NOVARTIS

Regulatory Affairs

Capmatinib

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	*Capmatinib*
Product(s) concerned (brand name(s)):	*Tabrecta®*
Document status:	*Final*
Version number of the RMP Public Summary:	*1.3*
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Tabrecta” is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Tabrecta” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Tabrecta”.

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I. The medicine and what it is used for

Tabrecta® is authorised for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation. It contains capmatinib as the active substance and it is given by oral administration with or without food, as film-coated tablets at a dose of 400 mg b.i.d.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Tabrecta®, together with measures to minimize such risks and the proposed studies for learning more about Tabrecta'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 Prescribing information addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack sizes - 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.

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

II.A: List of important risks and missing information

Important risks of Tabrecta® 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 Tabrecta®. 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);

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Hepatotoxicity
	Interstitial lung disease/pneumonitis
	Pancreatitis
Important potential risks	Renal dysfunction
	Photosensitivity
	CNS toxicity
Missing information	None

II B: Summary of important risks

Table 2 Important identified risk: Hepatotoxicity

Evidence for linking the risk to the medicine	Hepatotoxicity grouped events have been reported during treatment with capmatinib and therefore, hepatic function should be closely monitored. In preclinical studies: Slight changes in serum liver enzymes (ALT, AST, and/or SDH) were observed in several different studies in rats and monkeys. These changes were restricted to highly variable, minimal-to-mild elevations lacking a clear dose response. These liver enzyme elevations were mostly observed in the absence of any histological correlate within the liver, with the exception of a 13-week monkey study, which showed a reversible, minimal-to-mild subcapsular neutrophilic infiltration associated with single cell necrosis in males at 75 mg/kg/day.
Risk factors and risk groups	There are no identified risk factors for the occurrence of hepatotoxicity in capmatinib-treated patients. Common general causative/ risk factors for hepatotoxicity include: -Elderly patients are at increased risk of hepatic injury due to reduced blood flow to the liver, DDIs, and decreased drug clearance -Alcohol abuse in patients with cirrhotic liver changes -Concomitant use of hepatotoxic medications -Other concurrent liver illness such as hepatitis -Patient who have liver involvement of the malignancy, e.g. liver cancer (HCC) and liver metastasis

Risk minimization measures	**Routine risk communication** Prescribing information sections Dosage/Administration, Warnings and precautions, adverse events Patient information sections “What you need to know before and while you receive Tabrecta”, “Possible side effects” **Routine risk minimization activities recommending specific clinical measures:** Prescribing information sections Dosage/Administration includes detailed guidance for withholding or permanent discontinuation of doses. Prescribing information sections Warnings and precautions includes guidance on monitoring and management of hepatic effects. Also includes guidelines for withholding or permanent discontinuation of doses. Patient information sections “What you need to know before and while you receive Tabrecta”, provides guidance on blood tests prior to start of treatment and during the treatment with Tabrecta to check the liver function. Patient information sections “Possible side effects” includes guidance on monitoring and management of very common side effects of liver problems. **Other routine risk minimization measures beyond the Product Information:** Legal status: Medical prescription only product

Table 3 Important potential risk: Interstitial lung disease/pneumonitis

Evidence for linking the risk to the medicine	Interstitial lung disease/pneumonitis has been reported during treatment with capmatinib and therefore, should be closely monitored. In preclinical studies, no lung pathology was observed.
Risk factors and risk groups	There are no identified risk factors for the occurrence of ILD/pneumonitis in capmatinib-treated patients. Common causative/risk factors for ILD/pneumonitis include: -Elderly patients, smokers -Patients with history of ILD or underlying lung disease -Patients with prior radiation therapy or oxygen therapy, prior chemotherapy or treatment IO -Concomitant use with drugs causing ILD/ pneumonitis
Risk minimization measures	**Routine risk communication** Prescribing information sections Dosage/Administration, Warnings and precautions, adverse events Patient information sections “Possible side effects” **Routine risk minimization activities recommending specific clinical measures**: Prescribing information sections Dosage/Administration prompts for permanent discontinuation in case of treatment related interstitial lung disease/pneumonitis of any grade. Prescribing information sections Warnings and precautions includes guidance on monitoring and management of Interstitial lung disease/pneumonitis. Also includes guidelines for withholding or permanent discontinuation of doses. Patient information sections “Possible side effects” includes guidance on monitoring and management of common side effects of pneumonitis, interstitial lung disease. **Other routine risk minimization measures beyond the Product Information**: Legal status: Medical prescription only product

Table 1 Important identified risk: Pancreatitis

Evidence for linking the risk to the medicine	Amylase and lipase increases have been reported during treatment with capmatinib in clinical studies and therefore, should be closely monitored. In preclinical studies: Reversible findings in the pancreas were observed in rats and monkeys in 28-day and 13-week studies, including pancreatic acinar cell vacuolation and/or apoptosis without inflammation, occasionally accompanied by increased amylase or lipase. In rats, the doses of 60 mg/kg/day or higher in males and 30 mg/kg/day or higher in females showed reversible low-grade pancreatic changes in 28-day and/or 13-week studies. In monkeys, pancreatic findings included reversible low-grade acinar cell apoptosis in all groups with higher serum amylase at the high dose of 150 mg/kg/day in the 28-day study, and increases in amylase and lipase in a small number of animals at 75 mg/kg/day in the 13-week study.
Risk factors and risk groups	There are no identified risk factors for the occurrence of increased amylase/lipase in capmatinib-treated patients. -Common causative /risk factors include: -Alcohol (more common in men) -Gallstones, esp. microlithiasis (more common in women) -Autoimmune diseases -Blockage of the pancreatic duct or common bile duct -Damage to the ducts or pancreas during surgery -Hypertriglyceridemia -Injury to the pancreas from accident
Risk minimization measures	**Routine risk communication** Prescribing information sections Dosage/Administration, Warnings and precautions, adverse events Patient information sections “What you need to know before and while you receive Tabrecta”, “Possible side effects” **Routine risk minimization activities recommending specific clinical measures**: Prescribing information sections Dosage/Administration includes guidance on temporarily withhold, dose reduce, or permanently discontinue treatment, depending on severity. Prescribing information sections Warning and precautions includes guidance on regular monitoring of pancreatic enzymes (amylase and lipase) prior and during treatment with capmatinib. Patient information sections “What you need to know before and while you receive Tabrecta”, provides guidance on blood tests prior to start of treatment and during the treatment with Tabrecta to check the pancreatic function. Patient information sections “Possible side effects”includes guidance on monitoring and management of uncommon side effects of acute pancreatitis. **Other routine risk minimization measures beyond the Product Information**: Legal status: Medical prescription only product

Table 2 Important potential risk: Renal dysfunction

Evidence for linking the risk to the medicine	Increase in the blood creatinine levels have been observed in patients receiving capmatinib in the clinical studies. In preclinical studies: Histopathologic changes were observed in the kidneys in a 28-day monkey study where mild-to-moderate deposits of amphophilic, crystalline-like material surrounded by multinucleated giant cells within the renal interstitium and/or tubular lumen were present at a dose of 75 mg/kg/day and higher. However, in a 13-week monkey study, renal precipitates or kidney

	toxicity was not observed at any doses tested (up to 75 mg/kg/day). Follow-up investigations on the identity of the crystalline-like material indicated that the material is not capmatinib or its metabolites, but rather calcium phosphate precipitates.
Risk factors and risk groups	There are no identified risk factors for the occurrence of increased creatinine in capmatinib-treated patients. Common causative/ risk factors for increased creatinine include: -Pre-existing medical conditions such as diabetes, hypertension and heart disease -Concomitant use of nephrotoxic medications. -Patient who has disease progression e.g. kidney metastasis -Inadequate fluid intake due to nausea, vomiting and fasting state
Risk minimization measures	Routine risk communication Prescribing information sections Dosage/Administration, adverse events, phamacokinetics, Patient information sections “Possible side effects” Routine risk minimization activities recommending specific clinical measures: Prescribing information sections Dosage/Administration includes detailed guidance for temporarily withholding treatment until recovery to baseline serum creatinine grade or permanent discontinuation of treatment. Patient information sections “Possible side effects” includes guidance on monitoring and management of side effects which may be a sign of problems with your kidney. Other routine risk minimization measures beyond the Product Information: Legal status: Medical prescription only product

Table 3 Important potential risk: Photosensitivity

Evidence for linking the risk to the medicine	In pre-clinical studies; In vitro and in vivo photosensitization assays with capmatinib suggested that capmatinib has the potential for photosensitization. The NOAEL for in vivo photosensitization is 30 mg/kg/day (Cmax of 14000 ng/mL, approximately 2.9X human Cmax at 400 mg b.i.d tablet dose).
Risk factors and risk groups	There have been no identified risk factors for the occurrence of photosensitivity in patients treated with capmatinib. Common causative/risk factors for photosensitivity include: -Direct exposure to sunlight or ultraviolet light -Patients with known photosensitivity or atopy
Risk minimization measures	**Routine risk communication** Prescribing information sections Warnings and precautions and Preclinical data Patient information sections “Possible side effects” **Routine risk minimization activities recommending specific clinical measures**: Prescribing information sections Warnings and precautions includes guidance on monitoring and management of photosensitivity. Patient information sections “Possible side effects” includes guidance on monitoring and management of possible common side effects of skin infection. **Other routine risk minimization measures beyond the Product Information**: Legal status: Medical prescription only product

Table 4 Important potential risk: CNS toxicity

Evidence for linking the risk to the medicine	In pre-clinical studies, there was inconsistency in the preclinical findings as the different species were used in different preclinical studies (observed in rats; not present in monkeys).
Risk factors and risk groups	There are no identified risk factors for the occurrence of CNS toxicity in capmatinib-treated patients. Common causative/ risk factors for CNS toxicity include: -Baseline/concurrent brain metastasis -Elderly age
Risk minimization measures	**Routine risk communication** Prescribing information sections preclinical data **Routine risk minimization activities recommending specific clinical measures**: None **Other routine risk minimization measures beyond the Product Information**: Legal status: Medical prescription only product

II C: Post-authorization development planII.C.1 Studies which are conditions of the marketing authorization

There are no proposed studies which should become conditions of the marketing authorization or specific obligation for Tabrecta®.

II.C.2. Other studies in post-authorization development plan

There are no proposed studies for Tabrecta®.