Roche Products (Ireland) Limited
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Important additional warnings for hemorrhage and rhabdomyolysis with Cotellic™ ▼ (cobimetinib), including new dose modification recommendations

Dear Healthcare professional,

Roche Products (Ireland) Limited, in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA) would like to inform you of two additional warnings for Cotellic, including associated dose modification recommendations:

Severe Haemorrhage

- Severe haemorrhagic events, including intracranial and gastrointestinal tract bleeds have been reported in patients receiving Cotellic in clinical trials and post-marketing.
- Cotellic treatment should be interrupted in the event of grade 3 or 4 bleeding events and should not be restarted after grade 4 events or cerebral haemorrhage attributed to Cotellic. Clinical judgement should be applied when considering restarting treatment after grade 3 bleeds. Vemurafenib dosing can be continued if indicated when Cotellic is interrupted.
- Cotellic should be used with caution when given to patients with additional risk factors for bleeding, such as brain metastases, and/or concomitant medications that increase the risk of bleeding (such as antiplatelet and anticoagulant therapy).

Rhabdomyolysis and Creatine Phosphokinase (CPK) Elevations

- Rhabdomyolysis and CPK elevations have been reported in patients receiving Cotellic in clinical trials and post-marketing.
- Baseline serum CPK and creatinine levels should be measured before starting treatment, and then monitored monthly during treatment or as clinically indicated. If serum CPK is elevated, check for signs and symptoms of rhabdomyolysis or other causes.

- If grade ≤3 asymptomatic CPK elevation occurs and rhabdomyolysis has been ruled out, Cotellic dosing does not need to be modified.
- Cotellic treatment should be interrupted if rhabdomyolysis, any symptomatic CPK elevation, or grade 4 asymptomatic CPK elevation occur.
    - If they do not improve within 4 weeks, Cotellic should not be restarted.
    - If severity improves by at least one grade within 4 weeks, Cotellic may be restarted under close monitoring, with the previous dose reduced by 20 mg.
    - Vemurafenib dosing can be continued during any changes to Cotellic dosing.

You are advised to discuss the risks that may be associated with Cotellic therapy with patients and their caregivers.

Background on Haemorrhage Events

Haemorrhage is a known adverse drug reaction for Cotellic. An analysis of post-marketing safety reports and ongoing clinical trials has identified additional severe haemorrhagic events in patients receiving Cotellic. At the time of the analysis, a total of thirty cases of severe haemorrhage have been reported from an estimated 2,817 patients exposed to Cotellic. Events include intracranial and gastrointestinal tract bleeds. In most cases of severe haemorrhage, the patients had additional risk factors for bleeding, such as central nervous system metastasis, pre-existing gastrointestinal disorders, and/or concomitant medications that increase the risk of bleeding, such as antiplatelet or anticoagulant therapy.

Background on Rhabdomyolysis and Elevated CPK Events

Rhabdomyolysis was initially reported in one patient in each treatment arm of study GO28141 (Cotellic plus vemurafenib vs placebo plus vemurafenib). Since that time, additional cases of rhabdomyolysis have been reported in the post-marketing setting and in other ongoing clinical trials.

Further information

Cotellic is indicated for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

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No. 214337

Call for reporting

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

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.

Healthcare professionals are asked to report any suspected adverse reactions in accordance with the national spontaneous reporting system: HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie.

Adverse events should also be reported to the Drug Surveillance Centre in Roche Products (Ireland) Limited by mail, telephone (01-4690700), fax (01-4690793) or email (Ireland.drug_surveillance_centre@roche.com).

Company contact point

Should you have any questions regarding the use of Cotellic, please feel free to contact us at:

Roche Medical Information by mail, telephone (01-4690700), fax (01-4690791) or email (ireland.druginfo@roche.com).

Full prescribing information for Cotellic is available via:

- www.medicines.ie
- www.ema.europa.eu
- www.hpra.ie

Please distribute this communication further within your team.

Yours sincerely,

Dr. Michal Starnawski
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