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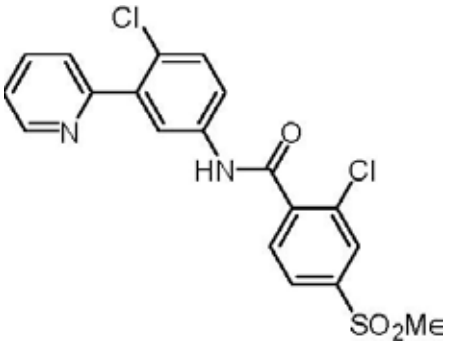
NAME OF THE MEDICINE

ERIVEDGE®

Vismodegib



CAS: 879085-55-9

DESCRIPTION

Vismodegib is described chemically as 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide. The molecular formula is $C_{19}H_{14}Cl_2N_2O_3S$. 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.

ERIVEDGE is available as a pink/grey hard capsule containing 150 mg of vismodegib and the following excipients: cellulose – microcrystalline, lactose, sodium lauryl sulfate, povidone, sodium starch glycollate, talc – purified and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, iron oxide red (CI77491) and iron oxide black (CI77499). The black printing ink contains shellac and iron oxide black (CI77499).

PHARMACOLOGY

Pharmacodynamics

Vismodegib is a low molecular weight, orally available inhibitor of the Hedgehog pathway. Hedgehog pathway signalling through the Smoothened 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 utilized the human embryonic palatal mesenchymal (HEPM) cell line, established in 1979, and HEK293 (human embryonic kidney) cell line, established in the early 1970s.

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Cardiac Electrophysiology

There was no effect of therapeutic doses of ERIVEDGE on the QTc interval. In a randomized, 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).

Pharmacokinetics

Absorption

Vismodegib is a highly permeable compound with low aqueous solubility (BCS Class 2). The 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.

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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 and hepatic impairment

There is insufficient data in patients with renal or hepatic impairment. Based on population PK analysis of combined data from 5 clinical studies, renal function (creatinine clearance) or hepatic function (ALT, AST, total protein, or total bilirubin) did not appear to affect the PK of vismodegib.

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.

CLINICAL TRIALS

An international, single-arm, multi-center, 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 9.8 months (range, 0.7 to 18.7).

The primary endpoint was objective response rate as assessed by an independent review facility (IRF) as summarized in Table 1. 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

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by radiography; (2) ≥ 30% reduction in SLD from baseline in externally visible dimension of target lesions; (3) Complete resolution of ulceration in all target lesions.

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Table 1. Objective Response Rate: Efficacy-Evaluable Patients*,†

	Primary Endpoint: IRF-Assessed ORR		Secondary Endpoint: Investigator-Assessed ORR	
	mBCC (n = 33)	laBCC (n = 63)	mBCC (n = 33)	laBCC (n = 63)
Responders	10 (30.3%)	27 (42.9%)	15 (45.5%)	38 (60.3%)
Stable disease	21	24	15	15
Progressive disease ‡	1	8	2	6
95% CI for overall response	(15.6% - 48.2%)	(30.5% - 56.0%)	(28.1% - 62.2%)	(47.2% - 71.7%)
p-value (one-sided)	0.0011	< 0.0001	N/A	N/A

N/A = not applicable.

* 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) ≥ 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.

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

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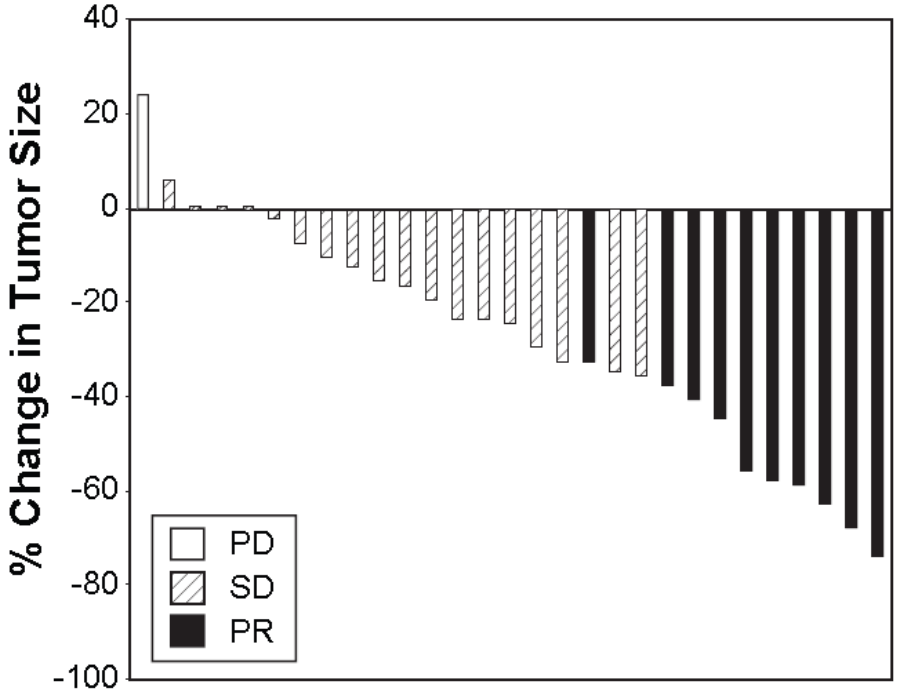
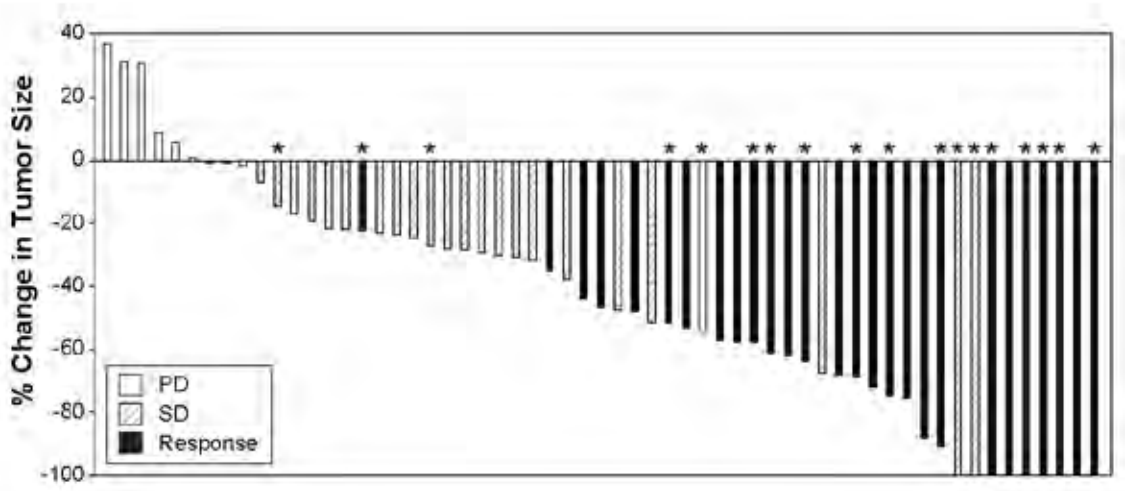
Figure 1. Metastatic BCC Cohort



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 non-target lesions only and 1 patient was unevaluable.

Figure 2. Locally Advanced BCC Cohort



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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.

Additional secondary endpoints include duration of response (DoR), progression-free survival (PFS), histopathologic response and overall survival (OS).

For mBCC, the median DoR was 7.6 months (95% CI: 5.62, not estimable) by IRF, and 12.9 months (95% CI: 5.55, 12.91) by investigator (INV). The majority of IRF-assessed responses (6 of 10 responders) occurred by week 8 and additional responses were observed at later assessments. Median PFS was 9.5 months (95% CI: 7.36, not estimable) by IRF, and 9.2 months (95% CI: 7.39, not estimable) by INV. The median OS has not been reached (95% CI: 13.86, not estimable).

For laBCC, median DoR was 7.6 months (95% CI: 5.65, 9.66) by IRF, and 7.6 months (95% CI: 7.43, not estimable) by INV. 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. Median PFS was 9.5 months (95% CI: 7.39, 11.93) by IRF, and 11.3 months (95% CI: 9.46, 16.82) by INV. The median OS has not been reached (95% CI: 17.61, not estimable).

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.

CONTRAINDICATIONS

ERIVEDGE is contraindicated in;

- Pregnant women (see *PRECAUTIONS, Use in Pregnancy - Category X*).
- Women of child-bearing potential, unless two reliable methods of contraception are being used during treatment and for 7 months after the last dose (see *PRECAUTIONS, Use in Pregnancy - Category X*).
- Nursing mothers during the course of treatment and for 7 months after the last dose because of the potential to cause serious development defects in breast-fed infants and children (see *PRECAUTIONS, Use in Lactation*).

PRECAUTIONS

General Warnings

Blood Donation

Patients should not donate blood or blood products while on treatment and for 7 months after the last dose of ERIVEDGE.

Effects on Fertility

ERIVEDGE may impair fertility. Amenorrhea has been observed in clinical trials in women of child-bearing potential (see *ADVERSE EFFECTS*). Based on animal studies, reversibility

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of fertility impairment is unknown. Fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with ERIVEDGE.

Dedicated studies to assess the potential of ERIVEDGE to affect fertility have not been performed. Repeat dose toxicity studies in rats and dogs suggest that male and female reproductive function and fertility may be impaired in patients receiving ERIVEDGE.

Increased numbers of degenerating germ cells and hypospermia were observed in relatively young dogs treated for 4 weeks at ≥ 50 mg/kg/day (corresponding to 2.2-fold greater than the $AUC_{0\text{-}24h}$ steady-state exposure at the recommended human dose), and the effects were not fully reversed by the end of a 4-week recovery period. No corresponding findings were observed at similar doses in 13-week and 26-week toxicity studies with sexually mature dogs.

A decrease in percent motile sperm was observed in male rats treated for 26 weeks at ≥ 15 mg/kg/day (corresponding to 34% of the estimated $AUC_{0\text{-}24h}$ steady-state exposure at the recommended human dose), and was not reversed by the end of an 8-week recovery period. No corresponding microscopic changes in the testis or epididymis or changes in sperm count, staging, or morphology were observed.

A decrease in the number of corpora lutea was observed in female rats treated for 26 weeks at 100 mg/kg/day (corresponding to 1.1-fold of the estimated $AUC_{0\text{-}24h}$ steady-state exposure at the recommended human dose), and was not reversed by the end of an 8-week recovery period.

Use in Pregnancy – Category X

ERIVEDGE may cause embryofoetal 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 embryofoetal death or severe birth defects caused by ERIVEDGE (see *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 embryofoetal development, women of childbearing potential must use two acceptable methods of contraception during treatment with ERIVEDGE and for 7 months after the last dose (see *CONTRAINDICATIONS*).

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 7 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

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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

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.

In an embryofoetal 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 $AUC_{0\text{-}24hr}$ 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 $AUC_{0\text{-}24hr}$ 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 7 months (see *CONTRAINDICATIONS*).

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

Paediatric Use

The safety and efficacy of ERIVEDGE in paediatric patients has not been established.

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.

Renal Impairment

The safety and efficacy of ERIVEDGE in patients with renal impairment has not been established.

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Hepatic Impairment

The safety and efficacy of ERIVEDGE in patients with hepatic impairment has not been established.

Carcinogenicity

Dedicated studies to evaluate the carcinogenicity of vismodegib have not been performed. However, pilomatricoma (a benign subcutaneous neoplasm) was observed in rats administered vismodegib, which may be related to pharmacologically mediated disruption of the hair follicle morphogenesis. Pilomatricoma has not been reported in clinical trials with vismodegib, and the relevance of this finding to patients is therefore uncertain.

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).

Effect on the Ability to Drive or Use Machinery

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

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 characterized 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.

INTERACTIONS WITH OTHER MEDICINES

Results of a drug-drug interaction study conducted in cancer patients demonstrated that the systemic exposure of rosiglitazone (a CYP2C8 substrate) or oral contraceptives (ethinyloestradiol and norethisterone) is not altered when either drug is co-administered with ERIVEDGE.

Based on *in vitro* data, vismodegib is a weak inhibitor of the hepatic drug metabolizing enzymes CYP2C8 and CYP2C9 (K_i = 6.0 µM and 5.4 µM, respectively). Considering the high degree of plasma protein binding (> 99% *ex vivo* in patients) and the unbound exposures achieved in patients (0.109 to 0.163 µM), it is highly unlikely that unbound drug

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concentrations of vismodegib will be reached in patients to cause a clinically relevant drug-drug interaction through CYP inhibition.

Vismodegib is not an inhibitor of P-glycoprotein (P-gp) and has low potential to act as a potent inhibitor of breast cancer resistance protein (BCRP) due to its high protein binding. Vismodegib does not induce CYP1A2, 2B6, 3A4/5 in human hepatocytes, nor does it exhibit strong binding to pregnane X receptor (PXR) suggesting it is not a potent enzyme inducer. Vismodegib is therefore unlikely to cause clinically relevant drug-drug interactions due to drug transport inhibition or enzyme induction.

In vitro studies indicate that vismodegib is a substrate of P-gp. The absorption or distribution of vismodegib may be affected by P-gp inhibitors or inducers. When vismodegib is co-administered with medicines that inhibit P-gp (e.g. clarithromycin, erythromycin, azithromycin), systemic exposure of vismodegib and incidence of adverse events of vismodegib may be increased.

Medicinal products that alter the pH of the upper GI tract (e.g. proton pump inhibitors, H_2-receptor antagonists and antacids) may alter the solubility of vismodegib and reduce its bioavailability. However, no formal clinical study has been conducted to evaluate the effect of gastric pH altering agents on the systemic exposure of vismodegib. Increasing the dose of vismodegib when co-administered with such agents is not likely to compensate for the loss of exposure. When vismodegib is co-administered with a proton pump inhibitor, H_2-receptor antagonist or antacid, systemic exposure of vismodegib may be decreased and the effect on efficacy of vismodegib is unknown.

Based on *in vitro* data, vismodegib is a substrate of CYP2C9 and CYP3A4. It is unlikely, however, that administration of vismodegib with concomitant CYP3A4/5 and CYP2C9 inhibitors/inducers would result in a clinically relevant drug-drug interaction. CYP inhibition would unlikely alter vismodegib concentrations because of the slow elimination of vismodegib via multiple elimination pathways, including metabolism by several CYPs and excretion of unchanged drug. In clinical trials, the range of total and unbound plasma vismodegib concentrations was similar in patients taking known CYP3A4 inducers (i.e. carbamazepine, modafinil, phenobarbital) or CYP3A4 inhibitors (i.e. erythromycin, fluconazole) with vismodegib. These findings suggest that the pharmacokinetics of vismodegib are not affected by CYP3A4 inhibitors and inducers.

ADVERSE EFFECTS

The safety of ERIVEDGE has been evaluated in > 450 patients and healthy volunteers in clinical studies. The data below come from 138 patients with advanced BCC treated in 4 open-label phase 1 and 2 clinical trials with at least one dose of ERIVEDGE monotherapy at dosages ³ 150 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.

The most frequent (≥ 10%) adverse drug reactions (ADRs) reported from these clinical studies with ERIVEDGE are summarized in the table below.

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Table 2. Adverse Drug Reactions Occurring in ≥ 10% of Advanced BCC Patients

MedDRA Preferred Term	All aBCC Patients (*n* = 138)		
	All Grades* (%)	**Grade 3* (%)**	**Grade 4* (%)**
Gastrointestinal Disorder			
Nausea	42 (30.4%)	1 (0.7%)	-
Diarrhoea	40 (29.0%)	1 (0.7%)	-
Constipation	29 (21.0%)	-	-
Vomiting	19 (13.8%)	-	-
General Disorders and administration site conditions			
Fatigue	55 (39.9%)	7 (5.1%)	1 (0.7%)
Investigations			
Weight decreased	62 (44.9%)	10 (7.2%)	-
Metabolism and nutrition disorders			
Decreased appetite	35 (25.4%)	3 (2.2%)	-
Musculoskeletal and connective tissue disorders			
Muscle spasms	99 (71.7%)	5 (3.6%)	-
Nervous system disorder			
Dysgeusia	76 (55.1%)	-	-
Ageusia	15 (10.9%)	-	-
Skin and subcutaneous tissue disorders			
Alopecia	88 (63.8%)	-	-

MedDRA = Medical Dictionary for Regulatory Activities.
*NCI-CTCAE v3.0

Other Adverse Reactions Occurring in >10% of an At-Risk Subset of Patients:

Reproductive 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 Reaction in < 10% of Advanced BCC Patients Treated with ERIVEDGE include:

Gastrointestinal disorders: abdominal pain (*common*).

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

Musculoskeletal disorders: musculoskeletal pain (*common*).

Nervous system disorders: hypogeusia (*common*).

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 with change from baseline to Grade 3 were decreased sodium ($n = 6$), decreased potassium ($n = 2$), and elevated blood urea nitrogen (BUN) ($n = 3$).

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DOSAGE AND ADMINISTRATION

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.

Dosage Adjustment

Elderly Patients

No dose adjustment is required in patients > 65 year years of age (see *PRECAUTIONS, Use in the Elderly*).

Paediatric Patients

The safety and effectiveness of ERIVEDGE in paediatric patients have not been established.

Patients with Renal Impairment

The safety and efficacy of ERIVEDGE have not been studied in patients with renal impairment.

Patients with Hepatic Impairment

The safety and efficacy of ERIVEDGE have not been studied in patients with hepatic impairment.

OVERDOSAGE

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).

PRESENTATION AND STORAGE CONDITIONS

ERIVEDGE 150 mg hard capsules are available in packs of 28 capsules in polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC)/aluminium blister packs.

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.

Store below 30 °C.

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Disposal of medicines

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.

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4- 10 Inman Road
Dee Why NSW 2099
AUSTRALIA

Customer enquiries: 1800 233 950

POISON SCHEDULE OF THE MEDICINE

Schedule 4. Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

9 May 2013