PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

Summary of Risk Management Plan for COTELLIC (COBIMETINIB)

This is a summary of the risk management plan (RMP) for Cotellic. The RMP details important risks of Cotellic, how these risks can be minimized, and how more information will be obtained about Cotellic risks and uncertainties (missing information).

Cotellic summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cotellic should be used.

This summary of the RMP for Cotellic should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cotellic's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Cotellic is authorized for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600. It contains cobimetinib as the active substance and it is given by oral administration.

Further information about the evaluation of Cotellic's benefits can be found in Cotellic's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Cotellic, together with measures to minimize such risks and the proposed studies for learning more about Cotellic's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size—the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status—the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events (AEs) is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Cotellic is not yet available, it is listed under 'missing Information' below.

II.A List of Important Risks and Missing Information

Important risks of Cotellic are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cotellic. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Ocular events related to serous retinopathy (e.g., retinal detachment) Left ventricular dysfunction (including decreased LVEF and cardiomyopathy) Rhabdomyolysis and CPK elevations
Important potential risks	None
Missing information	Safety in patients with cardiac impairment (including congestive heart failure, current unstable angina, or left ventricular ejection fraction < 50%)

CPK=creatine phosphokinase; LVEF= left ventricular ejection fraction.

II.B Summary of Important Risks

Important identified risk: Ocular events related to serous retinopathy (e.g., retinal detachment	
Evidence for linking the risk to the medicine	Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK-inhibitors, including Cotellic. Well-controlled randomized clinical trial (Study GO28141) showed that more patients had ocular events (the majority of which were reported as chorioretinopathy or retinal detachment) in comparison to patients who did not.

Risk factors and risk groups	Serous retinopathy is considered a class effect for MEK inhibitors.
Risk minimization measures	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **PL:** Section 2 (What you need to know before you take Cotellic) Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances are identified, an ophthalmologic examination is recommended. If serous retinopathy is diagnosed, Cotellic treatment should be withheld until visual symptoms improve to Grade ⩽1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Table 1 in section 4.2). This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information** **Medicine's legal status:** Cotellic is a prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

MEK=MAPK/ERK kinase; PL=package leaflet; SmPC=Summary of Product Characteristics.

Important identified risk: Left ventricular dysfunction (including decreased LVEF and cardiomyopathy)	
Evidence for linking the risk to the medicine	Decrease in left ventricular ejection fraction (LVEF) from baseline has been reported in patients receiving Cotellic. In well controlled randomized clinical trial GO28141, median time to initial onset of events was 4 months (1-13 months). The majority of the events were Grade 1 or 2.
Risk factors and risk groups	General risk factors for decreased LVEF include family or individual history of cardiac dysfunction. Additionally, prior treatment with cytotoxic drugs, including anthracyclines, is known to induce cardiomyopathy-related ADRs. However, given the current clinical data for cobimetinib, specific risk groups or factors were not identified.
Risk minimization measures	***Routine risk communication:*** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **PL:** Section 2 (What you need to know before you take Cotellic) Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** LVEF should be evaluated at baseline followed by additional monitoring after 1 month and then every 3 months or as needed. This has adequately described in section 4.4 and 4.8 of SmPC. **Other risk minimization measures beyond the Product Information** **Medicine's legal status:** Cotellic is a prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

ADRs=Adverse Drug Reactions; LVEF=Left Ventricular Ejection Fraction; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

Important identified risk: Rhabdomyolysis and CPK elevations	
Evidence for linking the risk to the medicine	In the well-controlled randomized clinical trial GO28141, one event of rhabdomyolysis was reported in a patient treated with cobimetinib + vemurafenib, and rhabdomyolysis has been reported in postmarketing experience. Laboratory elevations of creatine phosphokinase (CPK) of all grades were reported as an AE in 33.2% of patients treated with cobimetinib + vemurafenib (in the integrated safety population), of which 5.6% were Grade 3 and 3.2% were Grade 4. In Study GO28141, there were 11 patients (4.5%) in the cobimetinib + vemurafenib arm and 1 patient (0.4%) in the placebo + vemurafenib arm that presented with Grade 4 increased CPK. The majority of CPK elevations reported is asymptomatic, non-serious, and resolved with or without study drug interruption.
Risk factors and risk groups	None yet identified.
Risk minimization measures	**Routine risk minimization measures:** Routine risk communication: **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **PL:** Section 2 (What you need to know before you take Cotellic) Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** CPK should be monitored at baseline and monthly following treatment initiation. This has adequately described in section 4.4 and section 4.8 of the SmPC. **Other risk minimization measures beyond the Product Information** **Medicine's legal status:** Cotellic is a prescription only medicine. **Additional risk minimization measures:** None

Important identified risk: Rhabdomyolysis and CPK elevations	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

AE=adverse event; CPK=creatine phosphokinase; PL=package leaflet; SmPC=Summary of Product Characteristics.

Missing information: Safety in patients with cardiac impairment (including congestive heart failure, current unstable angina, or left ventricular ejection fraction < 50%)	
Evidence for linking the risk to the medicine	Safety in patients with cardiac impairment is need of further characterization, as patients with cardiac impairment have not been studied in clinical trials. Additionally, congestive heart failure is one of the most common comorbidities in the target population of metastatic melanoma for patients 65 years or older, and left ventricular dysfunction (including decreased LVEF and cardiomyopathy) is considered an important identified risk for cobimetinib. Therefore, the missing information is relevant in clinical practice.
Risk minimization measures	**Routine risk minimization measures:** *Routine risk communication:* **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) **PL:** Section 2 (What you need to know before you take Cotellic) **Routine risk minimization activities recommending specific clinical measures to address the risk:** LVEF should be evaluated at baseline followed by additional monitoring after 1 month of treatment and then every 3 months or as clinically indicated. This has adequately described in section 4.4 and 4.8 of SmPC. **Other risk minimization measures beyond the Product Information** **Medicine's legal status:** Cotellic is a prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

LVEF=Left ventricular ejection fraction; PL= Package leaflet; SmPC=Summary of Product Characteristics.

II.C Post-Authorization Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorization

None

II.C.2 Other Studies in Post-Authorization Development Plan

There are no studies required for Cotellic.