Cabometyx 20/40/60 mg
(Cabozantinib)
Film-coated tablets

Elements for a Public Summary -
Summary of the Safety Risk Management Plan (RMP)

Reference RMP EU RMP version 2.0
Products concerned (brand names): Cabometyx 20/40/60 mg
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1 INTRODUCTION
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 for “Cabometyx” is a concise document and does not claim to be exhaustive.

Please note that the reference document that is valid and relevant for the effective and safe use of “Cabometyx” in Switzerland is the “Arzneimittelinformation/Information sur le medicament” (see www.swissmedic.ch) approved and authorised by Swissmedic. Future Health Pharma GmbH is fully responsible for the accuracy and correctness of the content of the published RMP summary for “Cabometyx”.

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

2 OVERVIEW OF DISEASE EPIDEMIOLOGY
Renal cell carcinoma (RCC) is the third most frequent cancer of the urinary tract. Kidney cancer (of which approximately 90% of cases are RCC; Znaor et al 2015) is diagnosed in about 330,000 individuals worldwide (North America 64,000, Europe 115,000) each year and results in 140,000 deaths annually (North America 17,000, Europe 50,000) (Ferlay et al 2015). The incidence of RCC has generally increased over the past several years (International Surveillance, Epidemiology, and End Results Program, SEER, 2014; Znaor et al 2015). There is a higher incidence and mortality in men than women. Incidence peaks between the ages of 60 and 70.

3 SUMMARY OF TREATMENT BENEFITS
Cabozantinib is a restricted prescription medicine used to treat adult patients with RCC that has advanced locally or has spread to other parts of the body despite prior vascular endothelial growth factor (VEGF)-targeted therapy. Cabozantinib’s safety and efficacy were tested against another approved drug (everolimus) that is used in patients with RCC. Patients were assigned by chance to receive either cabozantinib 60 mg daily or everolimus 10 mg daily. A total of 331 patients received cabozantinib and 322 patients received everolimus until they experienced disease progression or drug toxicity.

The main study goals were to measure the time until patients’ disease progressed, how long they lived, and how many initially responded to treatment. Significant improvements were seen for cabozantinib patients versus the everolimus group for each goal. Median time until disease progression or death was 7.4 vs 3.8 months. For survival, an updated analysis showed median time was 21.4 vs 16.5 months. Response to treatment (≥30% reduction in tumour size) was seen in 17% of patients in the cabozantinib group and 3% in the everolimus group. Fewer patients in the cabozantinib group had cancer that did not initially respond to treatment (12% vs 27%).

4 UNKNOWNS RELATING TO TREATMENT BENEFITS
In the cabozantinib pivotal study 82% patients were White and 60% were under 65. There is no evidence to suggest that results would be any different in non-White patients or in older patients.
## 5 SUMMARY OF SAFETY CONCERNS

### 5.1 Important Identified Risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal perforation which is a tear or hole that develops in your stomach or intestine that could be life-threatening</td>
<td>Approximately 1 in 100 patients with RCC treated with cabozantinib may present with a perforation of the gastrointestinal tract.</td>
<td>Yes, this may be lessened via monitoring patients, especially those at higher risk, and for early symptoms. Symptoms include pain in the abdomen, nausea, vomiting, constipation, or fever. These may be signs of a gastrointestinal perforation. Cabozantinib should be discontinued if a gastrointestinal perforation occurs that cannot be adequately managed.</td>
</tr>
<tr>
<td>Fistula, an abnormal connection between two organs in your body or to the outside of your body</td>
<td>Approximately 1 in 100 patients with RCC treated with cabozantinib may present with a fistula. A fistula may lead to abscess or gastrointestinal perforation</td>
<td>Yes, this may be lessened via monitoring patients, especially those at higher risk, and for early symptoms. Symptoms can include pain in the abdomen or other locations (depending on the location of the fistula), nausea, vomiting, constipation, fever, or mucositis. Persistent or recurring diarrhoea while on treatment may be a risk factor for the development of anal fistula. Cabozantinib should be discontinued if a fistula that cannot be adequately managed occurs.</td>
</tr>
<tr>
<td>Blood clots (thromboembolism) in the arteries or veins</td>
<td>Approximately 1 in 100 patients with RCC treated with cabozantinib may present with blood clots in the arteries and 7 in 100 with blood clots in the veins. Patients with cancer are at an increased risk of having blood clots which could be fatal.</td>
<td>Yes, this may be lessened via monitoring patients, especially those at higher risk, and for early symptoms such as pain and swelling of arms or legs. The use of anticoagulants in patients at risk for clots may also help prevent them. Patients with serious blood clots in arteries (eg, myocardial infarction [heart attack]), cerebral infarction [stroke]) should discontinue cabozantinib.</td>
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<tr>
<td>Bleeding (haemorrhage)</td>
<td>Approximately 2 in 100 patients with RCC treated with cabozantinib may experience bleeding that is severe. If the tumour is invading other organs or blood vessels, they may be at higher risk for bleeding.</td>
<td>Yes, this can be lessened via careful monitoring of patients, especially those that are using anticoagulants or have risk factors. Treatment for bleeding events should also be given as medically indicated to prevent a more serious outcome. Patients with severe bleeding should discontinue cabozantinib.</td>
</tr>
<tr>
<td>Wound complications</td>
<td>Approximately 2 in 100 patients with RCC treated with cabozantinib may experience wound closure complications. Poor wound healing can result in infections, bleeding, fistula, or abscess.</td>
<td>Yes, this can be lessened by stopping cabozantinib treatment at least 4 weeks before surgery, including dental surgery. Restarting cabozantinib treatment depends on adequate wound healing.</td>
</tr>
<tr>
<td>Risk</td>
<td>What is known</td>
<td>Preventability</td>
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<tr>
<td>High blood pressure (hypertension)</td>
<td>Approximately 39 in 100 patients with RCC treated with cabozantinib may experience hypertension. Patients with uncontrolled hypertension or pre-existing hypertension may be at a higher risk of developing severe hypertension.</td>
<td>Yes, this can be lessened by careful monitoring of patients with existing hypertension and regularly measuring blood pressure of patients receiving cabozantinib. Hypertension should also be treated with standard blood pressure medications as clinically appropriate. Patients with severe and persistent hypertension despite optimal management should discontinue cabozantinib.</td>
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<tr>
<td>Brain dysfunction caused by brain swelling (reversible posterior leukoencephalopathy syndrome; RPLS)</td>
<td>RPLS has not been found in RCC patients but has occurred in other cabozantinib trials in less than 1 in 100 patients. Risk factors include hypertension, renal failure, and the use of immunosuppressive treatment. Due to the frequency of hypertension in the RCC population, this population may be at a higher risk.</td>
<td>No. Patients who develop with RPLS should discontinue treatment with cabozantinib.</td>
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<tr>
<td>Diarrhoea</td>
<td>Approximately 70 in 100 patients with RCC may present with diarrhoea while treated with cabozantinib and it is severe in 11%. If diarrhoea is prolonged severe electrolyte disturbances (imbalances in the salts in the bloodstream) could result which should be treated. Diarrhoea can also cause irritation of the gut and may lead to rectal inflammation, perforations, abscesses or fistulas.</td>
<td>Yes, diarrhoea can be treated as medically indicated. Early intervention may prevent more severe outcomes. Modification of the diet may also help.</td>
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<tr>
<td>Hand-foot syndrome (palmar plantar erythrodysaesthesia syndrome; PPES)</td>
<td>Approximately 42 in 100 patients with RCC may develop PPES while treated with cabozantinib. Only 8 in 100 patients may have severe PPES. Patients at higher risk include those with a prior history of PPES. In addition, patients with lung or liver metastasis have a higher chance of getting PPES.</td>
<td>Yes, PPES can be treated as medically indicated. Preventative measures include prophylactic skin care; early intervention with supportive treatment may prevent more severe outcomes.</td>
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<tr>
<td>Underactive thyroid gland (hypothyroidism)</td>
<td>Approximately 21 in 100 patients with RCC may develop hypothyroidism while treated with cabozantinib; severe events have not occurred. Patients at higher risk include those with a prior history of hypothyroidism.</td>
<td>Yes, the impact can be lessened by assessing patients for early symptoms and treating patients as medically indicated.</td>
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## Risk Analysis

<table>
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<tr>
<th>Risk</th>
<th>What is known</th>
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</tr>
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<tbody>
<tr>
<td>Breakdown of the bone (osteonecrosis)</td>
<td>Approximately 1 in 100 patients with RCC treated with cabozantinib may experience osteonecrosis, mainly of the jaw. Osteonecrosis can result from metastasis of malignancy, osteoporosis, or prolonged ischemia or lack of blood supply to the bone. Patients with bone metastasis taking bisphosphonates, corticosteroids, chemotherapy or with radiotherapy to the bone may be at a higher risk. Dental surgery is also a risk factor.</td>
<td>Yes, the risk of osteonecrosis of the jaw can be mitigated with good oral hygiene. Monitoring after invasive dental procedures can recognise early symptoms of osteonecrosis. Osteonecrosis should be treated as medically appropriate to avoid a poor outcome.</td>
</tr>
<tr>
<td>Protein in urine (proteinuria)</td>
<td>Approximately 12 in 100 patients with RCC may develop proteinuria while treated with cabozantinib. This is similar to the number of untreated RCC patients expected to present with proteinuria. Patients at risk include those with a history of renal failure.</td>
<td>Yes, this can be lessened by carefully monitoring kidney function (including protein in urine). Control of blood pressure and diabetes can also reduce the occurrence of proteinuria. Cabozantinib should be discontinued in patients who develop nephrotic syndrome (too much protein in the urine as well as swelling, particularly in the feet and ankles).</td>
</tr>
</tbody>
</table>
## 5.2 Important Potential Risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known (Including reason why it is considered a potential risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in the electrical activity of the heart, seen on electrocardiogram (QT prolongation)</td>
<td>Cabozantinib (but none of its metabolites) did produce a mild but significant inhibition of hERG- trafficking activity but only at significantly higher concentrations than those in the human. During clinical trials few patients presented an event of QT prolongation that was clinically significant. However, QT prolongation was also seen in patients not taking cabozantinib. Conditions or therapies that lead to electrolyte disturbances such as diarrhoea, vomiting or the use of diuretics may be indirect risk factors.</td>
</tr>
<tr>
<td>Kidney failure (renal failure)</td>
<td>Renal failure has been reported in less than 1 in 100 patients during the development of cabozantinib in the RCC population. Cases of renal failure are uncommon and relationship to the identified risk of proteinuria or underlying disease process is unclear. Blood pressure should be monitored in patients.</td>
</tr>
<tr>
<td>Liver toxicity (hepatotoxicity)</td>
<td>Hepatotoxicity cases are infrequent, occur in less than 1 in 100 RCC patients treated with cabozantinib, but the relationship to cabozantinib or underlying disease process is unclear. Similar drugs have been reported to cause hepatotoxicity but no direct hepatotoxic effect has been identified in patients taking cabozantinib</td>
</tr>
<tr>
<td>Fertility impairment</td>
<td>Cabozantinib administration resulted in reduced fertility in animal studies. Although the mechanism(s) leading to impaired fertility are unknown, these findings are consistent with cabozantinib-mechanism of action.</td>
</tr>
<tr>
<td>Toxicity affecting the early development of a baby (embryotoxicity)</td>
<td>No clinical data exist on events related to embryotoxicity. However, preclinical data suggest that serious effects on a foetus could result from cabozantinib therapy in the mother. Pregnant patients may have the risk of foetal damage that could be fatal for the unborn baby. Patients who are pregnant should not take cabozantinib. Patients who are fertile should avoid becoming pregnant while on cabozantinib by the use of proper and effective contraception for at least 4 months after the last dose of cabozantinib. Because oral contraceptives might possibly not be considered as “effective methods of contraception”, they should be used together with another method, such as a barrier method.</td>
</tr>
<tr>
<td>Medication error</td>
<td>Potential risk based on the possibility that patients might take a higher dose of Cabometyx than prescribed, as it occurred in one patient in a clinical trial with cabozantinib tablets. An additional risk is that a patient could be prescribed the capsule formulation of cabozantinib available under the invented name of Cometriq. Cabometyx (cabozantinib) tablets and Cometriq (cabozantinib) capsules are not bioequivalent and should not be used interchangeably.</td>
</tr>
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<td>Carcinogenicity</td>
<td>The carcinogenic potential of cabozantinib has been evaluated in mice and rats. Cabozantinib was not carcinogenic in a 26-week mouse study. In a 2-year rat carcinogenicity study, administration of cabozantinib resulted in benign and malignant pheochromocytoma in males and females at doses equivalent to doses less than the 60 mg human dose in RCC patients. However, there is no evidence this translates to an increased risk in humans.</td>
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### 5.3 Missing Information

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<td>Use in children</td>
<td>No clinical study to evaluate the safety and efficacy of cabozantinib in children and adolescents has been completed. It is not recommended to use cabozantinib in paediatric patients outside of clinical studies.</td>
</tr>
<tr>
<td>Use in pregnant or lactating women</td>
<td>There are no studies in pregnant women using cabozantinib, and it is not known whether cabozantinib is present in human milk. Therefore, pregnant women should not use cabozantinib unless deemed medically necessary, and women should discontinue breast-feeding while taking cabozantinib.</td>
</tr>
<tr>
<td>Use in patients with cardiac (heart) impairment</td>
<td>No clinical study to evaluate the safety and efficacy of cabozantinib in cardiac impaired subjects has been completed. The number of subjects with cardiac impairment other than hypertension during the development of cabozantinib is limited.</td>
</tr>
<tr>
<td>Use in patients with severe hepatic (liver) impairment</td>
<td>A clinical study to evaluate the safety and drug concentrations of cabozantinib in patients with mild or moderate hepatic impairment has been completed and a lower starting dose should be used. However, patients with severe hepatic impairment were not enrolled in this study.</td>
</tr>
<tr>
<td>Use in patients with severe renal (kidney) impairment</td>
<td>A clinical study to evaluate the safety and drug concentrations of cabozantinib in patients with mild or moderate renal impairment has been completed and dosing recommendations in this population have been established. However, patients with severe renal impairment were not enrolled in this study.</td>
</tr>
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### 6 SUMMARY OF RISK MINIMISATION MEASURES BY SAFETY CONCERN

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Cabometyx can be found in the Cabometyx EPAR page.

This medicine has no additional risk minimisation measures.

### 7 PLANNED POSTAUTHORISATION DEVELOPMENT PLAN

#### 7.1 List of Studies in Postauthorisation Development Plan

<table>
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<th>Study/activity (including study number)</th>
<th>Objectives</th>
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<td>A Phase 3, Randomised, Controlled Study of Cabozantinib (XL184) vs Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy</td>
<td>Final analysis of study secondary endpoint: overall survival</td>
<td>Confirmation of rejection of the null hypothesis for OS</td>
<td>Study completed primary (PFS) and secondary endpoints (OS and ORR). An additional OS analysis was completed after a total of 430 events was reached</td>
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### 7.2 Studies which are a Condition of the Marketing Authorisation

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### 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Changes from version 1.2 (initial MAA submission) of the Cabometyx RMP to version 2.0 (currently approved RMP by EMA) are;

- Rat carcinogenicity study
- Finalisation of XL184-308 (METEOR) study
- Voluntary PASS details