomy, when he has sex

with a female partner during Erivedge® treatment and for 2 months after his final dose.

- Inform the male patients that they must not donate sperm while taking Erivedge® and for 2 months after their final dose. Patients must not donate blood during treatment and for 24 months after their last dose.
- Provide patient with the brochure Erivedge® PPP: Information for patients taking Erivedge®, which contains information and advice about taking Erivedge®.

1.2.2 Patient Counselling Guidelines

Within the documentation provided to HCPs, the MAH provides a Patient Counselling Guidelines to assist HCPs with the education of patients on the teratogenic risk associated with Erivedge®.

2. PATIENTS/CARERS

2.1 PATIENT BROCHURE

- Erivedge® may harm or cause the death of your unborn child.
- Recommendation: do not become pregnant during treatment and for 24 months after your final dose. Always use 2 forms of recommended contraception during treatment.
- Have monthly pregnancy tests to monitor for pregnancy.
- Recommendation: if you are pregnant, you must not start taking Erivedge®.
- Do not breast-feed during treatment and for 24 months after your final dose.
- Male patients must:
    - Always use a condom (with spermicide, if available) when having sex with female partners during treatment and for 2 months from final dose.
    - Not donate semen during treatment and for 2 months after the final dose.
- You must talk to your doctor or healthcare provider immediately if you or your sex partner miss a period, suspect a pregnancy, or are pregnant.
- Female patients: Talk to your doctor if you suspect a pregnancy while taking Erivedge® and for 24 months after your final dose.
- Male patients: Talk to your doctor if your female partner suspects that she is pregnant while you are taking Erivedge® and for 2 months after your final dose.
- All patients must:
    - Never give this medicine to anyone else.
    - Not donate blood during treatment and for 24 months after their final dose. Return all unused capsules at the end of the treatment.