Erivedge®▼ Pregnancy Prevention Programme:
(vismodegib)

Information for healthcare professionals prescribing Erivedge

Erivedge is contraindicated in:

- Patients with hypersensitivity to the active substance or to any of the excipients.
- Women who are pregnant or breast-feeding.
- Women of childbearing potential (WCBP) who do not comply with the Erivedge Pregnancy Prevention Programme.
- Coadministration of St. John's wort *(Hypericum perforatum)*.

Erivedge may cause embryo-foetal death or severe birth defects when administered to a pregnant woman. Hedgehog pathway inhibitors, such as vismodegib have been demonstrated to be embryotoxic and/or teratogenic in multiple animal species and can cause severe malformations, including craniofacial anomalies, midline defects and limb defects. Erivedge must not be used during pregnancy.

For comprehensive safety information please see accompanying Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL).

This booklet is produced by Roche Products Ltd.

Contents

1. Introduction

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*

The recommended dose is one 150 mg capsule taken once daily.

Please familiarise yourself with the complete Summary of Product Characteristics (SmPC) before prescribing Erivedge. This brochure contains only a summary of some of the most important information about the risks of teratogenicity associated with Erivedge.

The Erivedge Pregnancy Prevention Programme (PPP) is designed to provide information and support to healthcare professionals and patients concerning the safe and appropriate use of Erivedge in regards to teratogenicity.

1. Introduction

1.1. Prescriber's role in the Erivedge Pregnancy Prevention Programme

As a prescriber, your role is to:
Educate patients about the risks of teratogenicity associated with exposure to Erivedge during pregnancy.
Where appropriate, provide contraceptive counselling to your patients or ensure they receive such counselling by an appropriate specialist.
Ensure all patients complete and sign the Erivedge Verification of Counselling Form.
Ensure that patients who are women of childbearing potential have a negative medically supervised pregnancy test within 7 days prior to initiating treatment, and have monthly medically supervised pregnancy tests during treatment.
Ensure that patients who are women of childbearing potential, prescriptions of Erivedge should be limited to 28 days of treatment. Continuation of treatment requires a new prescription.
Ensure that patients who are of childbearing potential are able to comply with contraceptive measures during Erivedge treatment and for 24 months after their final dose.
Since Erivedge is contained in semen, every male patient must understand the risks to the unborn child and use condoms (with spermicide if available) even if he has had a vasectomy, during sex with female partners whilst on treatment and for 2 months after their final dose, to prevent exposure to Erivedge.
Provide to your patient the brochure "Erivedge Pregnancy Prevention Programme: Important information for men and women taking Erivedge about pregnancy prevention and contraception", which contains information and advice about taking Erivedge, and a "Patient Reminder Card".
Complete the survey for this patient in the HCP web portal **www.erivedge-ppp.com.mt**
Report immediately any pregnancies to Roche using the "Roche Pregnancy Report Form".
Refer the patient to a specialist obstetrician in the event of pregnancy.

Please refer to the Erivedge Summary of Product Characteristics and Patient Information Leaflet for additional important safety information.

2. IMPORTANT RISK INFORMATION

2.1. Biological mechanisms of teratogenic risk

The Hedgehog (Hh) pathway plays an essential, highly conserved role in regulating cell fate specification, cell proliferation, and cell survival during embryonic development. Expression of the hedgehog pathway component *Sonic hedgehog (Shh)* has been localised to several embryonic structures, including the notochord, neural tube floorplate, limb buds, and embryos from mice deficient in *Shh* exhibited severe malformations consistent with defective neural patterning and notochord maintenance, repression of the notochord-derived signal required for development of the axial skeleton, patterning during limb outgrowth, and failure to establish the ventral midline and spinal cord (Chiang *et al.* 1996)[1].

Consistent with those findings, treatment of pregnant rats with vismodegib throughout organogenesis resulted in a 100% incidence of embryolethality at clinically relevant exposures. At subclinical exposures that did not result in embryolethality, vismodegib administration induced a variety of malformations, including missing and/or fused digits, open perineum and craniofacial anomalies, and retardations or variations (including dilated renal pelvis, dilated ureter, and incompletely or unossified sternal elements, centra of vertebrae, or proximal phalanges and claws). Treatment of pregnant mice with other small-molecule inhibitors of the Hh signalling pathway during a portion of organogenesis resulted in embryos with a spectrum of craniofacial and brain defects, including but not limited to cleft lip and palate or holoprosencephaly (Lipinski *et al.* 2010)[2].

2.2 Women of childbearing potential (WCBP)

Erivedge is contraindicated in WCBP who do not comply with the Erivedge Pregnancy Prevention Programme.

A WCBP is defined in the Erivedge Pregnancy Prevention Programme as a sexually mature female who:

- has menstruated at any time during the previous 12 consecutive months
- has not undergone a hysterectomy or a bilateral oophorectomy, or who does not have medically-confirmed permanent premature ovarian failure
- does not have a XY genotype, Turner's syndrome, or uterine agenesis
- becomes amenorrhoeic following cancer therapy, including treatment with Erivedge

WCBP should not start taking Erivedge unless:

- they have a negative pregnancy test, conducted by a healthcare professional within 7 days before starting Erivedge treatment
- they agree and are able to comply with the terms of the Erivedge Pregnancy Prevention Programme, and will use recommended contraception during Erivedge treatment and for 24 months after their final dose

References:
1. Chiang C, *et al.* Cyclopia and defective axial patterning in mice lacking Sonic Hedgehog gene function. *Nature* 1996;**383**:407–413.
2. Lipinski RJ, Song C, Sulik KK, *et al.* Cleft lip and palate results from Hedgehog signaling antagonism in the mouse: Phenotypic characterization and clinical implications. *Birth Defects Res A Clin Mol Teratol* 2010;**88**:232–40.

2. IMPORTANT RISK INFORMATION

It is important that WCBP are counselled about the importance of recommended contraception, and the avoidance of pregnancy. Unless they commit to not having sexual intercourse (abstinence), they must use 2 recommended forms of birth control at the same time, one of which must be a barrier method.

2.2.1 Recommended methods of contraception

Recommended forms of contraception

Patients must use **2** forms of contraception.
Patients must use **1** form of contraception from **each** of the columns below.

Barrier methods		Highly effective forms of contraception
• male condom with spermicide **OR** • diaphragm with spermicide	**AND**	• hormonal depot injection **OR** • intrauterine device ("the coil" or IUD) **OR** • tubal sterilisation **OR** • vasectomy

Patients should be individually counselled about which contraception method is most appropriate for them.

If you have any doubt about a patient's childbearing potential, or what contraceptive advice to give her, seek expert advice from an appropriate specialist.

Remind your patients of the importance of recommended contraception, and adherence to the terms of the Erivedge Pregnancy Prevention Programme, during treatment and for 24 months after their final dose.

Monitor your patient's pregnancy status monthly during therapy with a medically supervised pregnancy test conducted by a healthcare professional, even if she is/or becomes amenorrhoeic.

Pregnancy tests should be performed within 7 days prior to initiating treatment and monthly during treatment.

Pregnancy tests should have a minimum sensitivity of 25 mIU/mL as per local availability. Patients who present with amenorrhoea during treatment with Erivedge should continue pregnancy testing.

For WCBP, prescriptions of Erivedge should be limited to 28 days of treatment and continuation of treatment requires a new prescription.

2.3. Male patients

Erivedge is transferred and contained in semen. To avoid potential foetal exposure during pregnancy, a male patient 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. It is also important that the female partner uses contraception to avoid pregnancy. Men must not donate semen while taking Erivedge and for 2 months after their final dose.

2.4. Pregnancy and Erivedge

If a woman becomes pregnant while taking Erivedge and for 24 months after her final dose, or becomes pregnant while her male sexual partner is taking Erivedge and for 2 months after his final dose:

- you should ask your patient to notify her healthcare professional immediately, stop taking Erivedge, and receive further evaluation and counselling from a specialist obstetrician
- you should report the pregnancy immediately to Roche UK Drug Safety using the "Roche Pregnancy Report Form" (Section 4)

Women who miss a menstrual period or think that they may be pregnant should be directed to talk to their healthcare professional as soon as possible for evaluation and counselling and stop taking Erivedge.

2.5. Healthcare professional (HCP) web portal (www.erivedge-ppp.com.mt)

Complete the survey for all new patients via the HCP web portal.
Login: hcpportal
Password: erivedge

2.6. Fertility

Dedicated nonclinical studies to assess fertility have not been performed. However, data from animal studies suggest that male and female fertility may be irreversibly compromised by treatment with Erivedge. Additionally, amenorrhoea has been observed in clinical trials in WCBP. Fertility preservation strategies should be discussed with WCBP and male patients prior to starting treatment with Erivedge.

2.7. Additional safety information

Tell all patients that they should:

- not donate blood while taking Erivedge and for 24 months after their final dose
- never give this medicinal product to another person
- keep their medication out of the sight and reach of children
- dispose of any unused capsules at the end of treatment (if applicable, e.g. by returning the capsules to their pharmacist or healthcare professional)

Tell female patients of childbearing potential that, while they are taking Erivedge and for 24 months after their final dose they must:

- not become pregnant
- not have unprotected sex. They should use 2 forms of recommended contraception at the same time
- not breast-feed

Tell male patients that, while they are taking Erivedge and for 2 months after their final dose, they should:

- not have unprotected sex with female partners
- use condoms (with spermicide, if available) even after a vasectomy
- not donate semen

▼ This medicinal product is subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse reaction should be reported. Report forms can be found at **www.medicinesauthority.gov.mt/adrportal** and sent by email to postlicensing.medicinesauthority@gov.mt or posted to ADR Reporting, The Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554.

3. Healthcare professional reminder card

Roche

4. Roche pregnancy report form

RO-GNE: PREGNANCY REPORT FORM

FOR ROCHE USE ONLY

Roche Received Date *(dd-MMM-yyyy)*: _____ Local No: _____ MCN: _____

Report Type: ☐ Prospective ☐ Retrospective

1. REPORTER INFORMATION

☐ Initial ☐ Follow-up

Reporter Name: _____

Type: ☐ Physician *(Specialty)*: _____

☐ Pharmacist ☐ Consumer ☐ Other *(Specify)*: _____

Contact Address: _____

_____ Postal/zip Code: _____

Telephone Number: _____ Fax Number: _____

E-mail: _____

2. EXPOSED PARENT'S DETAILS

Who was exposed: ☐ Father ☐ Mother

Initials: _____ Date of Birth *(dd-MMM-yyyy)*: _____

Height: _____ ☐ inch ☐ cm

Weight: _____ ☐ lb ☐ kg

Age at Conception: _____ Postal Code *(France only)*: _____

Ethnic origin: ☐ Black ☐ Caucasian ☐ Hispanic ☐ Asian ☐ Other *(Specify)*: _____

3. PRODUCT INFORMATION

(Enter all relevant medications taken before (up to 24 months for Erivedge® female treated patients), and during pregnancy or if the father exposed enter medications taken prior to conception or up to 2 months after the last dose of Erivedge).

	Product Name *(Generic/Trade)*	**Suspect**	**Lot/Batch #**	**Time of Exposure** *(× as applicable)*					**Route**	**Strength & Formulation** *(mg, cap, tab)*
				Preconception	**Trimester** 1	2	3	**Delivery**		
1.	_____	☐	_____	☐	☐	☐	☐	☐	_____	_____
2.	_____	☐	_____	☐	☐	☐	☐	☐	_____	_____
3.	_____	☐	_____	☐	☐	☐	☐	☐	_____	_____
4.	_____	☐	_____	☐	☐	☐	☐	☐	_____	_____
5.	_____	☐	_____	☐	☐	☐	☐	☐	_____	_____

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3. PRODUCT INFORMATION

	Dosage Regimen	Start Date *(dd-MMM-yyyy)*	Stop Date *(dd-MMM-yyyy)*	Ongoing	Indication for Use
1.				☐	
2.				☐	
3.				☐	
4.				☐	
5.				☐	

4. PREGNANCY INFORMATION

LMP Date: last menstrual period *(dd-MMM-yyyy)*: _____ ☐ Est

Conception Date *(dd-MMM-yyyy)*: _____ ☐ Est

Estimated Date of Delivery *(dd-MMM-yyyy)*: _____ ☐ Est

5. MEDICAL HISTORY

Contraception *(may choose more than one)*

☐ None ☐ IUD ☐ Condom ☐ Spermicide ☐ Withdrawal

☐ Diaphragm ☐ Rhythm ☐ Infertility *(Female)* ☐ Infertility *(Male)* ☐ Unknown

☐ Surgical sterilization *(Male)* ☐ Surgical sterilization *(Female)*

☐ Contraceptive medication *(Please specify in Section 3 on page 9)*

Number of previous

_____ Pregnancies _____ Stillbirth _____ Spontaneous Abortions

_____ Therapeutic Abortions _____ Deliveries _____ Babies born with defects

Risk Factors/Medical History ***(*specify below)***

☐ Unknown ☐ Alcohol ☐ Smoking

☐ **Diabetes*** ☐ **Infection*** ☐ **Allergies***

☐ Drug abuse ☐ Other/relevant history

Details *(include dates & outcome as applicable)*: _____

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6. PREGNANCY OUTCOME

☐ Ongoing ☐ Ectopic pregnancy ☐ Spontaneous abortion

☐ Unknown ☐ Live birth ☐ Stillbirth

☐ Therapeutic abortion ☐ Lost to follow-up

Provide date if applicable *(dd-MMM-yyyy)*: _____

7. RELEVANT LABORATORY TESTS/PROCEDURES PRE AND POST OUTCOME

(e.g. Amniocentesis, ultrasound)

	Tests	Results *(Units and normal values if applicable)*	Pending	Pre/Post outcome?	Date *(dd-MMM-yyyy)*
1.			☐	*Pre* ☐ *Post* ☐	
2.			☐	*Pre* ☐ *Post* ☐	
3.			☐	*Pre* ☐ *Post* ☐	

Further details: _____

8. BIRTH OUTCOME

Infant/Foetal Outcome:

Number of infants/foetuses: _____

(in the event of more than 1 infant/foetus, complete Infant Information sections 8–11 on a separate form)

☐ Normal

☐ Abnormal *(birth defects/congenital abnormalities and other events experienced by the foetus/baby)*

Specify: _____

☐ Unknown

☐ Death Date *(dd-MMM-yyyy)*: _____ Cause of death: _____

Autopsy results: _____

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9. INFANT INFORMATION

Gender:	**Weight:**	**Length:**	**Head circumference:**
☐ Male	☐ _____ lb	☐ _____ inch	☐ _____ inch
☐ Female	☐ _____ kg	☐ _____ cm	☐ _____ cm

Gestational age at delivery/abortion *(weeks)*: _____

Apgar scores: 1 minute _____ 5 minutes _____ 10 minutes _____

Were there any unusual features about the pregnancy or its outcome?

☐ Yes ☐ No

If yes, specify: _____

_____

_____

Follow-up examination of the child:

Date *(dd-MMM-yyyy)*: _____

Findings: _____

_____

_____

Paediatrician *(in case of referral)*; Name: _____

Address: _____

_____ Postal/zip Code: _____

Telephone Number: _____ Fax Number: _____

E-mail: _____

RO-GNE: PREGNANCY REPORT FORM

FOR ROCHE USE ONLY

Roche Received Date *(dd-MMM-yyyy)*: _____ Local No: _____ MCN: _____

Report Type: ☐ Prospective ☐ Retrospective

10. RELEVANT LABORATORY TESTS/PROCEDURES FOR BABY/FOETUS

	Tests	**Results** *(Units and normal values if applicable)*	**Pending**	**Date** *(dd-MMM-yyyy)*
1.				
2.				
3.				
4.				

11. ADDITIONAL INFORMATION *(continue on optional supplementary form if necessary)*

_____

_____

_____

Reporter Signature: _____ **Date** *(dd-MMM-yyyy)*: _____

Contact name for further information on pregnancy *(if different from Reporter)*:

_____

Contact Address: _____

_____ Postal/zip Code: _____

Telephone Number: _____ Fax Number: _____

E-mail: _____

If completed by Roche delegate, ensure the data completed reflects the reporter's opinion

FOR ROCHE USE ONLY

Signature: _____ **Print Name:** _____

Date *(dd-MMM-yyyy)*: _____

RO-GNE: PREGNANCY REPORT FORM OPTIONAL SUPPLEMENTARY INFORMATION FORM

FOR ROCHE USE ONLY

Roche Received Date *(dd-MMM-yyyy)*: _____ Local No: _____ MCN: _____

Report Type: ☐ Prospective ☐ Retrospective

ADDITIONAL INFORMATION *(Optional)*:

Signature: _____ **Date** *(dd-MMM-yyyy)*: _____

Marketing authorisation holder: Roche Registration Ltd, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom. Erivedge is a registered trademark.

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