SUMMARY OF PRODUCT CHARACTERISTICS

Cabozanix 60mg Tablet

1. Name of the medicinal product

Cabozanix 60 mg Tablet

2. Qualitative and quantitative composition

One tablet contains Cabozantinib (S)-malate equivalent to 60 mg Cabozantinib.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form Tablet.

4. Clinical particulars

4.1 Therapeutic indications

Cabozanix is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.

4.2 Posology and method of administration

Therapy with Cabozanix should be initiated by a physician experienced in the administration of anticancer medicinal products.

Posology

The recommended dose of Cabozanix is 140 mg once daily, taken as one 60 mg Tablet and four 20 mg capsules. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

It should be expected that a majority of patients treated with Cabozanix will require one or more dose adjustments (reduction and/or interruption) due to toxicity. Patients should therefore be closely monitored during the first eight weeks of therapy.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of Cabozanix therapy. When dose reduction is necessary, it is recommended to reduce to 100 mg daily, taken as one 60 mg Tablet and one 20 mg capsule, and then to 60 mg daily, taken as four 20 mg tablets.

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.

As most events can 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), and gastrointestinal (GI) events (abdominal or mouth pain, mucosal inflammation, constipation, diarrhoea, vomiting).

The occurrence of some serious adverse reactions (like GI fistula) might be dependent on the cumulative dose and might present in a later stage of treatment.

If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose.

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.

Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered. **Elderly patients**

No specific dose adjustment for the use of Cabozantinib in older people (≥ 65 years) is recommended. However, a trend in increased rate of SAEs has been observed in subjects aged 75 years and older.

Race

There is little experience with Cabozantinib in non-White patients.

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.

Hepatic impairment

In patients with mild or moderate hepatic impairment the recommended dose of cabozantinib is 60 mg once daily. Monitor for adverse events and adjust dose or use dosing interruption as needed. Cabozantinib is not recommended for use in subjects with severe hepatic impairment as safety and efficacy have not been established in this population.

Patients with cardiac impairment

There is limited data in patients with cardiac impairment. No specific dosing recommendations can be made.

Pediatric population

The safety and efficacy of cabozantinib in children aged <18 years have not yet been established. No data are available.

Method of administration

The Tablet should be swallowed whole and not opened. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking Cabozanix.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Dose reductions and dose interruptions occurred in 79% and 72%, respectively, of cabozantinib-treated patients in the pivotal clinical trial. Two dose reductions were required in 41% of patients. The median time to first dose reduction was 43 days, and to first dose interruption was 33 days. Close monitoring of patients is therefore recommended during the first eight weeks of therapy (see section 4.2).

Perforations, fistulas, and intra-abdominal abscesses

Serious GI perforations and fistulas, sometimes fatal, and intra-abdominal abscesses have been observed with cabozantinib. Patients who have had recent radiotherapy, have inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, peritonitis, or diverticulitis), have tumour infiltration of trachea, bronchi, or oesophagus, have complications from prior GI surgery (particularly when associated with delayed or incomplete healing), or have complications from prior radiation therapy to the thoracic cavity (including mediastinum) should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas. Non-GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy. Cabozantinib should be discontinued in patients who experience a GI perforation or a GI or non-GI fistula.

Thromboembolic events

Events of venous thromboembolism and events of arterial thromboembolism have been observed with cabozantinib. Cabozantinib should be used with caution in patients who are at risk for, or who have a history of, these events. Cabozantinib

should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.

Hemorrhage

Hemorrhage has been observed with cabozantinib. Patients who have evidence of involvement of the trachea or bronchi by tumour or a history of haemoptysis prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients with serious haemorrhage or recent haemoptysis.

Wound complications

Wound complications have been observed with cabozantinib. Cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery, if possible. The decision to resume cabozantinib therapy after surgery should be based on clinical judgment of adequate wound healing. Cabozantinib should be discontinued in patients with wound healing complications requiring medical intervention.

Hypertension

Hypertension has been observed with cabozantinib. All patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensives, the cabozantinib dose should be reduced. Cabozantinib should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of cabozantinib. In case of hypertensive crisis, cabozantinib should be discontinued.

Osteonecrosis

Events of osteonecrosis of the jaw (ONJ) have been observed with cabozantinib. An oral examination should be performed prior to initiation of cabozantinib and periodically during cabozantinib therapy. Patients should be advised regarding oral hygiene practice. For invasive dental procedures, cabozantinib treatment should be held at least 28 days prior to scheduled surgery, if possible. Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. Cabozantinib should be discontinued in patients who experience ONJ.

Palmar-plantar erythrodysaesthesia syndrome

Palmar-plantar erythrodysaesthesia syndrome (PPES) has been observed with cabozantinib. When PPES is severe, interruption of treatment with cabozantinib should be considered. Cabozantinib should be restarted with a lower dose when PPES has been resolved to grade 1.

Proteinuria

Proteinuria has been observed with cabozantinib. Urine protein should be monitored regularly during cabozantinib treatment. Cabozantinib should be discontinued in patients who develop nephrotic syndrome.

Reversible posterior leukoencephalopathy syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES) has been observed with cabozantinib. Cabozantinib treatment should be discontinued in patients with RPLS.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on Cabozantinib

CYP3A4 inhibitors and inducers

Administration of the strong CYP3A4 inhibitor ketoconazole (400 mg daily for 27 days) to healthy volunteers decreased cabozantinib clearance (by 29%) and increased single-dose plasma cabozantinib exposure (AUC) by 38%. Therefore co-

administration of strong CYP3A4 inhibitors (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) with cabozantinib should be approached with caution.

Administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 31 days) to healthy volunteers increased cabozantinib clearance (4.3-fold) and decreased single-dose plasma cabozantinib exposure (AUC) by 77%. Chronic co-administration of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort [Hypericum perforatum]) with cabozantinib should therefore be avoided.

Gastric pH modifying agents

Co-administration of proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single dose of 100 mg cabozantinib to healthy volunteers resulted in no clinically-significant effect on plasma cabozantinib exposure (AUC). No dose adjustment is indicated when gastric pH modifying agents (i.e., PPIs, H2 receptor antagonists, and antacids) are co-administered with 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 (see section 5.2). 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 (section 5.2) a plasma protein displacement interaction with warfarin may be possible. In case of such combination, INR values should be monitored. **P-glycoprotein substrates**

Cabozantinib was an inhibitor (IC50 = 7.0 μM), but not a substrate, of P-gp transport activities in a bidirectional assay system using MDCK-MDR1 cells. Therefore, 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must be advised to avoid pregnancy while on cabozantinib. Female partners of male patients taking cabozantinib must also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least 4 months after completing therapy. 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.

Pregnancy

There are no studies in pregnant women using cabozantinib. Studies in animals have shown embryo-foetal and teratogenic effects (see section 5.3). The potential risk for humans is unknown. Cabozantinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with cabozantinib.

Breast-feeding

It is not known whether cabozantinib and/or its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should discontinue breast-feeding during treatment with cabozantinib, and for at least 4 months after completing therapy.

Fertility

There are no data on human fertility. Based on non-clinical safety findings, male and female fertility may be compromised by treatment with cabozantinib (see section 5.3). Both men and women should be advised to seek advice and consider fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

Cabozantinib has a 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

Summary of safety profile

The most common serious adverse reactions associated with cabozantinib are pneumonia, mucosal inflammation, hypocalcaemia, dysphagia, dehydration, pulmonary embolism, and hypertension. The most frequent adverse reactions of any grade (experienced by at least 20% of patients) included diarrhea, PPES, weight decreased, decreased appetite, nausea, fatigue, dysgeusia, hair colour changes, hypertension, stomatitis, constipation, vomiting, mucosal inflammation, asthenia, and dysphonia.

The most common laboratory abnormalities were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased alkaline phosphatase (ALP), lymphopenia, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, hyperbilirubinemia, hypomagnesaemia, and hypokalemia.

Description of selected adverse reactions

A thyroid stimulating hormone (TSH) value above normal after first dose was observed in 57% of patients on cabozantinib versus 19% of patients on placebo (regardless of baseline values). Ninety-two percent of patients on the cabozantinib arm had a prior thyroidectomy, and 89% were taking thyroid hormones prior to first dose.

An increase from baseline in corrected QT interval by Fridericia (QTcF) of 10 - 15 ms on Day 29 (but not on Day 1) following initiation of cabozantinib treatment (at a dose of 140 mg qd) was observed in a controlled clinical study in cancer patients. This effect was not associated with a change in cardiac wave form morphology or new rhythms. No cabozantinib-treated subjects had a QTcF >500 ms.

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 the national reporting system listed at: www.mhra.gov.uk/yellowcard.

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 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor, ATC code: L01XE26.

Mechanism of action

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including RET, the GAS6 receptor (AXL), the stem cell factor receptor (KIT), and Fms-like tyrosine kinase-3 (FLT3).

Pharmacodynamic effects

Cabozantinib exhibited dose-related tumour growth inhibition, tumor regression, and/or inhibited metastasis in a broad range of preclinical tumour models.

Efficacy with cabozantinib was observed in medullary thyroid cancer patients with wild-type or mutant RET.

Pediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with cabozantinib in one or more subsets of the paediatric population in the treatment of malignant solid tumours.

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary

5.2 Pharmacokinetic properties

Absorption

Following oral administration of cabozantinib, peak cabozantinib plasma concentrations are reached at 2 to 5 hours post-dose. Plasma-concentration time profiles show a second absorption peak approximately 24 hours after administration, which suggests that cabozantinib may undergo enterohepatic recirculation.

Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in an approximately a 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state is achieved by approximately Day 15.

A high-fat meal moderately increased Cmax and AUC values (41% and 57%, respectively) relative to fasted conditions in healthy volunteers administered a single 140 mg oral cabozantinib dose. There is no information on the precise food-effect when taken 1 hour after administration of cabozantinib.

Distribution

Cabozantinib is highly protein bound in vitro in human plasma (≥ 99.7%). Based on the populationpharmacokinetic (PK) model, the volume of distribution (V/F) is approximately 349 L (SE: ± 2.73%). Protein binding was not altered in subjects with mild or moderately impaired renal or hepatic function.

Biotransformation

Cabozantinib was metabolized in vivo. Four metabolites were present in plasma at exposures (AUC) greater than 10% of parent: XL184-N-oxide, XL184 amide cleavage product, XL184 monohydroxy sulfate, and 6-desmethyl amide cleavage product sulfate. Two non-conjugated metabolites (XL184-N-oxide and XL184 amide cleavage product), which possess <1% of the on-target kinase inhibition potency of parent cabozantinib, each represent <10% of total drug-related plasma exposure.

Cabozantinib is a substrate for CYP3A4 metabolism in vitro, as a neutralizing antibody to CYP3A4 inhibited formation of metabolite XL184 N-oxide by >80% in a NADPH-catalyzed human liver microsomal (HLM) incubation; in contrast, neutralizing antibodies to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. A neutralizing antibody to CYP2C9 showed a minimal effect on cabozantinib metabolite formation (ie, a <20% reduction).

Elimination

The plasma terminal half-life of cabozantinib in single dose studies in healthy volunteers is approximately 120 hours. Mean clearance (CL/F) at steady-state in cancer patients was estimated to be 4.4 L/hr in a population PK analysis. Within a 48-day collection period after a single dose of 14C-cabozantinib in healthy volunteers, approximately 81% of the total administered radioactivity was recovered with 54% in faeces and 27% in urine.

Pharmacokinetics in special patient populations

Renal impairment

Results from a study in patients with renal impairment indicate that the ratios of geometric LS mean for plasma cabozantinib, Cmax and AUC0-inf were 19% and 30% higher, for subjects with mild renal impairment (90% CI for Cmax 91.60% to 155.51%; AUC0-inf 98.79% to 171.26%) and 2% and 6-7% higher (90% CI for Cmax 78.64% to 133.52%; AUC0-inf 79.61% to 140.11%), for subjects with moderate renal impairment, compared to subjects with normal renal function. Patients with severe renal impairment have not been studied.

Hepatic impairment

Results from a study in patients with hepatic impairment indicate that exposure (AUC0-inf) increased by 81% and 63% in subjects with mild and moderate hepatic impairment, respectively (90% CI for AUC0-inf: 121.44% to 270.34% for mild and 107.37% to 246.67% for moderate). Patients with severe hepatic impairment have not been studied.

Race

No data are available to determine a difference in PK based on race.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

In rat and dog repeat-dose toxicity studies up to 6 months duration, target organs for toxicity were GI tract, bone marrow, lymphoid tissues, kidney, adrenal and reproductive tract tissues. The no observed adverse effect level (NOAEL) for these findings were below human clinical exposure levels at intended therapeutic dose.

Cabozantinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays. Cabozantinib was not carcinogenic in the rasH2 mouse model at a slightly higher exposure than the intended human therapeutic exposure.

Fertility studies in rats have shown reduced male and female fertility. Further, hypospermatogenesis was observe in male dogs at exposure levels below human clinical exposure levels at intended therapeutic dose.

Embryo-foetal development studies were performed in rats and rabbits. In rats, cabozantinib caused postimplantation loss, foetal oedema, cleft palate/lip, dermal aplasia and kinked or rudimentary tail. In rabbits, cabozantinib produced foetal soft tissue changes (reduced spleen size, small or missing intermediate lung lobe) and increased foetal incidence of total malformations. NOAEL for embryo-foetal toxicity and teratogenic findings were below human clinical exposure levels at intended therapeutic dose.

Juvenile rats (comparable to a >2 year old pediatric population) administered cabozantinib showed increased WBC parameters, decreased haematopoiesis, pubescent/immature female reproductive system (without delayed vaginal opening), tooth abnormalities, reduced bone mineral content and density, liver pigmentation and bile duct hyperplasia. Findings in uterus/ovaries and decreased haematopoiesis appeared to be transient, while effects on bone parameters and liver

pigmentation were sustained. Evaluations in juvenile rats (comparable to a <2 year old pediatric population) have not been performed.

6. Pharmaceutical particulars

6.1 List of excipients

Pregelatinised Starch (Starch 1500)

Croscarmellose Sodium

Sodium Starch Glycolate (Primojel)

Polacrilin Pottasium (Kyron-T314)

Colloidal Anhydrous Silica (Aerosil 200)

Sodium Stearyl Fumarate

Microcrystalline Cellulose (Avicel PH 102)

Coating Materials:

Opadry II Orange (85G530012)

Opadry II White (85G68918)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Cabozanix 60mg Tablet: HDPE bottle containing 30 Tablets in a single HDPE Bottle.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer and Marketing authorisation holder

Beacon Pharmaceuticals Limited

Kathali, Bhaluka, Mymensingh, Bangladesh

8. Marketing in Pakistan by:

Himmel Pharmaceuticals (Pvt) Ltd.

Gound Floor, 6-Judicial Colony, Phase-1 (Ext) Shahrah Nazaria e Pakistan, Lahore

9. Registration Details:

Registration No: 122432

Date of Issuance of Registration Letter: 30 September, 2024