THE EU RISK MANAGEMENT PLAN FOR COBIMETINIB / COTELLIC®

Active substance (INN or common name):	Cobimetinib
Pharmaco-therapeutic group (ATC Code):	L01XE38
Name of Marketing Authorization Holder or Applicant:	Roche Registration Ltd.
Number of medicinal products to which this RMP refers:	One
Product concerned (brand name):	Cotellic

Data lock point for current RMP: 23 August 2016

Version number: 3.2

Date of final sign off:

VI.2 Elements for a Public Summary

VI.2.1. OVERVIEW OF DISEASE EPIDEMIOLOGY

Cotellic is a medicine which contains the active substance cobimetinib. It is used to treat melanoma (a type of skin cancer) that has metastasised (spread to other parts of the body) or cannot be surgically removed. Cotellic is given to patients whose melanoma has the BRAF V600 mutation and must be used with the medicine vemurafenib.

The number of people diagnosed with this cancer is increasing worldwide. In 2012, around 82,750 new melanomas occurred in 28 European countries. In about 6 out of 100 newly diagnosed cases, the melanoma is inoperable or has metastasised. This suggests that newly diagnosed inoperable or metastatic melanomas in these 28 European countries number close to 5,000 per year.

VI.2.2 SUMMARY OF BENEFITS

Cotellic has been studied in one main study involving 495 patients with melanoma that had spread or that could not be surgically removed, and whose melanoma had a BRAF V600 mutation. Patients had not been previously treated and were given either Cotellic with vemurafenib or placebo (a dummy treatment) with vemurafenib; the main measure of effectiveness was how long patients lived without their disease getting worse (progression-free survival). In this study, adding Cotellic to vemurafenib was more effective than adding placebo to vemurafenib: it took on average 12.3 months before the disease got worse in patients given Cotellic, compared with 7.2 months in patients given placebo.

VI.2.3 UNKNOWNS RELATING TO TREATMENT BENEFITS

There is limited information on the effectiveness of Cotellic in combination with vemurafenib in the following groups of patients:

- Children (patients under 18 years of age)
- Patients who are not white (non-Caucasian)
- Patients requiring long-term use of Cotellic
- Patients with severe kidney problems
- Patients with liver problems

VI.2.4 SUMMARY OF SAFETY CONCERNS

IMPORTANT IDENTIFIED RISKS

Risk	What is known	Preventability
Ocular events (e.g., retinal detachment) related to serous retinopathy (fluid accumulation within the layers of the retina, the back of the eye which is responsible for sight).	Ocular events related to serous retinopathy have been observed in patients treated with Cotellic or other medicines of the same class.	While this risk cannot be prevented, it can be mitigated if patients immediately report any visual disturbances to their doctor. The risk can be managed with treatment interruption, dose reduction or treatment discontinuation as described in the medicine's product information.
Left ventricular dysfunction (including decreased LVEF and cardiomyopathy) (a type of heart problem that occurs when the heart's ability to pump blood to the body is decreased)	Left ventricular dysfunction has been observed in patients treated with Cotellic or other medicines of the same class.	While this risk cannot be prevented, it can be mitigated by measuring heart function in the patient before treatment starts, monitoring heart function during treatment and by following the instructions included in the medicine's product information, for patients who experience a left ventricular dysfunction.
Photosensitivity (sunburn)	Photosensitivity has been observed in patients treated with Cotellic in combination with vemurafenib.	For patients being treated with Cotellic in combination with vemurafenib, photosensitivity is preventable by avoiding exposure to the sun. When outdoors, the patient may protect themselves against sunburn by using of protective clothing, broad spectrum UVA/UVB sunscreen and sun-protective lip balm (SPF 30). The product information for Cotellic and vemurafenib provide dose modification recommendations to mitigate this effect.
Diarrhoea	Diarrhoea has been observed in patients treated with Cotellic or other medicines of the same class.	For patients receiving Cotellic plus vemurafenib, monitoring, early identification, and management of diarrhoea (by dose modification and/or antidiarrhoeal agents) should help to protect against negative effects. Patients should report the occurrence of diarrhoea to their doctor so they may be appropriately treated.
Pneumonitis (inflammation of the lungs that may cause difficulty breathing, and can be life-threatening)	Inflammation of the lungs has been observed in some patients treated with Cotellic or other medicines of the same class.	While this risk cannot be prevented, it can be mitigated if patients immediately report any difficulty breathing to their doctor.
Rhabdomyolysis (muscle damage)	Elevated blood levels of creatine phosphokinase (a muscle enzyme, which may	While this risk cannot be prevented, it can be mitigated by measuring serum CPK and creatinine levels in the patient before treatment starts, and then monthly during treatment, or as clinically

	indicate muscle damage) have been observed in some patients treated with Cotellic or other medicines of the same class.	indicated. If serum CPK is elevated, check for signs and symptoms of rhabdomyolysis or other causes. Depending on the severity of symptoms or CPK elevation, treatment interruption, dose reduction or treatment discontinuation may be required as described in the medicine's product information.
Hemorrhage	Hemorrhage has been observed in patients treated with Cotellic in combination with vemurafenib.	While this risk cannot be prevented, caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

LVEF = left ventricular ejection fraction; SmPC = Summary of Product Characteristics.

IMPORTANT POTENTIAL RISKS

Risk	**What is known**
Serious hepatotoxicity, e.g., elevations of hepatic transaminases (abnormal blood test levels for liver enzymes)	Elevated liver enzymes, which may indicate liver damage, have been observed in some patients treated with Cotellic in combination with vemurafenib, or with other medicines of the same class.
Impaired female fertility (potential infertility in women)	Patients are advised to not become pregnant during treatment with Cotellic. There is no information regarding human fertility and Cotellic treatment. No dedicated fertility studies have been performed, but in animals adverse effects were seen in female reproductive organs but no dedicated fertility studies have been performed.
Teratogenicity and developmental toxicity (foetal developmental malformations)	When administered to pregnant rats, Cotellic caused embryo death and foetal malformations of the great vessels and skull at exposures similar to human exposure at the recommended dose. There is no information on the effects of Cotellic treatment in pregnant patients. Patients are advised to not become pregnant during treatment with Cotellic.

MISSING INFORMATION

Risk	What is known
Limited information on long-term safety	Additional data are being collected to determine the effect of Cotellic in combination with vemurafenib on long-term use.
Safety in patients with cardiac impairment (major heart problems)	No data are available in patients with known cardiac impairment before starting treatment with Cotellic.
Safety in patients with pre-existing retinal pathology or risk factors for retinal vein occlusion (major eye problems)	No data are available in patients with pre-existing retinal disease.
Safety and efficacy in patients with involvement of the central nervous system (melanoma in the brain)	No data are available in patients with active melanoma spreading into the brain.
Limited information on treatment of paediatric patients (patients under 18 years of age)	The safety and efficacy of Cotellic in children is not currently known.
Use in pregnancy and lactation (breastfeeding)	When administered to pregnant rats, Cotellic caused embryo death and foetal malformations of the great vessels and skull at exposures similar to human exposure at the recommended dose. There is no information on the effects of Cotellic treatment in pregnant or breastfeeding patients. Patients are advised to not become pregnant during treatment with Cotellic.

VI.2.5 SUMMARY OF RISK MINIMIZATION MEASURES BY SAFETY CONCERN

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as ‘routine risk minimisation measures’.

The SmPC and the package leaflet are part of the medicine’s product information. The product information for Cotellic can be found on Cotellic’s EPAR page.

This medicine has no additional risk minimization measures.

VI.2.6 PLANNED POST-AUTHORIZATION DEVELOPMENT PLAN

Table of ongoing and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan

Study/activity (including study number)	Objectives	Safety concerns/ efficacy issues addressed	Status	Date for submission of interim or final reports
Pediatric Investigation Plan (PIP) EMEA-001425-PIP01-13-M01 Two pediatric studies in patients 6 months to < 18 years of age (3)	First Study (GO29665): safety, tolerability, pharmacokinetics, pharmacodynamics (how Cotellic works), and efficacy dose finding study. Second Study: confirmatory safety and efficacy study in patients 6 months to less than 18 years of age	Use in patients 6 months to less than 18 years of age	PIP agreed on December 2013 with modification on 16 May 2014. A study in pediatric patients (Study GO29665) is ongoing.	First Study start date by Q2 2016 in North America Second Study start date by June 2021 Final CSRs to be available 6 months after each study completion
Study ML39302: A non-interventional study to investigate the effectiveness, safety and utilization of cobimetinib and vemurafenib in patients with and without brain metastasis with BRAF V600 mutant melanoma under real world conditions. (3)	A study to determine the safety and efficacy of Cotellic in combination with vemurafenib in patients with active melanoma brain metastases	Safety and efficacy in patients with CNS involvement	Planned	Study Completion: Q4 2020 Final CSR by 1 year after study completion

STUDIES WHICH ARE A CONDITION OF THE MARKETING AUTHORIZATION

None.

VI.2.7 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Major Changes to the Risk Management Plan over Time

Version	Date (At time of authorization dd/mm/yyyy)*	Safety Concerns	Comment
1.0	NA	NA	First version of the E.U. RMP
1.1	NA	– Addition of 'left ventricular dysfunction' as an important potential risk based on analysis of Phase III data (CSR 1060643 for Study GO28141) – Updated important identified risk of 'central serous retinopathy' to 'serous retinopathy' and updated frequency, seriousness, and severity values with Phase III data from Study GO28141 – Updated important potential risk of 'teratogenicity' to 'teratogenicity and developmental toxicity' – Removal of 'increased potential for QT prolongation when cobimetinib is used in combination with vemurafenib' as a proposed important potential risk based on analysis of Phase III data (CSR 1060643 for Study GO28141)	Major updates were based on the availability and analysis of Phase III data (CSR 1060643 for Study GO28141)
– 1.2	– NA	– Updated important potential risk of 'left ventricular dysfunction' to an important identified risk: 'Left ventricular dysfunction (including decreased LVEF and cardiomyopathy)' – Added the important identified risk of 'photosensitivity' – Added the important identified risk of 'diarrhea' – Added the important potential risk of 'rhabdomyolysis' – Added the important potential risk of 'pneumonitis' – Added the important potential risk of 'hepatotoxicity (e.g., elevations of hepatic transaminases)' – Added the important potential risk of 'impaired	Major updates were made in response to the Day 120 and Day 180 PRAC assessments

Version	Date (At time of authorization dd/mm/yyyy)*	Safety Concerns	Comment
		female fertility' – Updated 'safety in patients with severe hepatic impairment' to 'safety in patients with moderate and severe hepatic impairment' – Added 'safety in patients with cardiac impairment (including congestive heart failure, current unstable angina, or left ventricular ejection fraction < 50%)' to missing information – Added 'safety in patients with pre-existing retinal pathology or risk factors for retinal vein occlusion' to missing information	
– 1.3	– NA	– Updated important identified risk of 'serous retinopathy' to 'ocular events related to serous retinopathy (retinal detachment)' – Updated 'pneumonitis' from an important potential risk to an important identified risk – Updated important potential risk of 'hepatotoxicity (e.g., elevations of hepatic transaminases)' to 'serious hepatotoxicity' – Added 'safety and efficacy in patients with CNS involvement' to missing information – Added 'drug-drug interactions with CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 to missing information.'	
– 1.4	– NA	– Removed 'safety in patients with moderate and severe hepatic impairment' from missing information – Removed 'drug-drug interactions with CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 from missing information'	Major updates were based on analysis of Study GP29342 (CSR, MEA 002: submitted 11/12/2015) and Study 15-1983 (report, MEA 001: submitted 11/12/2015).

Version	Date (At time of authorization dd/mm/yyyy)*	Safety Concerns	Comment
– 1.5	– NA	– No new safety concern added	Updated in response to the assessment report of version 1.4
– 2.0	– NA	– No new safety concerns added	Version prepared to present final OS data from Study GO28141, updated results of Study NO25395, and new post authorization exposure data
– 2.1	– NA	– No new safety concerns added	Version prepared to merge versions 1.5 and 2.0
– 3.0	– NA	– Addition of Hemorrhage to list of important identified risks. Elevation of Rhabdomyolysis from important potential risk to important identified risk. Removal of Study ML29155.	
– 3.1	– NA	– Revised to match updated wording in SmPC and PIL. Updated to include details regarding Study ML39302. No new safety concerns added.	Updated in response to preliminary assessment of second Cotellic PSUR
– 3.2	– NA	– Revised to match updated wording in SmPC and PIL.	Updated in response to the final assessment of second Cotellic PSUR

CSR = clinical study report; NA = not applicable; PRAC = Pharmacovigilance Risk Assessment Committee; QT = Q wave to T wave interval; RMP = risk management plan. *Refers to the date of Committee for Medicinal Products for Human Use (CHMP) positive opinion. Note: not all versions of the E.U. RMP are approved by the CHMP.