

AUSTRALIAN PRODUCT INFORMATION – Erivedge® (vismodegib)

1. NAME OF THE MEDICINE

Vismodegib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Erivedge 150 mg hard capsule

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Erivedge 150 mg capsules are hard gelatin capsules, with a pink opaque body with “150mg” printed in black ink and a grey opaque cap with “VISMO” printed in black ink.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Erivedge is indicated for the treatment of adult patients with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma where surgery and/or radiation therapy are not appropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended daily dose of Erivedge is 150 mg.

Erivedge should be taken once a day, with or without food. Capsules must be swallowed whole with water and must not be opened or crushed under any circumstances.

Erivedge should be continued until disease progression or until unacceptable toxicity. In patients where treatment is discontinued prior to progression, patients should be monitored for disease recurrence or worsening of disease.

Missed Dose

If a dose of Erivedge is missed, patients should be instructed not to take the missed dose but to resume dosing with the next scheduled dose.

Special populations

Elderly Patients

No dose adjustment is required in patients > 65 year years of age (see section 4.4 Special warnings and precautions for use).

Paediatric Patients

The safety and efficacy of Erivedge in children and adolescents (<18 years) have not been established.

Patients with Renal Impairment

No dose adjustment is required in patients with renal impairment (see section 5.2 Pharmacokinetic properties). Very limited data is available in patients with severe renal impairment. Patients with severe renal impairment should be carefully monitored for adverse reactions.

Patients with Hepatic Impairment

No dose adjustment is required in patients with hepatic impairment (see section 5.2 Pharmacokinetic properties).

4.3 CONTRAINDICATIONS

Erivedge is contraindicated in;

- Pregnant women (see section 4.6 Fertility, pregnancy and lactation).
- Women of child-bearing potential, unless two reliable methods of contraception are being used during treatment and for 24 months after the last dose (see section 4.6 Fertility, pregnancy and lactation).
- Nursing mothers during the course of treatment and for 24 months after the last dose because of the potential to cause serious development defects in breast-fed infants and children (see section 4.6 Fertility, pregnancy and lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General Warnings

Blood Donation

Patients should not donate blood or blood products while on treatment and for 24 months after the last dose of Erivedge.

Paediatric Use

The safety and efficacy of Erivedge in children and adolescents (<18 years) have not been established. Premature fusion of the epiphyses (EPF) and precocious puberty have been reported in paediatric patients exposed to Erivedge. In some cases of EPF, fusion progressed after drug discontinuation.

Use in the Elderly

Of the total number of patients in clinical studies of Erivedge with advanced basal cell carcinoma, approximately 40% of patients were ≥ 65 years old. There was an insufficient number of subjects in this older age category to rule out a lower objective response rate or to rule out an increased frequency of severe adverse events.

Use in renal impairment

No dedicated clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of vismodegib. Results of a population PK analysis demonstrated no impact of renal impairment on the pharmacokinetics of vismodegib. No dose adjustment is required in patients with renal impairment. Very limited data is available in patients with severe renal impairment. Patients with severe renal impairment should be carefully monitored for adverse reactions.

Use in hepatic impairment

The pharmacokinetics, safety and tolerability of vismodegib were evaluated in patients with mild, moderate or severe hepatic impairment in a dedicated clinical study, following multiple doses of vismodegib. Results demonstrated no impact of hepatic impairment on the pharmacokinetics of vismodegib. No dose adjustment is required in patients with mild, moderate or severe hepatic impairment.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Effects of Vismodegib on Other Medicines

Clinically significant PK interactions between vismodegib and CYP450 substrates are not expected.

Results of a drug-drug interaction study conducted in cancer patients demonstrated no clinically significant PK interaction between vismodegib and rosiglitazone (a CYP2C8 substrate). Thus, inhibition of CYP enzymes by vismodegib may be excluded.

Results of a drug-drug interaction study conducted in cancer patients demonstrated no clinically significant PK interaction between vismodegib and the oral contraceptives ethinylloestradiol and norethisterone.

Vismodegib inhibits OATP1B1 *in vitro* at clinically relevant concentrations. Vismodegib may increase the exposure to substrates of OATP1B1 (e.g., bosentan, ezetimibe, glibenclamide, valsartan and statins). Particular caution should be exercised if vismodegib is administered in combination with any statin. Vismodegib also inhibits OATP1B3 *in vitro*, but more weakly. An interaction with co-administered medicines that are substrates of OATP1B3 cannot be excluded.

Clinically significant PK interactions between vismodegib and breast cancer resistance protein (BCRP) substrates are not expected. *In vitro* data indicate that vismodegib is an inhibitor of the BCRP transporter. However, the *in vitro* concentrations at which inhibition occurred are significantly greater than the unbound vismodegib concentrations observed in patients.

Effects of Other Medicines on Vismodegib

Medicines that Inhibit Drug Transport Systems

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

Medicines that Affect Gastric pH

Clinically significant PK interactions between vismodegib and pH elevating agents are not expected. Results from a clinical study demonstrated no clinically significant PK interaction between vismodegib and rabeprazole (a proton pump inhibitor) in healthy volunteers.

Medicines that Inhibit or Induce Drug Metabolising Enzymes

Vismodegib elimination involves multiple pathways. Vismodegib is predominantly excreted as an unchanged drug. Several minor metabolites are produced by multiple CYP450 enzymes.

Clinically significant PK interactions between vismodegib and CYP450 inhibitors are not expected. Results from a clinical study demonstrated no clinically significant PK interaction between vismodegib and fluconazole (a moderate CYP2C9 inhibitor) or itraconazole (a strong CYP3A4 inhibitor) in healthy volunteers.

Inducers of CYP3A4 are not predicted to alter vismodegib systemic exposure since similar steady-state plasma vismodegib concentrations were observed in patients in clinical trials concomitantly treated with CYP3A4 inducers (i.e. carbamazepine, modafinil, phenobarbital) and those concomitantly treated with CYP3A4 inhibitors (i.e. erythromycin, fluconazole).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Erivedge may impair fertility. Amenorrhea has been observed in clinical trials in women of child-bearing potential (see section 4.8). Reversibility of fertility impairment is unknown. Fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Erivedge.

In a dedicated rat fertility study, no effects on male reproductive organs or fertility endpoints were observed with treatment with vismodegib at 100 mg/kg/day for 26 weeks (corresponding to 1.3-fold of the steady-state AUC_{0-24h} at the recommended human dose) either at the end of the dosing period or following a 15-week recovery phase. In addition, in general toxicity studies with vismodegib of up to 26 weeks duration conducted in sexually mature rats and dogs, no effects on male reproductive organs were observed. An increased number of degenerating germ cells and hypospermia in sexually immature dogs observed at \geq 50 mg/kg/day in a 4-week general toxicity study were of undetermined relationship to vismodegib.

In a dedicated fertility study in female rats, treatment with vismodegib at 100 mg/kg/day for 27 weeks resulted in embryotoxicity immediately after treatment discontinuation, evident as decreased implantations, increased percent preimplantation loss, and decreased number of dams with viable embryos. Similar findings were not observed after a 15-week recovery period. No correlative histopathological changes were observed. The exposure in female rats at 100 mg/kg corresponds to 1.2-fold of the steady-state AUC_{0-24h} at the recommended human dose. In addition, in a general 26-week toxicity study in rats, decreased number of corpora lutea was observed with vismodegib at 100 mg/kg/day; the effect was not reversed by the end of an 8-week recovery period.

Use in Pregnancy – Category X

Erivedge may cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Hedgehog pathway inhibitors such as Erivedge have been demonstrated to be embryotoxic and/or teratogenic in multiple animal species and can cause severe midline defects, missing digits, and other irreversible malformations in the developing embryo or foetus.

Pregnant women must not take Erivedge because of the risk of embryo-fetal death or severe birth defects caused by Erivedge (see section 4.3 Contraindications).

There are no adequate or well-controlled studies in pregnant women using Erivedge. Erivedge has been shown to be embryotoxic and teratogenic in animals. Due to the key role of the Hedgehog pathway in embryogenesis and the known effects of Erivedge on embryo-fetal development, women of childbearing potential must use two acceptable methods of contraception during treatment with Erivedge and for 24 months after the last dose (see section 4.3 Contraindications).

Contraception in males and females

Female patients

Women of childbearing potential must use 2 forms of acceptable contraception (including one acceptable barrier method with spermicide, where available) during therapy and for 24 months after completing therapy. Contraceptive advice should be given to the patient.

The following are acceptable forms of primary contraception where medically appropriate: combination hormonal contraceptives (combined oral contraceptives, vaginal ring), subcutaneous hormonal implant, hormonal patch, hormonal contraceptives (progestogen-only oral contraceptives, levonorgestrel-releasing intrauterine system, medroxyprogesterone acetate depot), tubal sterilisation, vasectomy and intrauterine device (copper IUD). The following are acceptable forms of secondary contraception (barrier methods): any male condom (with spermicide, where available) or diaphragm (with spermicide, where available).

A pregnancy test should be performed at a medical office or laboratory within 7 days prior to initiating Erivedge treatment and monthly during treatment.

If pregnancy occurs, the patient must notify her treating physician immediately to discuss further evaluation and counselling.

Male patients

Vismodegib is present in semen. To avoid potential embryo-fetal exposure during pregnancy, male patients must use condoms with spermicide (where available), even after a vasectomy, during sexual intercourse with women while being treated with Erivedge and for 2 months after the last dose.

Male patients should not donate semen while being treated with Erivedge and for 2 months after the final dose.

In an embryo-fetal development study in which pregnant rats were administered vismodegib daily during organogenesis, vismodegib 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 10 mg/kg/day (corresponding to an AUC_{0-24hr} exposure 20% of that at the recommended human dose). The incidence of foetal retardations or variations (including dilated renal pelvis, dilated ureter, and incompletely or unossified sternal elements, centra of cervical vertebrae, or proximal phalanges and claws) was also increased at 10 mg/kg/day. Vismodegib was embryolethal at ≥ 60 mg/kg/day (corresponding to an AUC_{0-24hr} exposure 2.8-fold greater than that at the recommended human dose).

Use in Lactation

The extent to which vismodegib is excreted in breast milk is not known. Due to its potential to cause serious developmental defects, Erivedge is contraindicated in nursing mothers who are taking Erivedge or who have taken Erivedge within the last 24 months (see section 4.3 Contraindications).

Irreversible adverse effects on growing teeth and premature closure of the epiphyseal plate have been observed in rats treated with vismodegib.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of Erivedge on the ability to drive or operate machinery have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of Erivedge has been evaluated in clinical trials with 138 patients treated for advanced BCC, which includes both mBCC and laBCC. In 4 open-label phase 1 and 2 clinical trials patients were treated with at least 1 dose of Erivedge monotherapy at dosages ≥ 150 mg. Doses > 150 mg did not result in higher plasma concentrations in clinical trials and patients on doses > 150 mg have been included in the analysis. Additionally, safety was assessed in a post-approval study that included 1215 aBCC patients evaluable for safety and treated with 150 mg. In general the safety profile observed was consistent in both mBCC and laBCC patients and across studies as described below.

The most frequent ($\geq 10\%$) adverse drug reactions (ADRs) reported from these clinical studies with Erivedge are summarised in the table below.

Table 1. Very Common ($\geq 10\%$) Adverse Drug Reactions in \geq Advanced BCC Patients

MedDRA Preferred Term	All aBCC Patients (n = 138)		
	All Grades* (%)	Grade 3* (%)	Grade 4* (%)
Gastrointestinal Disorder			
Nausea	48 (34.8%)	0	0
Diarrhoea	46 (33.3%)	3 (2.2%)	0
Constipation	32 (23.2%)	0	0
Vomiting	23 (16.7%)	0	0
Dyspepsia	15 (10.9%)	0	0
General Disorders and administration site conditions			
Fatigue	65 (47.1%)	8 (5.8%)	1 (0.7%)
Investigations			
Weight decreased	69 (50.0%)	14 (10.1%)	0
Metabolism and nutrition disorders			
Decreased appetite	41 (29.7%)	3 (2.2%)	0
Musculoskeletal and connective tissue disorders			
Muscle spasms	103 (74.6%)	7 (5.1%)	0
Arthralgia	23 (16.7%)	1 (0.7%)	0
Pain in extremity	14 (10.1%)	1 (0.7%)	0
Nervous system disorder			
Dysgeusia	81 (58.7%)	0	0
Ageusia	15 (10.9%)	0	0
Skin and subcutaneous tissue disorders			
Alopecia	91 (65.9%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities.

*NCI-CTCAE v3.0

Other Very Common ($\geq 10\%$) Adverse Reactions in an At-Risk Subset of Patients:

Reproductive system and breast disorders: Of the 138 patients with advanced BCC, 10 were women of child bearing potential. Amongst these women, amenorrhoea was observed in 3 patients (30%).

Adverse Reactions in $< 10\%$ of Advanced BCC Patients Treated with Erivedge include:

Gastrointestinal disorders: abdominal pain (*common*), upper abdominal pain (*common*).

General disorders and administration site conditions: asthenia (*common*).

Investigations: hepatic enzyme increased (*common*)[#], blood creatine phosphokinase increased (*common*).

Metabolism and nutrition disorders: dehydration (*common*).

Musculoskeletal disorders: musculoskeletal pain (*common*), back pain (*common*), musculoskeletal chest pain (*common*), myalgia (*common*), flank pain (*common*).

Nervous system disorders: hypogeusia (*common*).

Skin and subcutaneous tissue disorders: madarosis (*common*), abnormal hair growth (*common*).

[#]Hepatic enzyme increased includes the following reported adverse event preferred terms: hepatic enzyme increased, aspartate aminotransferase increased, liver function test abnormal, blood alkaline phosphatase increased, gamma-glutamyl transferase increased and blood bilirubin increased.

In general, the safety profile observed was consistent in both metastatic BCC and locally advanced BCC patients as described above.

Laboratory Abnormalities

Amongst 138 aBCC patients, post-baseline changes in laboratory parameters of Grade 3 were uncommon, occurring in < 5% and there were no Grade 4 laboratory abnormalities.

Laboratory abnormalities ($n > 1$) that changed from baseline to Grade 3 were decreased sodium ($n = 7$), decreased potassium ($n = 2$), and elevated blood urea nitrogen (BUN) ($n = 3$).

Post Marketing Experience

The following adverse drug reactions have been identified during post-approval use of Erivedge (Table 2) based on reports from Investigator Initiated Studies and literature cases:

Table 2: Adverse Drug Reactions from Postmarketing Experience

MedDRA Preferred Term	Frequency category
Musculoskeletal and connective tissue disorders Epiphyses premature fusion ¹	Unknown
Endocrine disorders Precocious puberty ¹	Unknown
Hepatobiliary disorders Drug-induced liver injury	Unknown

¹See section 4.4 Special warnings and precautions for use

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problem.

4.9 OVERDOSE

Erivedge has been administered at doses 3.6 times higher than the recommended 150 mg daily dose. No increases in plasma drug levels or toxicity were observed.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Pharmacodynamic effect

Vismodegib is a low molecular weight, orally available inhibitor of the Hedgehog pathway. Hedgehog pathway signalling through the Smoothed transmembrane protein (SMO) leads to the activation and nuclear localisation of 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 SMO thereby preventing Hedgehog signal transduction.

Assays of Hedgehog pathway inhibition utilised the human embryonic palatal mesenchymal (HEPM) cell line, established in 1979, and HEK293 (human embryonic kidney) cell line, established in the early 1970s.

Cardiac Electrophysiology

There was no effect of therapeutic doses of Erivedge on the QTc interval. In a randomised, double-blind, placebo- and positive controlled, parallel-group QTc study, healthy subjects were administered Erivedge 150 mg every 24 hours for 7 days, placebo and a single oral dose of moxifloxacin. Similarly, Erivedge had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Clinical trials

Pivotal study: ERIVANCE BCC (SHH4476g)

An international, single-arm, multi-centre, open-label, 2-cohort pivotal study (ERIVANCE BCC) was conducted in 104 patients with advanced basal cell carcinoma (BCC), including metastatic BCC ($n = 33$) and locally advanced BCC ($n = 71$). Metastatic BCC (mBCC) was defined as BCC that had spread beyond the skin to other parts of the body, including the lymph nodes, lung, bones and/or internal organs. Locally advanced BCC (laBCC) patients had cutaneous lesions that were inappropriate for surgery (inoperable, multiply recurrent where curative resection deemed to be unlikely or for whom surgery would result in substantial deformity) and for which radiotherapy was unsuccessful or contraindicated. Prior to study enrolment, diagnosis of BCC was confirmed by histology. Patients with Gorlin syndrome who had at least one advanced BCC (aBCC) lesion and met inclusion criteria were eligible to participate in the study. Patients were treated with oral daily dosing of Erivedge at 150 mg.

The median age was 62 years for all patients with 45% of patients being older than 65 years. The majority of patients were male (61%) and Caucasian (100%), 32% of patients had mBCC and 68% of patients had laBCC. For the metastatic cohort, nearly all patients had prior therapies (97%) including surgery (97%), radiotherapy (58%), and systemic therapies (30%). For the locally advanced cohort, nearly all patients had prior therapies (94%) including surgery (89%), radiotherapy (27%), and systemic/topical therapies (11%). The median duration of treatment for all patients was 12.9 months (range: 0.7 to 47.8).

The primary endpoint was objective response rate (ORR) as assessed by an Independent Review Facility (IRF). Results from the Primary Analysis (9 months after last patient enrolment) and further 12-month follow up are summarised in Table 3.

Investigator assessment of ORR was a secondary endpoint. Results from the Primary Analysis (9 months after last patient enrolment) and further 30-month follow-up are summarised in Table 4.

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 Tumors (RECIST) version 1.0. In the laBCC cohort, tumour response was assessed based on visual assessment of external tumour and ulceration, tumour imaging (if appropriate), and tumour biopsy. A patient was considered a responder 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.

Additional secondary endpoints include duration of response (DoR), progression-free survival (PFS), histopathologic response and overall survival (OS). Results are shown in Tables 3 and 4.

Table 3. Summary of Efficacy by IRF Assessment: Efficacy-Evaluable Patients*[†]

	Primary Analysis		12-month update	
	mBCC (n = 33)	laBCC (n = 63)	mBCC (n = 33)	laBCC (n = 63)
<u>Primary Endpoint</u>				
<i>Objective Response Rate (ORR)</i>				
Responders	10 (30.3%)	27 (42.9%)	11 (33.3%)	30 (47.6%)
Complete response	0	13	0	14
Partial response	10	14	11	16
Stable disease	21	24	20	22
Progressive disease ‡	1	8	1	8
95% CI for overall response	(15.6% - 48.2%)	(30.5% - 56.0%)	(19.2%, 51.8%)	(35.5%, 60.6%)
p-value (one-sided) ††	0.0011	< 0.0001	N/A	N/A
<u>Secondary Endpoints</u>				
<i>Duration of Response (DoR)</i>				
Median DoR (months)	7.6	7.6	7.6	9.5
95% CI	(5.62, N/E)	(5.7, 9.7)	(5.5, 9.4)	(7.4, 21.4)
<i>Progression-free survival (PFS)</i>				
Median PFS (months)	9.5	9.5	9.5	9.5
95% CI	(7.36, N/E)	(7.39, 11.93)	(7.4, 11.1)	(7.4, 14.8)

N/A = not applicable

N/E = not estimable

* Efficacy-evaluable patient population is defined as all enrolled patients who received any amount of study medicine 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) $\geq 20\%$ 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.

†† Based on primary analysis conducted 9 months after last patient enrolled

Table 4 Summary of Efficacy by Investigator Assessment: Efficacy-Evaluable Patients^{*,†}

	Primary Analysis		30-month update	
	mBCC (n = 33)	laBCC (n = 63)	mBCC (n = 33)	laBCC (n = 63)
Secondary Endpoints				
<i>Objective Response Rate (ORR)</i>				
Responders	15 (45.5%)	38 (60.3%)	16 (48.5%)	38 (60.3%)
Complete response	0	20	0	20
Partial response	15	18	16	18
Stable disease	15	15	14	15
Progressive disease‡	2	6	2	6
95% CI for overall response	(28.1%, 62.2%)	(47.2%, 71.7%)	(30.8%, 66.2%)	(47.2%, 71.7%)
p-value (one-sided)††	< 0.0001	< 0.0001	N/A	N/A
<i>Duration of Response (DoR)</i>				
Median DoR (months)	12.9	7.6	14.8	26.2
95% CI	(5.55, 12.91)	(7.43, N/E)	(5.6, 17.0)	(9.0, 37.6)
<i>Progression-free survival (PFS)</i>				
Median PFS (months)	9.2	11.3	9.3	12.9
95% CI	(7.4, N/E)	(9.46, 16.8)	(7.4, 16.6)	(10.2, 28.0)
<i>Overall survival (OS)</i>				
Median OS (months)	Not reached	Not reached	33.4	Not reached
95% CI	(13.86, N/E)	(17.6, N/E)	(18.1, N/E)	(N/E)

N/A = not applicable

N/E = not estimable

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

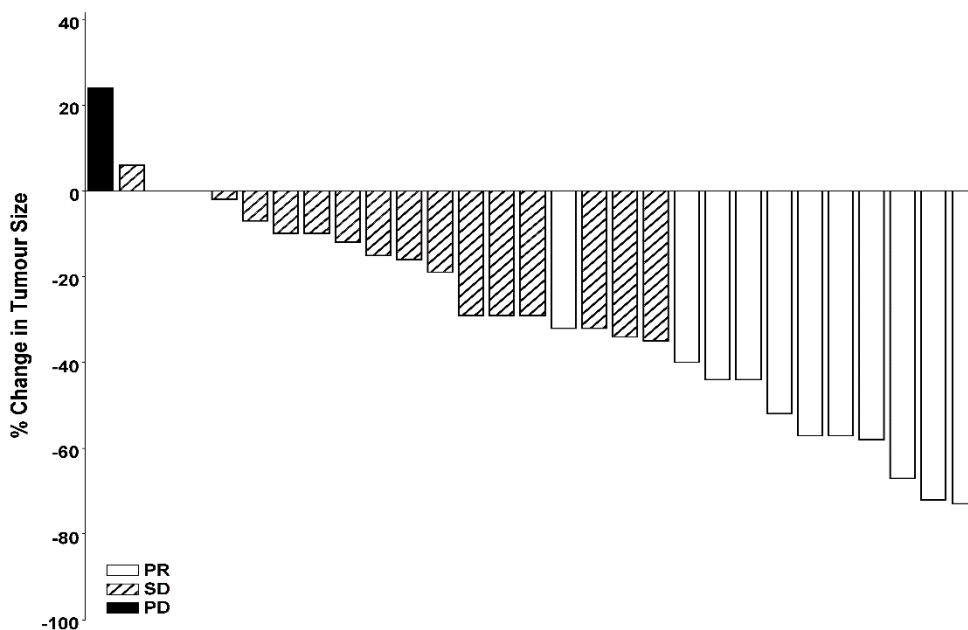
† Unevaluable/missing data included 1 mBCC and 4 laBCC patients.

‡ Progression in laBCC cohort is defined as meeting any of the following criteria: (1) $\geq 20\%$ 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

†† Based on primary analysis conducted 9 months after last patient enrolled

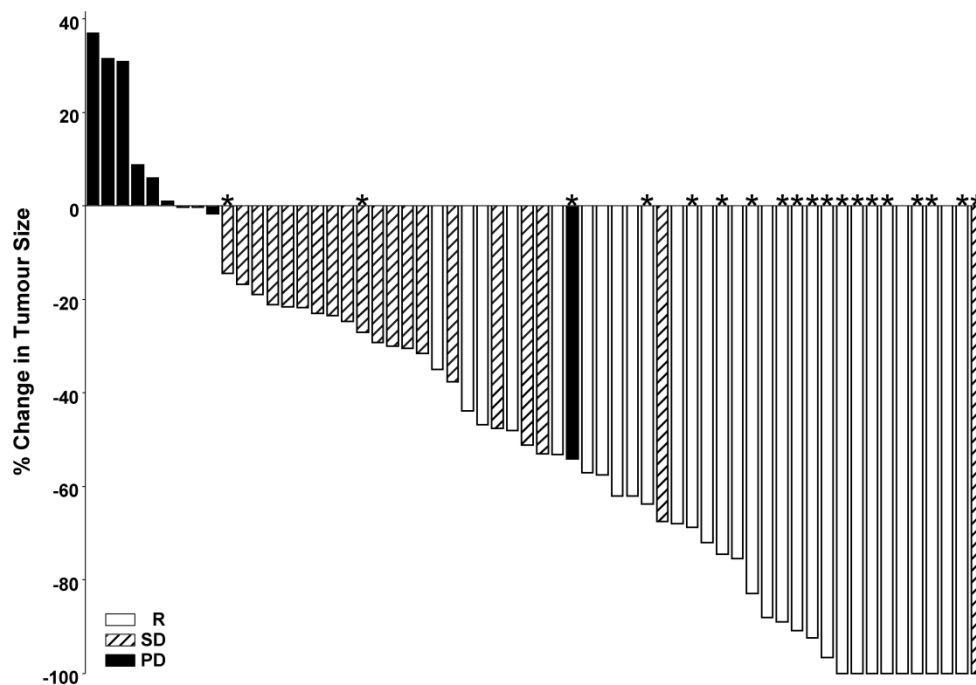
The waterfall plots in Figures 1 and 2 represent IRF assessment at 12-month follow up by charting the maximum reduction in target lesion(s) size for each patient. The majority of patients in both cohorts experienced tumour shrinkage.

Figure 1 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 only and 1 patient was unevaluable

Figure 2. Locally Advanced BCC Cohort



Note: Tumour size is based on sum of longest dimensions of target lesions. PD = progressive disease, SD = stable disease, * = 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.

At the time of the primary analysis for mBCC the majority of IRF-assessed responses (6 of 10 responders) occurred by week 8 and additional responses were observed at later assessments. For laBCC the majority of IRF-assessed responses (14 of 27 responders) occurred by week 8 and additional responses were observed at later assessments. 54% of laBCC patients ($n = 63$) had a histopathologic response with no evidence of BCC at 24 weeks.

Post-approval study: STEVIE (MO25616)

A post-approval, open-label, non-comparative, multicentre, phase II clinical trial (STEVIE) was conducted in 1232 patients with advanced BCC, of whom 1215 were evaluable for efficacy and safety. laBCC was defined as cutaneous lesions that were inappropriate for surgery (inoperable, or for whom surgery would result in substantial deformity) and for which radiotherapy was unsuccessful or contraindicated. mBCC was defined as histologically confirmed distant metastasis. Prior to study enrolment, diagnosis of BCC was confirmed by histology. Patients were treated with oral daily dosing of Erivedge at 150 mg.

The median age was 72 years for all patients. The majority of patients were male (57%), 8% had mBCC whereas 92% had laBCC. For the metastatic cohort, the majority of patients had prior therapies, including surgery (91%), radiotherapy (62%) and systemic therapy (16%). For the locally advanced cohort, the majority of patients had prior therapies, including surgery (85%), radiotherapy (28%) and systemic therapy (7%). The median duration of treatment for all patients was 8.6 months (range 0 to 44.1).

Among patients in the efficacy-evaluable population with measurable and histologically confirmed disease ($n = 1161$; laBCC $n = 1077$; mBCC $n = 84$), 68.5% and 36.9% responded to treatment (complete or partial response by RECIST v1.1) in the laBCC and mBCC cohorts, respectively. Of patients who had a confirmed response, the median Duration of Response was 23.0 months (95% CI: 20.4, 26.7) in the laBCC cohort and 13.9 months (95% CI: 9.2, NE) in the mBCC cohort. Complete response was achieved in 4.8% of patients in the mBCC cohort and 33.4% in the laBCC cohort.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Single dose absolute bioavailability of vismodegib is 31.8%. Absorption is saturable as evidenced by the lack of dose proportional increase in exposure after a single dose of 270 mg and 540 mg vismodegib. Under clinically relevant conditions (steady state), the pharmacokinetics (PK) of vismodegib is not affected by food. Therefore, vismodegib 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 drug over time and consistently low unbound drug levels.

Metabolism

Vismodegib is slowly eliminated by a combination of metabolism and excretion of parent drug. Vismodegib is predominant in plasma, with concentrations representing greater than 98% of the total circulating drug-related components. Metabolic pathways of vismodegib in human 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.

Excretion

After a single oral dose, vismodegib demonstrates a unique PK profile with sustained plasma levels and an estimated terminal half-life of 12 days.

After continuous once-daily dosing, the pharmacokinetics of vismodegib appear to be non-linear. Considering the single dose half-life, steady-state plasma concentrations in patients are achieved faster than expected (typically within approximately 7 days of continuous daily dosing), with lower than expected accumulation. The apparent half-life of vismodegib at steady state is estimated to be 4 days with continuous daily dosing.

After oral administration of radiolabeled drug, vismodegib is absorbed and slowly eliminated by a combination of metabolism and excretion of parent drug, 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.

Pharmacokinetics in Special Populations

Population PK analyses showed that weight (range: 41-140 kg) and sex do not have a clinically meaningful influence on the systemic exposure of vismodegib.

Renal impairment

Renal excretion of orally administered vismodegib is low (< 5%). Therefore, renal impairment is unlikely to have a clinically significant effect on the pharmacokinetics of vismodegib. Based on a population PK analysis in patients with mild (BSA-indexed CrCl 50 to 80 mL/min, n = 58), moderate (BSA-indexed CrCl 30 to 50 mL/min, n = 16) and severe (BSA-indexed CrCl < 30 mL/min, n = 1) renal impairment, impaired renal function had no clinically significant effect on the pharmacokinetics of vismodegib.

Hepatic impairment

The major elimination pathways of vismodegib involve hepatic metabolism and biliary/intestinal secretion. In a clinical study of subjects with degrees of hepatic impairment, results demonstrated that in patients with mild (n = 8), moderate (n = 6), and severe (n = 3)

hepatic impairment the pharmacokinetics of vismodegib was comparable to that of subjects with normal hepatic function (n = 9). The subjects' degree of hepatic impairment was based on the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria: mild (TB ≤ ULN, AST > ULN or ULN < TB ≤ 1.5 x ULN, AST any); moderate (1.5 x ULN < TB < 3 x ULN, AST any); severe (3 x ULN < TB < 10 x ULN, AST any).

Elderly patients

There is limited data in elderly patients. Population PK analysis suggests that age did not have a clinically significant impact on steady-state concentration of vismodegib.

Paediatric patients

There is no data in paediatric patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Vismodegib was not genotoxic in a battery of *in vitro* assays (Ames mutation test in *Salmonella* and *Escherichia coli* and chromosomal aberrations assay in human peripheral blood lymphocytes) in the presence or absence of metabolic activation systems.

Vismodegib was not genotoxic in an *in vivo* rat bone marrow micronucleus assay when tested at a single dose up to 2000 mg/kg (corresponding to > 5 times the C_{max} in patients at the recommended human dose).

Carcinogenicity

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

Other Toxicological Findings

Findings in toxicity studies with vismodegib indicated a risk of adverse effects during post-natal development. Administration of vismodegib to rats resulted in 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.

Neurologic effects characterised as twitching, or limb or body tremors were observed at a high frequency in rat toxicity studies with vismodegib. These observations completely resolved upon discontinuation of dosing and were not associated with microscopic 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 corresponding clinical signs were observed in dogs.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose
Lactose monohydrate
Sodium lauryl sulfate
Povidone
Sodium starch glycollate
Purified talc
Magnesium stearate

Capsule shell

Gelatin
Titanium dioxide
Iron oxide red (CI77491)
Iron oxide black (CI77499)

Printing ink

Shellac
Iron oxide black (CI77499)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C. The bottle should be kept tightly closed in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

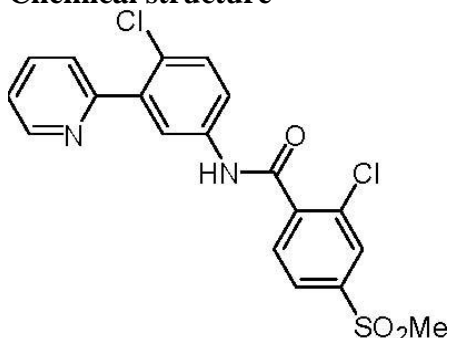
Erivedge 150 mg hard capsules are available in high-density polyethylene (HDPE) bottles of 28 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



CAS number
879085-55-9

Vismodegib is described chemically as 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide. The molecular formula is C₁₉H₁₄Cl₂N₂O₃S. The molecular weight is 421.30 g/mol.

Vismodegib is a crystalline free base with a pKa (pyridinium cation) of 3.8, appearing as a white to tan solid. The solubility of vismodegib is pH dependent; the solubility in water at pH 7 is 0.1 µg/mL and is 0.99 mg/mL at pH 1.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4. Prescription Only Medicine.

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

9 May 2013

10. DATE OF REVISION

19 September 2018

Summary table of changes

Section Changed	Summary of new information
4.8	Addition of the Adverse drug reaction of Hepatobiliary disorders- Drug induced liver injury under the heading, Post-marketing experience in Table 2 of Section 4.8.