Renib

Regorafenib INN 40 mg Tablet

DRUG INTERNATIONAL LTD.

Composition: Each film coated tablet contains Regorafenib 40mg as Regorafenib Monohydrate INN.

Mechanism of Action: Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumorangiogenesis, metastasis and tumor immunity. In vitro biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl and CSF1R at concentrations of regorafenib that have been achieved clinically. In vivo models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model and inhibition of tumor growth in several mouse xenograft models including some for human colorectal carcinoma, gastrointestinal stromal and hepatocellular carcinoma. Regorafenib also demonstrated anti-metastatic activity in a mouse xenograft model and two mouse orthotopic models of human colorectal carcinoma.

Pharmacodynamics: The effect of multiple doses of Renib (160 mg once daily for 21 days) on the QTc interval was evaluated in an open-label, single-armstudy in 25 patients with advanced solid tumors. No large changes in the mean QTc interval (i.e., > 20 msec) were detected in the study.

Pharmacokinetics

Absorption: Following a single 160 mg dose of Renib in patients with advanced solid tumors, Regorafenib reaches geometric mean peak plasma level (C_{max}) of 2.5 µg/mL at a median time of 4 hours and a geometric mean area under the plasma concentration vs. time curve (AUC) of 70.4 µg*h/mL. The AUC of Regorafenib at steady-state increases less than dose proportionally at doses greater than 60 mg. At steady-state, regorafenib reaches a geometric mean C_{max} of 3.9 µg/mL and a geometric mean AUC of 58.3 µg*h/mL. The coefficient of variation of AUC and C_{max} is between 35% and 44%. The mean relative bioavailability of tablets compared to an oral solution is 69% to 83%.

Distribution: Regorafenib undergoes enterohepatic circulation with multiple plasma concentration peaks observed across the 24-hour dosing interval. Regorafenib is highly bound (99.5%) to human plasma proteins.

Elimination: Following a single 160 mg oral dose of Renib, the geometric mean (minimum to maximum) elimination half-lives for regorafenib and the M-2 metabolite in plasma are 28 hours (14 to 58 hours) and 25 hours (14 to 32 hours), respectively. M-5 has a longer mean (minimum to maximum) elimination half-life of 51 hours (32 to 70 hours).

Metabolism: Regorafenib is metabolized by CYP3A4 and UGT1A9. The main circulating metabolites of Regorafenib measured at steady-state in human plasma are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl). Both metabolites have similar in vitro pharmacological activity and steady-state concentrations as Regorafenib. M-2 and M-5 are highly protein bound (99.8% and 99.95%, respectively).

Excretion: Approximately 71% of a radiolabeled dose was excreted in feces (47% as parent compound, 24% as metabolites) and 19% of the dose was excreted in urine (17% as glucuronides) within 12 days after administration of a radiolabeled oral solution at a dose of 120 mg.

Indications:

Colorectal Cancer: Renib is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy.

Gastrointestinal Stromal Tumors: Renib is indicated for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with Imatinib Mesylate and Sunitinib Malate.

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

Dosage and Administration: The recommended dose is 160 mg Renib (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle. Treatment should be continued until disease progression or unacceptable toxicity. Renib should be taken at the same time each day and swallowed tablet whole with water after a low-fat meal that contains less than 600 calories and less than 30% fat. Two doses of Renib should not be taken on the same day to make up for a missed dose from the previous day.

Dose Modifications: If dose modifications are required, the dose should be reduced in 40 mg (one tablet) increments; the lowest recommended daily dose of Renib is 80 mg daily. Or, as directed by the registered physicians.

Side Effects:

- Hepatotoxicity
- Infections
- Hemorrhage
- Gastrointestinal Perforation or Fistula
- Dermatological Toxicity
- Hypertension
- Cardiac Ischemia and Infarction
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Contraindication: It is contraindicated in patients with known hypersensitivity to Regorafenib or any other components of this product.

Use in Pregnancy and Lactation: There are no available data on Renib use in pregnant women. Pregnant women should be advised of the potential hazard to a fetus.

Lactation: There are no data on the presence of Regorafenib or its metabolites in human milk, the effects of Regorafenib on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions in breastfed infants from Renib, breastfeed should not be done during treatment with Renib and for 2 weeks after the final dose.

Females and Males of Reproductive Potential: Female: Effective contraception should be used during treatment and for 2 months after completion of therapy. **Males:** Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for 2 months following the final dose of Renib.

Infertility: There are no data on the effect of Renib on human fertility.

Pediatric Use: The safety and efficacy of Renib in pediatric patients less than 18 years of age have not been established.

Drug Interction:

Effect of Strong CYP3A4 Inducers on Regorafenib: Co-administration of a strong CYP3A4 inducer with Renib decreased the plasma concentrations of Regorafenib, increased the plasma concentrations of the active metabolite M-5, and resulted in no change in the plasma concentrations of the active metabolite M-2 and may lead to decreased efficacy. Concomitant use of Renib with strong CYP3A4 inducers (e.g. Rifampin, Phenytoin, Carbamazepine, Phenobarbital, and St. John's Wort) should be avoided.

Effect of Strong CYP3A4 Inhibitors on Regorafenib: Co-administration of a strong CYP3A4 inhibitor with Renib increased the plasma concentrations of Regorafenib and decreased the plasma concentrations of the active metabolites M-2 and M-5 and may lead to increased toxicity. Concomitant use of Renib with strong CYP3A4 inhibitors (e.g. Clarithromycin, Grapefruit juice, Itraconazole, Ketoconazole, Nefazodone, Posaconazole, Telithromycin, and Voriconazole) should be avoided.

Effect of Regorafenib on Breast Cancer Resistance Protein (BCRP) Substrates: Co-administration of Renib with a BCRP substrate increased the plasma concentrations of the BCRP substrate Patients should be monitored closely for signs and symptoms of exposure related toxicity to the BCRP substrate(e.g. Methotrexate, Fluvastatin, Atorvastatin). Concomitant BCRP substrate product information should be consulted when considering administration of such products together with Renib.

Precautions:

Hepatotoxicity: Severe drug-induced liver injury with fatal outcome occurred in Renib- treated patients in clinical trials. In most cases, liver dysfunction occurred within the first 2 months of therapy and was characterized by a hepatocellular pattern of injury. Liver function tests (ALT, AST, and bilirubin) should be obtained before initiation of Renib and monitored at least every two weeks during the first 2 months of treatment. Renib should be temporarily held and then reduced or permanently discontinued depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis.

Infections: Renib caused an increased risk of infections. The most common infections were urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic fungal infections (3.3%) and pneumonia (2.6%). Fatal outcomes caused by infection occurred more often in patients treated with Renib (1.0%) as compared to patients receiving placebo (0.3%); the most common fatal infections were respiratory (0.6% in Renib- treated patients vs 0.2% in patients receiving placebo). Renib should be withheld for Grade 3 or 4 infections, or worsening infection of any grade. Renib should be resumed at the same dose following resolution of infection.

Hemorrhage: Renib caused an increased incidence of hemorrhage. The incidence of fatal hemorrhagic events was 0.7%, involving the central nervous system or the respiratory, gastrointestinal, or genitourinary tracts. Renib should be permanently discontinued in patients with severe or life-threatening hemorrhage. INR levels should be monitored more frequently in patients receiving Warfarin.

Gastrointestinal Perforation or Fistula: Gastrointestinal perforation occurred in 0.6% of 4518 patients treated with Renib across all clinical trials of Renib administered as a single agent; this included eight fatal events. Renib should be permanently discontinued in patients who develop gastrointestinal perforation or fistula.

Dermatologic Toxicity: A higher incidence of Hand-foot skin reaction (HFSR) was observed in Asian patients treated with Renib (all grades: 72%; Grade 3: 18%). Renib should be withheld, reduced the dose, or permanently discontinued Renib depending on the severity and persistence of dermatologic toxicity. Supportive measures for symptomatic relief should be instituted.

Hypertension: Renib caused an increased incidence of hypertension (30% versus 8% in CORRECT, 59% versus 27% in GRID, and 31% versus 6% in RESORCE). The onset of hypertension occurred during the first cycle of treatment in most patients who developed hypertension (67% in randomized, placebo-controlled trials). Renib should not be initiated unless blood pressure is adequately controlled, monitored blood pressure weekly for the first 6 weeks of treatment and then every cycle, or more frequently, as clinically indicated. Renib should be temporarily or permanently withheld for severe or uncontrolled hypertension.

Cardiac Ischemia and Infarction: Renib increased the incidence of myocardial ischemia and infarction (0.9%vs 0.2%) in randomized placebo-controlled trials. Renib should be withheld in patients who develop new or acute onset cardiac ischemia or infarction. Renib should be resumed only after resolution of acute cardiac ischemic events, if the potential benefits outweigh the risks of further cardiac ischemia.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one of 1200 Renib- treated patients across all clinical trials. An evaluation for RPLS should be performed in any patient presenting with seizures, severe headache, visual disturbances, confusion or altered mental function. Renib should be discontinued in patients who develop RPLS.

Wound Healing Complications: No formal studies of the effect of Regorafenib on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as Renib can impair wound healing, discontinue treatment with Renib atleast 2 weeks prior to scheduled surgery. The decision to resume Renib after surgery should be based on clinical judgment of adequate wound healing. Renib should be discontinued in patients with wound dehiscence.

Embryo-Fetal Toxicity: There are no available data on Renib use in pregnant women. Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment with Renib and for 2 months after the final dose. Males with female partners of reproductive potential should be advised to use effective contraception during treatment with Renib and for 2 months after the final dose.

Overdose: The highest dose of Renib studied clinically is 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue. There is no known antidote for Renib overdose. In the event of suspected overdose, Renib should be interrupted, instituted supportive care, and observed until clinical stabilization.

Storage: Store below 30° C in a cool and dry place, away from sunlight. Keep out of the reach of children.

Packing: Each box contains 30 tablets in a blister pack.