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Erivedge® Pregnancy Prevention Programme: Information for Healthcare Providers prescribing Erivedge®

Erivedge® is contraindicated in

- Patients with hypersensitivity to the active substance or to any of the excipients.
- Women who are pregnant or breastfeeding,
- Women of childbearing potential 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 Prescribing Information (PI) and Patient Leaflet (PL).

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1. INTRODUCTION:

Erivedge is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

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

Please familiarise yourself with the complete Prescribing Information (PI) 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 providers and patients concerning the safe and appropriate use of Erivedge® in regards to teratogenicity.

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.
Provide contraceptive counselling to your patients or ensure they receive such counselling by an appropriate specialist.
Ensure that patients who are women of childbearing potential have a negative medically supervised pregnancy test within a maximum of 7 days prior to initiating treatment, and have monthly medically supervised pregnancy tests during treatment (day of pregnancy test=day 1)
Ensure that patients who are women of childbearing potential, prescriptions of Erivedge should be limited to 28 days of treatment and continuation of treatment requires a new prescription.
Ensure that patients who are of childbearing potential are able of complying 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 during treatment and for 2 months after final dose**,** to prevent exposure to Erivedge®.
Ensure that patients must not donate blood while taking Erivedge® and for 24 months after their final dose
Ensure that female patients must not breast-feed while taking Erivedge and for 24 months after the final dose
Provide to your patient the brochure "Erivedge® Pregnancy Prevention Programme: Information for patients taking Erivedge®", which contains information and advice about taking Erivedge®, and includes a "Patient Reminder Card".
Report any pregnancies to Roche

Refer the patient to a specialist physician in the event of pregnancy
Report any suspected adverse events to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il or by email (adr@MOH.HEALTH.GOV.IL).

Please refer to the Erivedge® Prescribing Information and Patient Leaflet for additional important safety information.

2. IMPORTANT RISK INFORMATION:

2.1 BIOLOGICAL MECHANISMS AND TERATOGENIC RISK

The Hedgehog 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). 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 signaling 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 WOMEN OF CHILDBEARING POTENTIAL

Erivedge is contraindicated in women of childbearing potential (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®.

Women of childbearing potential should not start taking Erivedge® unless:

- they have a negative pregnancy test, conducted by a healthcare provider within a maximum of 7 days before starting Erivedge® treatment (day of pregnancy test=day 1)
- 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.

2.2.1 Recommended methods of contraception:

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.

<table>
<tr><th colspan="3">Recommended forms of contraception</th></tr>
<tr><td colspan="3">Patients must use 2 forms of contraception.
Patients must use 1 form of contraception from each of the columns below.</td></tr>
<tr><td>Barrier methods</td><td rowspan="2">and</td><td>Highly effective forms of contraception</td></tr>
<tr><td>• Male condom with spermicide OR
• Diaphragm with spermicide</td><td>• Hormonal depot injection OR
• Intrauterine device (IUD) OR
• Tubal sterilisation OR
• Vasectomy</td></tr>
<tr><td colspan="3">Patients should be individually counselled about which contraception method is most appropriate for them.</td></tr>
</table>

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 HCP, even if she is and/or becomes amenorrhoeic. Pregnancy test should be performed within a maximum of 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 amenorrhea 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.

2.2.2 Men:

Vismodegib is 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.
Men must not donate sperm while taking Erivedge® and for 2 months after their final dose.

2.3 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 physician immediately, stop taking Erivedge®, and receive further evaluation and counselling from a specialist obstetrician
- You should report the pregnancy to Roche Drug Safety: Israel.DrugSafety@roche.com, phone: 09-9737722, Fax: 09-9737736

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

2.4 FERTILITY:

Human female fertility may be compromised by treatment with Erivedge®. Reversibility of fertility impairment is unknown. Additionally, amenorrhea has been observed in clinical trials in WCBP. Fertility preservation strategies should be discussed with WCBP prior to starting treatment with Erivedge®.

Fertility impairment in human males is not expected.

2.5 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 in accordance with local requirements. *(if applicable, e.g. by returning the capsules to their pharmacist or physician)*.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

Or to Roche Affiliate Safety Reporting contact information:
Israel.DrugSafety@roche.com, Phone: 09-9737722 Fax: 09-9737736