Erivedge®

Vismodegib

Composition

Active substance: Vismodegib
Excipients: Excipients for capsules. The capsules contain lactose.

Pharmaceutical form and quantity of active substance per unit

Erivedge 150 mg hard gelatin capsules with a pink opaque body (printed with "150 mg") and a grey opaque cap (printed with "VISMO").

Indications and potential uses

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

Dosage and administration

Usual dosage

Erivedge 150 mg (1 capsule) is taken once daily with or without food.

Treatment with Erivedge should be continued until progression of the underlying disease or the occurrence of unacceptable toxicity.

The capsules should under no circumstances be opened or crushed. In the event of contact with the capsule contents (as in capsule damage) the hands should be washed to avoid contaminating the environment.

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

Special dosage instructions

Elderly patients

Dose adjustment is unnecessary in patients ≥ 65 years of age.

Pediatrics

Safety and efficacy in children and adolescents (< 18 years of age) have not been studied.

Renal impairment

Safety and efficacy in patients with renal impairment have not been studied.

Hepatic impairment

Safety and efficacy in patients with hepatic impairment have not been studied.

Contraindications

Hypersensitivity to the active substance or any excipient.

Pregnancy and lactation.

Erivedge is contraindicated in women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme.

Warnings and precautions

Pregnancy Prevention Programme

Health care providers must educate the patients so they understand and acknowledge all the conditions of the Erivedge Pregnancy Prevention Programme.

This medicinal product is TERATOGENIC.

Embryo-fetal death or severe birth defects

Erivedge may cause embryo-fetal death or severe birth defects if administered to pregnant women. Hedgehog signalling pathway inhibitors such as vismodegib have shown embryotoxic and/or teratogenic effects in several animal species and can cause severe midline defects, missing fingers or toes and other irreversible malformations in the developing embryo or fetus. Erivedge should not be used in pregnancy except in serious life-threatening cases in which the potential benefit to the patient outweighs the risk to the fetus.

Female patients

Because of the risk of embryo-fetal death or severe birth defects Erivedge should not be used by pregnant women except in serious life-threatening cases in which the potential benefit to the patient outweighs the risk to the fetus.

Women of child-bearing potential

Erivedge is contraindicated in women of childbearing potential unless all the conditions of the Pregnancy Prevention Programme are met.

Women of child-bearing potential must undertake to use two reliable methods of contraception (including a reliable barrier method with spermicide, where available) during treatment and for 24 months thereafter. Patients must comply with all contraceptive measures even if amenorrheic. Individual patients should be counselled on methods of contraception. Reliable methods of primary contraception (if medically appropriate) are: combined hormone contraception, subcutaneous hormonal implants, hormone patches, hormone contraceptives (levonorgestrel-releasing intrauterine system, depot medroxyprogesterone acetate), tubal sterilisation, vasectomy and intrauterine devices (IUD). Reliable methods of secondary contraception (barrier methods) are: any male condoms (with spermicide, where available) or diaphragms (with spermicide, where available).

Women of child-bearing potential must also undertake not to breast-feed during treatment and for 24 months thereafter.

A pregnancy test with a minimum sensitivity of 25 mIU hCG/ml urine should be performed and documented at a medical office or laboratory within seven days prior to initiating Erivedge treatment and monthly during treatment, even if the patient has become amenorrheic.

If pregnancy occurs during treatment or within 24 months after the last dose, a menstrual period is overdue, the patient stops using contraception (except if completely abstinent) or there is any change in contraceptive method, the patient must inform their treating physician immediately to discuss further evaluation and receive counselling.

Male patients

During treatment with Erivedge and for two months thereafter male patients having sexual intercourse with women should use condoms with spermicide (where available), even after vasectomy, and should not donate sperm in order to avoid exposing an unborn embryo or fetus to vismodegib. In addition men must inform their treating physician if their female partner becomes pregnant while they are taking Erivedge or during the 2 months after their final dose.

Educational material

In order to assist treating physicians and patients in avoiding fetal exposure to vismodegib the Marketing Authorisation Holder provides informational material to reinforce the warning against the teratogenicity and embryotoxicity of vismodegib, advise on contraception before starting treatment and provide guidance on the need for pregnancy testing:

- Patient information brochure "Erivedge® Pregnancy Prevention Programme: Information brochure for patients taking Erivedge®"
- Patient reminder card
- Physician information brochure "Erivedge® Pregnancy Prevention Programme: Information brochure for physicians prescribing Erivedge®"
- Physician and health care provider reminder card
- Counselling attestation form with patient's informed consent

Physicians must fully inform all patients, both male and female, about the teratogenic risk and strict contraceptive measures as described in the Pregnancy Prevention Programme. In doing so, physicians must ensure that:

- The patient confirms by their informed consent on the counselling attestation form that they meet the above preconditions
- Female patients are ready and able to comply with effective contraceptive measures during treatment and for 24 months after taking the last dose
- Pregnancy tests with negative results were performed and duly documented within 7 days before and monthly during treatment

- Male patients are ready and able to use condoms with spermicide (if available) in sexual intercourse with women during treatment and for 2 months after taking the last dose.

Prescribing and dispensing restrictions

Prescriptions of Erivedge for women of child-bearing potential should be limited to 28 days of treatment. Continuation of treatment requires a new prescription. The initial prescription and dispensing of Erivedge should occur within 7 days of a negative pregnancy test.

Fertility

Preclinical data indicate that fertility can be irreversibly compromised by Erivedge (see Preclinical data).

Effects on postnatal development

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

Nursing women

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. Patients should not breast-feed for 24 months after the last dose of Erivedge treatment.

Blood donors

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

Interactions

Vismodegib is a weak in-vitro inhibitor of CYP2C8 and CYP2C9. No in-vivo interaction has been found with rosiglitazone (a CYP2C8 substrate) or oral contraceptives (ethinylestradiol and norethisterone).

Vismodegib does not inhibit P-glycoprotein (P-gp). Nor does vismodegib induce CYP1A2, 2B6 or 3A4/5 in human hepatocytes or bind strongly to PXR.

Vismodegib is a substrate of CYP2C9 and CYP3A4.

Pregnancy and lactation

Pregnancy

Erivedge is contraindicated in pregnant women (see Contraindications). If administered to a pregnant woman vismodegib may lead to the death of the embryo/fetus or cause congenital malformations. Women of child-bearing potential must use two reliable methods of contraception during treatment and for 24 months thereafter.

No adequate or well-controlled studies on the use of Erivedge have been performed in pregnant women. Vismodegib has proved embryotoxic and teratogenic in animal studies. Given the key role of the Hedgehog signalling pathway in embryogenesis and the known effects of vismodegib on pre- and postnatal development (see Preclinical data), patients of child-bearing potential should be instructed not to become pregnant during treatment with Erivedge or for 24 months thereafter. Women of child-bearing potential must undertake to use two acceptable methods of contraception (including an acceptable barrier method with spermicide, where available) during treatment with Erivedge and for 24 months thereafter (see Warnings and precautions). Acceptable methods of primary contraception (if medically appropriate) are: combined hormone contraception, subcutaneous hormonal implants, hormone patches, hormone contraceptives (levonorgestrel-releasing intrauterine system, depot medroxyprogesterone acetate), tubal sterilisation, vasectomy and intrauterine devices (IUD). Acceptable methods of secondary contraception (barrier methods) are: any male condoms (with spermicide, where available) or diaphragms (with spermicide, where available). If a patient becomes pregnant, her menstrual period is delayed or she suspects for other reasons that she may be pregnant, she must inform her treating physician and discontinue Erivedge treatment immediately.

Lactation

It is not known whether vismodegib is eliminated in breast milk. Given its potential for causing severe developmental defects in breast-fed infants and small children Erivedge is contraindicated in nursing mothers. Patients should not breast-feed for 24 months after the last dose of Erivedge therapy (see Contraindications).

Effects on ability to drive and use machines

No studies have been performed of the effects on the ability to drive and use machines. Because of adverse effects such as nausea and vomiting, however, caution is advised with regard to driving and using machines.

Undesirable effects

The safety of Erivedge has been studied in clinical trials in > 450 patients and healthy volunteers. The data listed below derive from 138 patients with advanced basal cell carcinoma receiving at least one dose of vismodegib ≥ 150 mg in four open single-arm Phase I and II monotherapy studies. In the clinical studies doses > 150 mg did not result in higher plasma levels; patients with doses > 150 mg were included in the analysis.

Adverse effects observed in the clinical studies were sorted by organ class and frequency and classified into the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100).

Metabolism and nutrition disorders

Very common: Decreased appetite 30% (Grade 3: 2%)

Common: Dehydration

Nervous system disorders

Very common: Dysgeusia 55%, ageusia 15%

Common: Hypogeusia

Gastrointestinal disorders

Very common: Nausea 30% (Grade 3: <1%), diarrhea 29% (Grade 3: <1%), constipation 21%, vomiting 14%

Common: Abdominal pain

Skin and subcutaneous tissue disorders

Very common: Alopecia 64%

Musculoskeletal system disorders

Very common: Muscle cramps 72% (Grade 3: 4%)

Common: Musculoskeletal pain

Reproductive system and breast disorders

Very common: Amenorrhea 30% (ten of the 138 patients with advanced basal cell carcinoma were women of child-bearing potential. Three of these patients [30%] developed amenorrhea on treatment)

General disorders

Very common: Fatigue 40% (Grade 3: 5%, Grade 4: <4%)

Investigations

Very common: Weight loss 45% (Grade 3: 7%)

Common: Changes in laboratory parameters (Grade 3): decreased serum sodium, decreased serum potassium and increased serum urea

Overdosage

Standard measures should be taken in overdosage.

Properties and effects

ATC code: L01XX43

Mechanism of action and pharmacodynamics

Vismodegib is an inhibitor of the Sonic Hedgehog (SHH) signalling pathway. When SHH binds to Patched it activates Smoothened and initiates an intracellular signal. Vismodegib inhibits this signal.

QT study

There was no effect of therapeutic doses of vismodegib on the QTc interval. In a randomized, double-blind, placebo- and positive-controlled, parallel-group QTc study,

healthy subjects were administered vismodegib 150 mg every 24 hours for 7 days, placebo and a single oral dose of moxifloxacin. Similarly, vismodegib had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Clinical efficacy

An international, single-arm, multi-centre, open-label, 2-cohort pivotal study was conducted in 104 patients with advanced basal cell carcinoma (BCC), including patients with 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, 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 lesion and met inclusion criteria were eligible to participate in the study. Patients were treated with oral daily dosing of vismodegib 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 metastatic disease (mBCC) and 68% of patients had locally advanced BCC (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 the objective response rate (ORR) as assessed by an independent review facility (IRF). Objective response was defined as a complete or partial response determined on two consecutive assessments separated by at least four weeks.

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 target lesion size (sum of the longest diameter [SLD]) from baseline by radiographic assessment;

(2) $\geq$ 30% reduction in SLD from baseline in externally visible dimension of target lesions;

(3) complete resolution of ulceration in all target lesions.

For mBCC, the response rate was 30.3% (10/33) and median duration of response 7.6 months (95% CI: 5.62, not estimable). The majority of responses occurred by week 8. Median PFS was 9.5 months (95% CI: 7.36, not estimable). The median OS has not been reached (95% CI: 13.86, not estimable).

For laBCC, the response rate was 42.9% (27/63) and median duration of response 7.6 months (95% CI: 5.65, not estimable). The majority of responses occurred by week 8; 54% of patients had a histopathological response with no evidence of BCC at 24 weeks. Median PFS was 9.5 months (95% CI: 7.39, 11.93) by IRF. The median OS has not been reached (95% CI: 17.61, not estimable).

Pharmacokinetics

Absorption

The single dose absolute bioavailability of vismodegib is 31.8%. Bioavailability is unaffected by food. The pharmacokinetics are not dose-proportional.

Distribution

The volume of distribution ranges from 16.4 to 26.6 l. Binding to plasma proteins (human serum albumin and alpha-1-acid glycoprotein) is high (99%).

Metabolism

Vismodegib is slowly metabolised. Vismodegib is the main component in plasma (98%). Metabolic pathways of vismodegib in humans include oxidation, glucuronidation and cleavage of the pyridine ring. CYP2C9 and CYP3A4/5 are involved in producing the two most abundant oxidative metabolites recovered in feces.

Elimination

The terminal elimination half-life is 12 days.

82% of the administered dose is recovered in the feces and 4.4% in the urine.

Pharmacokinetics in special patient groups

Elderly patients

There is limited data in elderly patients. Population PK analysis suggests that age has no clinically significant impact on steady-state concentrations of vismodegib.

Children and adolescents

There is no data in pediatric patients.

Renal and hepatic impairment

There is only insufficient data in patients with renal or hepatic impairment. Based on population PK analysis of combined data from five 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.

Preclinical data

Carcinogenicity

Dedicated studies to evaluate the carcinogenicity of vismodegib have not been performed. However, pilomatricoma (a benign subcutaneous neoplasm) was observed in

rats treated with vismodegib. Pilomatricoma has not been reported in clinical trials with vismodegib, and the relevance of this finding to patients is therefore uncertain.

Mutagenicity

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 micronucleus assay.

Fertility

Dedicated studies to assess the potential of vismodegib to affect fertility have not been performed. Data from animal studies in rats and dogs suggest, however, that male and female fertility may be impaired by treatment with vismodegib.

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 relative percent decrease in 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.

Teratogenicity

In an embryofetal development study in which pregnant rats were administered vismodegib daily during organogenesis, vismodegib crossed the placenta and was severely toxic to the conceptus. Malformations, including craniofacial anomalies, open perineum, and absent and/or fused digits, were observed in foetuses of dams treated with 10 mg/kg/day (corresponding to an $AUC_{0\text{-}24h}$ exposure 20% of that at the recommended human dose). The incidence of foetal retardations or variations and incomplete or unossified sternal elements, centra of cervical vertebrae, or proximal phalanges and claws was also increased at the dose of 10 mg/kg/day. Vismodegib was embryolethal at doses ≥ 60 mg/kg/day (corresponding to an $AUC_{0\text{-}24h}$ exposure 2.8-fold greater than that at the recommended human dose).

Other

Findings in toxicity studies with vismodegib indicate 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 hemorrhage) and closure of the epiphyseal growth plate.

Neurological 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.

Toxicity studies of vismodegib also revealed a reduced number of taste buds in rats and alopecia in rats and dogs. Both changes reversed on treatment withdrawal.

Additional information

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Disposal

Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Special storage instructions

Do not store above 30°C.

Packs

Capsules 150 mg 28

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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