▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section Undesirable effects for how to report adverse reactions. **NAME OF THE MEDICINAL PRODUCT** CABOMETYX 20 mg film-coated tablets CABOMETYX 40 mg film-coated tablets CABOMETYX 60 mg film-coated tablets **QUALITATIVE AND QUANTITATIVE COMPOSITION** CABOMETYX 20 mg film-coated tablets Each film-coated tablet contains cabozantinib (*S*)-malate equivalent to 20 mg cabozantinib. *Excipients with known effect* Each film-coated tablet contains 15.54 mg lactose. CABOMETYX 40 mg film-coated tablets Each film-coated tablet contains cabozantinib (*S*)-malate equivalent to 40 mg cabozantinib. *Excipients with known effect* Each film-coated tablet contains 31.07 mg lactose. CABOMETYX 60 mg film-coated tablets Each film-coated tablet contains cabozantinib (*S*)-malate equivalent to 60 mg cabozantinib. *Excipients with known effect* Each film-coated tablet contains 46.61 mg lactose. For the full list of excipients, see section List of excipients. **PHARMACEUTICAL FORM** Film-coated tablet. CABOMETYX 20 mg film-coated tablets The tablets are yellow round with no score, and debossed with "XL" on one side and "20" on the other side of the tablet. CABOMETYX 40 mg film-coated tablets The tablets are yellow triangle shaped with no score, and debossed with "XL" on one side and "40" on the other side of the tablet. CABOMETYX 60 mg film-coated tablets The tablets are yellow oval shaped with no score, and debossed with "XL" on one side and "60" on the other side of the tablet. **CLINICAL PARTICULARS. Renal Cell Carcinoma (RCC)** CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC): - in treatment-naïve adults with intermediate or poor risk (see section Pharmacodynamic properties) - in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. **Hepatocellular Carcinoma (HCC)** CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib. **Posology and method of administration** Therapy with CABOMETYX should be initiated by a physician experienced in the administration of anticancer medicinal products. Posology CABOMETYX (cabozantinib) tablets and COMETRIQ (cabozantinib) capsules are not bioequivalent and should not be used interchangeably (see section Pharmacokinetic properties). For RCC and HCC, the recommended dose of CABOMETYX is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction of CABOMETYX therapy (see "Recommended CABOMETYX dose modifications for adverse reactions"). When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable. If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose. **Recommended CABOMETYX dose modifications for adverse reactions:** Grade 1 and Grade 2 adverse reactions which are tolerable and easily managed: Dose adjustment is usually not required. Add supportive care as indicated. Grade 2 adverse reactions which are intolerable and cannot be managed with a dose reduction or supportive care: Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Consider re-initiating at a reduced dose. Grade 3 adverse reactions (except clinically nonrelevant laboratory abnormalities): Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Re-initiate at a reduced dose. Grade 4 adverse reactions (except clinically nonrelevant laboratory abnormalities): Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to Grade ≤1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue CABOMETYX. Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4) *Concomitant medicinal products* Concomitant medicinal products that are strong inhibitors of CYP3A4 should be used with caution, and chronic use of concomitant medicinal products that are strong inducers of CYP3A4 should be avoided (see sections Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction). Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered. Special populations. *Elderly patients* No specific dose adjustment for the use of cabozantinib in older people (≥ 65 years) is recommended. *Race* No dose adjustment is necessary based on ethnicity (see section Pharmacokinetic properties). *Patients with renal impairment* Cabozantinib should be used with caution in patients with mild or moderate renal impairment. Cabozantinib is not recommended for use in patients with severe renal impairment as safety and efficacy have not been established in this population. *Patients with hepatic impairment* In patients with mild hepatic impairment no dose adjustment is required. Since only limited data are available for patients with moderate hepatic impairment (Child Pugh B), no dosing recommendation can be provided. Close monitoring of overall safety is recommended in these patients (see sections Special warnings and precautions for use and Pharmacokinetic properties). There is no clinical experience in patients with severe hepatic impairment (Child Pugh C), so cabozantinib is not recommended for use in these patients (see section Pharmacokinetic properties). *Patients with cardiac impairment* There are limited data in patients with cardiac impairment. No specific dosing recommendations can be made. *Paediatric population* The safety and efficacy of cabozantinib in children and adolescents aged <18 years have not yet been established. No data are available. Method of administration CABOMETYX is for oral use. The tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking CABOMETYX. **Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section List of excipients. **Undesirable effects** Summary of safety profile The most common serious adverse drug reactions in the RCC population (≥1% incidence) are abdominal pain, diarrhoea, nausea, hypertension, embolism, hyponatraemia, pulmonary embolism, vomiting, dehydration, fatigue, asthenia, decreased appetite, deep vein thrombosis, dizziness, hypomagnesaemia and palmar-plantar erythrodysaesthesia syndrome (PPES). The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the RCC population included diarrhoea, fatigue, nausea, decreased appetite, PPES, hypertension, weight decreased, vomiting, dysgeusia, constipation, and AST increased. Hypertension was observed more frequently in the treatment naïve RCC population (67%) compared to RCC patients following prior VEGF-targeted therapy (37%). The most common serious adverse drug reactions in the HCC population (≥1% incidence) are hepatic encephalopathy, asthenia, fatigue, PPES, diarrhoea, hyponatraemia, vomiting, abdominal pain and thrombocytopenia. The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the HCC population included diarrhoea, decreased appetite, PPES, fatigue, nausea, hypertension and vomiting. Adverse reactions identified in clinical studies of cabozantinib or reported after post-marketing use of cabozantinib are listed, according to MedDRA System Organ Class and frequency categories. Frequencies are based on all grades and defined as: very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. **Adverse drug reactions (ADRs) reported in clinical trials or after post-marketing use in patients treated with cabozantinib:** Infections and infestations: Common, abscess. Blood and lymphatic disorders: Very Common, anaemia, thrombocytopenia[a]. Common, neutropenia[a], lymphopenia[a]. Endocrine disorders: Very Common, hypothyroidism[c]. Metabolism and nutrition disorders: Very Common, decreased appetite, hypomagnesaemia[b], hypokalaemia[b], hypoalbuminaemia[b]. Common, dehydration, hypophosphataemia[b], hyponatraemia[b], hypocalcaemia[b], hyperkalaemia[c], hyperbilirubinemia[c], hyperglycaemia[c], hypoglycaemia[b]. Nervous system disorders: Very Common, dysgeusia, headache, dizziness. Common, peripheral neuropathy (including sensory). Uncommon, convulsion. Not known, cerebrovascular accident. Ear and labyrinth disorders: Common, tinnitus. Cardiac disorders: Not Known, myocardial infarction. Vascular disorders: Very Common, hypertension[e], haemorrhage[*]. Common, deep vein thrombosis, venous thrombosis, arterial thrombosis. Not known, aneurysms and artery dissections. Respiratory, thoracic, and mediastinal disorders: Very Common, dysphonia, dyspnoea, cough. Common, pulmonary embolism. Gastrointestinal disorders: Very Common, diarrhoea[*], nausea, vomiting, stomatitis, constipation, abdominal pain[d], dyspepsia, upper abdominal pain. Common, gastrointestinal perforation[*], fistula[*], gastroesophageal reflux disease, haemorrhoids, oral pain, dry mouth, dysphagia, glossodynia. Uncommon, pancreatitis. Hepatobiliary disorders: Common, hepatic encephalopathy[*]. Uncommon, hepatitis cholestatic. Skin and subcutaneous tissue disorders: Very Common, palmar-plantar erythrodysaesthesia syndrome, rash. Common, pruritus, alopecia, dry skin, dermatitis acneiform, hair colour change, hyperkeratosis. Musculoskeletal and connective tissue disorders: Very Common, pain in extremity. Common, muscle spasms, arthralgia. Uncommon, osteonecrosis of the jaw. Renal and urinary disorders: Common, proteinuria. General disorders and administration site conditions: Very Common, fatigue, mucosal inflammation, asthenia, peripheral oedema. Investigations: Very Common, weight decreased, serum ALT increased, AST increased. Common, blood ALP increased, GGT increased, blood creatinine increased, amylase increased, lipase increased, blood cholesterol increased[c], blood triglycerides increased[c]. Injury, poisoning and procedural complications: Uncommon, wound complications[f]. *See section Undesirable effects, Description of selected adverse reactions for further characterisation. The following terms have been combined to derive appropriate frequency categorisation: [a]Lowered haematology parameters: Lymphopenia and lymphocyte count decreased; Neutropenia and neutrophil count decreased; Thrombocytopenia and platelet count decreased. [b]Lowered biochemistry parameters: Hypoalbuminaemia and blood albumin decreased; Hypocalcaemia and blood calcium decreased; Hypoglycaemia and blood glucose decreased; Hypokalaemia and blood potassium decreased; Hypomagnesaemia and blood magnesium decreased; Hyponatraemia and blood sodium decreased; Hypohosphataemia and blood phosphorus decreased. [c]Elevated biochemistry parameters: Blood cholesterol increased and hypercholesterolaemia; Hyperbilirubinaemia and blood bilirubin increased; Hyperglycaemia and blood glucose increased; Hypothyroidism and blood thyroid stimulating hormone increased; Hyperkalaemia and blood potassium increased; Triglycerides increased and hypertriglyceridaemia. [d]Abdominal pain, abdominal discomfort, abdominal pain upper and abdominal pain lower. [e]Hypertension and blood pressure increased. [f]Impaired healing and incision site complication. Description of selected adverse reactions Data for the following reactions are based on patients who received CABOMETYX 60 mg qd po in the pivotal studies in RCC following prior VEGF-targeted

therapy and in treatment-naïve RCC and in HCC following prior systemic therapy (section Pharmacodynamic properties). *Gastrointestinal (GI) perforation (see section Special warnings and precautions for use)* In the study in RCC following prior VEGF-targeted therapy (METEOR), GI perforations were reported in 0.9% (3/331) of cabozantinib-treated RCC patients. Events were Grade 2 or 3. Median time to onset was 10.0 weeks. In the treatment-naïve RCC study (CABOSUN), GI perforations were reported in 2.6% (2/78) of cabozantinib-treated patients. Events were Grade 4 and 5. In the HCC study (CELESTIAL), GI perforations were reported in 0.9% of cabozantinib-treated patients (4/467). All events were Grade 3 or 4. Median time to onset was 5.9 weeks. Fatal perforations have occurred in the cabozantinib clinical program. *Hepatic encephalopathy (see section Special warnings and precautions for use)* In the HCC study (CELESTIAL), hepatic encephalopathy (hepatic encephalopathy, encephalopathy, hyperammonaemic encephalopathy) was reported in 5.6% of cabozantinib-treated patients (26/467); Grade 3-4 events in 2.8%, and one (0.2%) Grade 5 event. Median time to onset was 5.9 weeks. No cases of hepatic encephalopathy were reported in the RCC studies (METEOR and CABOSUN). *Diarrhoea (see section Special warnings and precautions for use)* In the study in RCC following prior VEGF-targeted therapy (METEOR), diarrhoea was reported in 74% of cabozantinib-treated RCC patients (245/331); Grade 3-4 events in 11%. Median time to onset was 4.9 weeks. In the treatment-naïve RCC study (CABOSUN), diarrhoea was reported in 73% of cabozantinib-treated patients (57/78); Grade 3-4 events in 10%. In the HCC study (CELESTIAL), diarrhoea was reported in 54% of cabozantinib-treated patients (251/467); Grade 3-4 events in 9.9%. Median time to onset of all events was 4.1 weeks. Diarrhoea led to dose modifications, interruptions and discontinuations in 84/467 (18%), 69/467 (15%) and 5/467 (1%) of subjects, respectively. *Fistulas (see section Special warnings and precautions for use)* In the study in RCC following prior VEGF-targeted therapy (METEOR), fistulas were reported in 1.2% (4/331) of cabozantinib-treated patients and included anal fistulas in 0.6% (2/331) cabozantinib-treated patients. One event was Grade 3; the remainder were Grade 2. Median time to onset was 30.3 weeks. In the treatment-naïve RCC study (CABOSUN), no cases of fistulas were reported. In the HCC study (CELESTIAL), fistulas were reported in 1.5% (7/467) of the HCC patients. Median time to onset was 14 weeks. Fatal fistulas have occurred in the cabozantinib clinical program. *Haemorrhage (see section Special warnings and precautions for use)* In the study in RCC following prior VEGF-targeted therapy (METEOR), the incidence of severe haemorrhagic events (Grade ≥ 3) was 2.1% (7/331) in cabozantinib-treated RCC patients. Median time to onset was 20.9 weeks. In the treatment-naïve RCC study (CABOSUN), the incidence of severe haemorrhagic events (Grade ≥ 3) was 5.1% (4/78) in cabozantinib-treated RCC patients. In the HCC study (CELESTIAL), the incidence of severe haemorrhagic events (Grade ≥ 3) was 7.3% in cabozantinib-treated patients (34/467). Median time to onset was 9.1 weeks. Fatal haemorrhages have occurred in the cabozantinib clinical program. *Posterior Reversible Encephalopathy Syndrome (PRES) (see section Special warnings and precautions for use)* No case of PRES was reported in the METEOR or CABOSUN or CELESTIAL studies, but PRES has been reported rarely in other clinical studies (in 2/4872 subjects; 0.04%). Reporting of suspected adverse reactions 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 via, Belgium: Federal Agency for Medicines and Health Products, Vigilance Division, Eurostation II, Place Victor Horta 40/40, B-1060 Brussels. Website: www.famhp.be E-mail: adversedrugreactions@fagg-afmps.be Luxembourg: Direction de la Santé, Division de la Pharmacie et des Médicaments, Villa Louvigny, Allée Marconi-L-2120 Luxembourg. Website: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html.

MARKETING AUTHORISATION HOLDER Ipsen Pharma, 65 quai Georges Gorse, 92100 Boulogne-Billancourt, France. Local representative: Ipsen nv **MARKETING AUTHORISATION NUMBER(S)** Cabometyx 20 mg film-coated tablets EU/1/16/1136/002 Cabometyx 40 mg film-coated tablets EU/1/16/1136/004 Cabometyx 60 mg film-coated tablets EU/1/16/1136/006 **DELIVERY** prescription only medicine **DATE OF FIRST AUTHORISATION** 9 September 2016 **DATE OF REVISION OF THE TEXT** 10/2020