Package insert for use in India only

Cabolong

कैबोलॉन्ग

To be sold by retail on the prescription of an Oncologist only.

PRESCRIBING INFORMATION

1. GENERIC NAME

Cabozantinib Tablets 20 mg, 40 mg and 60 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20mg film-coated tablet contains
Cabozantinib (S)-malate equivalent to Cabozantinib 20mg

CABOZANTINIB TABLETS 40MG

Each 40mg film-coated tablet contains:
Cabozantinib (S)-malate equivalent to Cabozantinib 40mg.

CABOZANTINIB TABLETS 60MG

Each 60mg film-coated tablet contains:
Cabozantinib (S)-malate equivalent to Cabozantinib 60mg

3. DOSAGE FORM AND STRENGTH

Cabozantinib tablets are available as 20 mg, 40 mg and 60 mg film coated tablets.

4. CLINICAL PARTICULARS

4.1. Indications

Renal Cell Carcinoma
Cabozantinib is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

Hepatocellular Carcinoma
Cabozantinib is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

4.2. Posology and Method of Administration

Important Dosage Information

- Stop treatment with Cabozantinib at least 3 weeks prior to scheduled surgery, including dental surgery.
- Do not substitute cabozantinib tablets with cabozantinib capsules.
- Do not administer cabozantinib with food. Administer at least 1 hour before or at least 2 hours after eating.
- Swallow cabozantinib tablets whole. Do not crush cabozantinib tablets.
- Do not take a missed dose within 12 hours of the next dose.
- Modify the dose for certain patients with hepatic impairment and for patients taking drugs known to strongly induce or inhibit CYP450.

Recommended Dosage for Renal Cell Carcinoma

The recommended dosage of cabozantinib is 60 mg once daily without food until the patient no longer experiences clinical benefit or experiences unacceptable toxicity.

Recommended Dosage for Hepatocellular Carcinoma

The recommended dosage of cabozantinib is 60 mg once daily without food until disease progression or unacceptable toxicity.

Dosage Modifications for Adverse Reactions

Withhold cabozantinib for:

- Intolerable Grade 2 adverse reactions
- Grade 3 or 4 adverse reactions
- Osteonecrosis of the jaw

Upon resolution/improvement (i.e., return to baseline or resolution to Grade 1) of an adverse reaction, reduce the dose as follows:

- If previously receiving 60 mg daily dose, resume treatment at 40 mg daily.
- If previously receiving 40 mg daily dose, resume treatment at 20 mg daily.
- If previously receiving 20 mg daily dose, resume at 20 mg if tolerated, otherwise, discontinue cabozantinib.

Permanently discontinue cabozantinib for any of the following:

- Severe hemorrhage
- Development of gastrointestinal (GI) perforation or Grade 4 fistula
- Acute myocardial infarction or arterial or venous thromboembolic events that require
- medical intervention
- Severe hypertension that cannot be controlled with anti-hypertensive therapy or hypertensive crisis
- Nephrotic syndrome
- Reversible posterior leukoencephalopathy syndrome

Dosage Modifications for Coadministration with Strong CYP3A4 Inhibitors

Reduce the daily cabozantinib dose by 20 mg (for example, from 60 mg to 40 mg daily or from 40 mg to 20 mg daily). Resume the dose that was used prior to initiating the strong CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor.

Dosage Modifications for Coadministration with Strong CYP3A4 Inducers

Increase the daily cabozantinib dose by 20 mg (for example, from 60 mg to 80 mg daily or from 40 mg to 60 mg daily) as tolerated. Resume the dose that was used prior to initiating the strong CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. Do not exceed a daily dose of 80 mg.

Dosage Modifications for Patients with Moderate and Severe Hepatic Impairment

Reduce the starting dose of cabozantinib to 40 mg once daily in patients with moderate hepatic impairment (Child-Pugh B). Avoid cabozantinib in patients with severe hepatic impairment (Child-Pugh C).

4.3. Contraindications

- Hypersensitivity to cabozantinib or to any of the components used in the formulation.

4.4. Special Warnings and Precautions for Use

As most events occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. Events that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmar-plantar erythrodysaesthesia syndrome (PPES), proteinuria, and gastrointestinal (GI) events (abdominal pain, mucosal inflammation, constipation, diarrhoea, vomiting).

Hemorrhage
Severe and fatal hemorrhages occurred with cabozantinib. The incidence of Grade 3 to 5 hemorrhagic events was 5% in cabozantinib-treated patients. Discontinue cabozantinib for Grade 3 or 4 hemorrhage. Do not administer cabozantinib to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas
Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue cabozantinib in patients who experience a fistula which cannot be appropriately managed or a GI perforation.

Thrombotic Events
Discontinue cabozantinib in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

Hypertension and Hypertensive Crisis
Cabozantinib can cause hypertension, including hypertensive crisis.
Do not initiate cabozantinib in patients with uncontrolled hypertension. Monitor blood pressure regularly during cabozantinib treatment. Withhold cabozantinib for hypertension that is not adequately controlled with medical management; when controlled, resume cabozantinib at a reduced dose. Discontinue cabozantinib for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea
Withhold cabozantinib until improvement to Grade 1 and resume cabozantinib at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia
Withhold cabozantinib until improvement to Grade 1 and resume cabozantinib at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Proteinuria
Discontinue cabozantinib in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of cabozantinib and periodically during cabozantinib. Advise patients regarding good oral hygiene practices. Withhold cabozantinib for at least 28 days prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold cabozantinib for development of ONJ until complete resolution.

Wound Complications
Wound complications have been reported with cabozantinib.
Stop cabozantinib at least 3 weeks prior to scheduled surgery. Do not administer cabozantinib for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of cabozantinib after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with cabozantinib. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue cabozantinib in patients who develop RPLS.

Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, cabozantinib can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits.
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with cabozantinib and for 4 months after the last dose.

Prolongation of QT interval
Cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances.

When using cabozantinib, periodic monitoring with on-treatment ECGs and electrolytes (serum calcium, potassium, and magnesium) should be considered.

Thrombocytopenia
Platelet levels should be monitored during cabozantinib treatment and the dose modified according to the severity of the thrombocytopenia.

Hepatic effects
Abnormalities of liver function tests (increases in alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have been frequently observed in patients treated with cabozantinib. It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of cabozantinib treatment and to monitor closely during treatment. For patients with worsening of liver function tests considered related to cabozantinib treatment (i.e. where no alternative cause is evident), the dose modification should be followed.

Cabozantinib is eliminated mainly via the hepatic route. Closer monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment. A higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed hepatic encephalopathy with cabozantinib treatment. Cabozantinib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as cabozantinib has not been studied in this population and exposure might be increased in these patients.

Hepatic encephalopathy
Cabozantinib has been associated with diarrhoea, vomiting, and decreased appetite and electrolyte abnormalities. In HCC patients with compromised livers, these non-hepatic effects may be precipitating factors for the development of hepatic encephalopathy. Patients should be monitored for signs and symptoms of hepatic encephalopathy.

Biochemical laboratory test abnormalities
Cabozantinib has been associated with an increased incidence of electrolyte abnormalities (including hypo- and hyperkalaemia, hypomagnesaemia, hypocalcaemia, hyponatremia). It is recommended to monitor biochemical parameters during cabozantinib treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Cases of hepatic encephalopathy in HCC patients can be attributed to the development of electrolyte disturbances. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant abnormalities.

CYP3A4 inducers and inhibitors
Cabozantinib is a CYP3A4 substrate. Concurrent administration of cabozantinib with the strong CYP3A4 inhibitor ketoconazole resulted in an increase in cabozantinib plasma exposure. Caution is required when administering cabozantinib with agents that are strong CYP3A4 inhibitors. Concurrent administration of cabozantinib with the strong CYP3A4 inducer rifampicin resulted in a decrease in cabozantinib plasma exposure. Therefore, chronic administration of agents that are strong CYP3A4 inducers with cabozantinib should be avoided.

P-glycoprotein substrates
Cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Patients should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.

MRP2 inhibitors
Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (e.g. cyclosporine, efavirenz, emtricitabine) should be approached with caution.

4.5. Drug Interactions

Effect of other medicinal products on cabozantinib
Strong CYP3A4 Inhibitors
Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of cabozantinib with strong CYP3A4 inhibitors. Reduce the dosage of cabozantinib if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

Strong CYP3A Inducers
Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid co-administration of cabozantinib with strong CYP3A4 inducers. Increase the dosage of cabozantinib if coadministration with strong CYP3A4 inducers cannot be avoided. Avoid St. John's Wort which may also decrease exposure of cabozantinib.

MRP2 inhibitors
In vitro data demonstrate that cabozantinib is a substrate of MRP2. Therefore, administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations.

Bile salt-sequestering agents
Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure. The clinical significance of these potential interactions is unknown.

Effect of cabozantinib on other medicinal products
The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. As unchanged contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended.

Because of high plasma protein binding levels of cabozantinib a plasma protein displacement interaction with warfarin may be possible. In case of such combination, INR values should be monitored.

P-glycoprotein substrates
Cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.

Excipient related warnings
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy
Based on findings from animal studies and its mechanism of action, cabozantinib can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose. Advice pregnant women of the potential risk to a fetus.

Lactation
There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with cabozantinib and for 4 months after the final dose.

Females and Males of Reproductive Potential
Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating cabozantinib.

Contraception
Cabozantinib can cause fetal harm when administered to a pregnant woman.

Females
Advise females of reproductive potential to use effective contraception during treatment with cabozantinib and for 4 months after the final dose.

Infertility
Females and Males
Based on findings in animals, cabozantinib may impair fertility in females and males of reproductive potential.

Paediatric Use
The safety and effectiveness of cabozantinib in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness were observed between these patients and younger patients.

Hepatic impairment
Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the cabozantinib dose in patients with moderate hepatic impairment. Avoid cabozantinib in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

Renal impairment
No dosage adjustment is recommended in patients with mild or moderate renal impairment.
There is no experience with cabozantinib in patients with severe renal impairment.

4.7. Effects on Ability to Drive and Use Machines

Cabozantinib has minor influence on the ability to drive and use machines. Adverse reactions such as fatigue and weakness have been associated with cabozantinib. Therefore, caution should be recommended when driving or operating machines.

4.8. Undesirable Effects

Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following conventions: Very common (≥1/10), Common (≥1/100 to <1/10),
Uncommon (≥1/1,000 to <1/100),
Rare (≥1/10,000 to <1/1,000),
Very rare (<1/10,000),
Not known (cannot be estimated from the available data).

MedDRA System Organ Class	Very Common	Common	Uncommon	Not Known
Infections and infestations		abscess		
Blood and lymphatic disorders	anaemia, thrombocytopenia[a]	neutropenia[a], lymphopenia[a]		
Endocrine disorders	hypothyroidism[c]			
Metabolism and nutrition disorders	decreased appetite, hypomagnesaemia[b], hypokalaemia[b], hypoalbuminaemia[b]	dehydration, hypophosphataemia[b], hyponatraemia[b], hypocalcaemia[b], hyperkalaemia[c], hyperbilirubinemia[c], hyperglycaemia[c], hypoglycaemia[b]		
Nervous system disorders	dysgeusia, headache, dizziness	peripheral neuropathy (including sensory)	convulsion	cerebro-vascular accident
Ear and labyrinth disorders		tinnitus		
Cardiac disorders				myocardial infarction
Vascular disorders	hypertension[e], haemorrhage*	deep vein thrombosis, venous thrombosis, arterial thrombosis		aneurysms and artery dissections
Respiratory, thoracic, and mediastinal disorders	dysphonia, dyspnoea, cough	pulmonary embolism		
Gastrointestinal disorders	diarrhoea*, nausea, vomiting, stomatitis, constipation, abdominal pain[d], dyspepsia, upper abdominal pain	gastrointestinal perforation*, fistula*, gastroesophageal reflux disease, haemorrhoids, oral pain, dry mouth, dysphagia, glossodynia	pancreatitis,	
Hepatobiliary disorders		hepatic encephalopathy*	hepatitis cholestatic	
Skin and subcutaneous tissue disorders	palmar-plantar erythrodysaesthesia syndrome, rash	pruritus, alopecia, dry skin, dermatitis acneiform, hair colour change, hyperkeratosis		
Musculoskeletal and connective tissue disorders	pain in extremity	muscle spasms, arthralgia	osteonecrosis of the jaw	
Renal and urinary disorders		proteinuria		
General disorders and administration site conditions	fatigue, mucosal inflammation, asthenia, peripheral oedema			
Investigations	weight decreased, serum ALT increased, AST increased	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			wound complications[f]	

[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.

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. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

There is no specific treatment for cabozantinib overdose and possible symptoms of overdose have not been established.
In the event of suspected overdose, cabozantinib should be withheld and supportive care instituted. Metabolic clinical laboratory parameters should be monitored at least weekly or as deemed clinically appropriate to assess any possible changing trends. Adverse reactions associated with overdose are to be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

In vitro biochemical and/or cellular assays have shown that cabozantinib inhibits the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.

Pharmacodynamics
The exposure-response or –safety relationship for cabozantinib is unknown.

Cardiac Electrophysiology
The effect of cabozantinib on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled trial in patients with medullary thyroid cancer administered a cabozantinib capsule formulation. A mean increase in QTcF of 10 - 15 ms was observed at 4 weeks after initiation. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed.

5.2 Pharmacokinetic Properties

Repeat daily dosing of a cabozantinib capsule formulation for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15.

Absorption
Median time to peak cabozantinib concentrations (Tmax) ranged from 3 to 4 hours post-dose. A 19% increase in the Cmax of cabozantinib compared to a cabozantinib capsule formulation was observed following a single 140 mg dose. A less than 10% difference in the AUC was observed between cabozantinib and a cabozantinib capsule formulation.

Food Effect
Cabozantinib C_{max} and AUC increased by 41% and 57%, respectively, following a high-fat meal relative to fasted conditions administered a single oral dose of a cabozantinib capsule formulation.

Distribution
The oral volume of distribution (V_z/F) of cabozantinib is approximately 319 L. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

Elimination
The predicted terminal half-life is approximately 99 hours and the clearance (CL/F) at steadystate is estimated to be 2.2 L/hr.

Metabolism
Cabozantinib is a substrate of CYP3A4 *in vitro*.

Excretion
Approximately 81% of the total administered radioactivity was recovered within a 48-day collection period following a single dose of radiolabeled 14C-cabozantinib. Approximately 54% was recovered in feces and 27% in urine. Unchanged cabozantinib accounted for 43% of the total radioactivity in feces and was not detectable in urine following a 72-hour collection.

Elimination
The predicted terminal half-life is approximately 99 hours and the clearance (CL/F) at steady state is estimated to be 2.2 L/hr.

Specific Populations
Patients with Hepatic Impairment
Based on a population pharmacokinetic analysis of cabozantinib, no clinically significant differences in the mean cabozantinib exposure were observed with normal liver function (total bilirubin and AST ≤ ULN) and those with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5x ULN and any AST value).

In vitro Studies

CYP Enzymes:

Inhibition of CYP3A4 reduced the formation of the oxidative metabolite by > 80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation.

Although cabozantinib is an inhibitor of CYP2C8 *in vitro*, a clinical study of this potential interaction concluded that concurrent use did not result in a clinically relevant effect on CYP2C8 substrate exposure. Given this finding, other less sensitive substrates of pathways affected by cabozantinib *in vitro* (i.e., CYP2C9, CYP2C19, and CYP3A4) were not evaluated in a clinical study, because, although a clinically relevant exposure effect cannot be ruled out, it is unlikely. Cabozantinib does not inhibit CYP1A2 and CYP2D6 isozymes *in vitro*.

Cabozantinib is an inducer of CYP1A1 mRNA; however, the clinical relevance of this finding is unknown. Cabozantinib does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4.

Transporters:
Cabozantinib is an inhibitor, but not a substrate, of P-gp transport activities and has the potential to increase concentrations of co-administered substrates of P-gp. The clinical relevance of this finding is unknown.

Cabozantinib is a substrate of MRP2 *in vitro* and MRP2 inhibitors have the potential to increase concentrations of cabozantinib. The clinical relevance of this finding is unknown.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of cabozantinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. In the 2-year rat carcinogenicity study, once daily oral administration of cabozantinib resulted in a statistically significant increase in the incidence of malignant/complex malignant pheochromocytoma in combination with benign pheochromocytoma or in benign pheochromocytoma alone in male rats at a dose of 1 mg/kg (approximately 5 times the human exposure by AUC at the recommended 60 mg dose).

Cabozantinib was not carcinogenic in a 26-week carcinogenicity study in rasH2 transgenic mice at a slightly higher exposure than the intended human therapeutic exposure. Cabozantinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using human lymphocytes or in the *in vivo* mouse micronucleus assay. Based on nonclinical findings, male and female fertility may be impaired by treatment with Cabozantinib. In a fertility study in which cabozantinib was administered to male and female rats at doses of 1, 2.5, and 5 mg/kg/day, male fertility was significantly compromised at doses equal to or greater than 2.5 mg/kg/day (approximately 13-fold of human AUC at the recommended dose), with a decrease in sperm counts and reproductive organ weights. In females, fertility was significantly reduced at doses equal to or greater than 1 mg/kg/day (5-fold of human AUC at the recommended dose) with a significant decrease in the number of live embryos and a significant increase in pre- and post-implantation losses.

Observations of effects on reproductive tract tissues in general toxicology studies were supportive of effects noted in the dedicated fertility study and included hypospermia and absence of corpora lutea in male and female dogs in a 6-month repeat dose study at plasma exposures (AUC) approximately 0.5-fold (males) and <0.1-fold (females) of those expected in humans at the recommended dose. In addition, female rats administered 5 mg/kg/day for 14 days (approximately 9-fold of human AUC at the recommended dose) exhibited ovarian necrosis [Cabometyx. USFDA Label dated Jul-2020].

7. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities
None.

8.2 Packing Information
30's HDPC bottle pack.

8.3 Storage and Handling Instructions
Do not store above 30°C. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

8.4 Shelf life
24 months.

8.5 Nature and specification of the container
Base Foil: Clear 250 mic PVC/51 mic Aclar.
Lidding Foil: 0.025 mm plain foil 7 gsm HSL coating aluminium lid Foil.

9. PATIENT COUNSELING INFORMATION

Advise the patient to read package insert.

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.

Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during Cabozantinib treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking Cabozantinib.

Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occur.

Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advice patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.

Impaired wound healing: Advice patients that Cabozantinib may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.
Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.

Embryo-fetal toxicity: Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.

Advise females of reproductive potential to use effective contraception during treatment with Cabozantinib and for 4 months after the final dose.

Lactation: Advise women not to breastfeed during treatment with Cabozantinib and for 4 months following the last dose.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort.

Important administration information
Instruct patients to take Cabozantinib at least 1 hour before or at least 2 hours after eating.

10. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,
Formulation Division, Unit II,
Sy.no.1277, 1319 to 1324,
Nandigama (Village & Mandal),
Ranga Reddy District
Telangana-509228,
India.

C030338-00

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Not Applicable

12. DATE OF REVISION

Apr-2021