Regora

Regorafenib

COMPOSITION

Regora Tablet: Each film coated tablet contains Regorafenib Monohydrate INN equivalent to Regorafenib 40 mg.

CLINICAL PHARMACOLOGY

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, tumor angiogenesis, metastasis and tumor immunity. In *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, Trk2A, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, and Abl and CSFIR at concentrations of Regorafenib that have been achieved clinically. In *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

Cardiac Electrophysiology

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

PHARMACOKINETICS

Absorption

Following a single 160 mg dose of Regorafenib in patients with advanced solid tumors, Regorafenib reaches a 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%.

In a food-effect study, 24 healthy men received a single 160 mg dose of Regorafenib on three separate occasions: under a fasted state, with a high-fat meal and with a low-fat meal. A high-fat meal (945 calories and 54.6 g fat) increased the mean AUC of Regorafenib by 48% and decreased the mean AUC of the M-2 and M-5 metabolites by 20% and 51%, respectively, as compared to the fasted state. A low-fat meal (319 calories and 8.2 g fat) increased the mean AUC of Regorafenib, M-2 and M-5 by 36%, 40% and 23%, respectively as compared to fasted conditions. Regorafenib was administered with a low-fat meal.

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.

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 Metabolits 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).

Elimination

Following a single 160 mg oral dose of Regorafenib, 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).

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.

Specific Populations

Age, sex, race and weight had no clinically meaningful effect on the pharmacokinetics of Regorafenib.

Hepatic Impairment

Based on a population pharmacokinetic analysis, no clinically important differences in the mean total exposure of Regorafenib, including M-2 and M-5, were noted amongst patients with normal liver function (total bilirubin and AST ≤ULN, n=744), mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >ULN to ≤1.5x ULN, n=437), and moderate hepatic impairment (total bilirubin >1.5x to ≤3x ULN and any AST, n=36). The pooled analysis included 391 patients with HCC of whom 116, 249, and 26 were categorized as having normal liver function, mild, and moderate hepatic impairment, respectively. The pharmacokinetics of Regorafenib were not evaluated in patients with severe hepatic impairment (total bilirubin >3x ULN).

Renal Impairment

The pharmacokinetics of Regorafenib, M-2, and M-5 was evaluated in 6 patients with severe renal impairment (CLcr 15-29 mL/min) and 18 patients with normal/mild renal function (CLcr ≥60 mL/min) following the administration of Regorafenib at a dose of 160 mg daily for 21 days. No differences in the mean steady-state exposure of Regorafenib, M-2, or M-5 were observed in patients with severe renal impairment compared to patients with normal renal function. The pharmacokinetics of Regorafenib has not been studied in patients with end-stage renal disease on dialysis.

Drug-drug interactions

Effect of Regorafenib on Cytochrome P450 Substrates: In vitro studies suggested that Regorafenib is an inhibitor of CYP2C8, CYP2C9, CYP2B6, CYP3A4 and CYP2C19; M-2 is an inhibitor of CYP2C9, CYP2C8, CYP3A4 and CYP2D6, and M-5 is an inhibitor of CYP2C8. In vitro studies suggested that Regorafenib is not an inducer of CYP1A2, CYP2B6, CYP2C19, and CYP3A4 enzyme activity.

Patients with advanced solid tumors received single oral doses of CYP substrates, 2 mg of Midazolam (CYP3A4), 40 mg of Omeprazole (CYP2C19) and 10 mg of Warfarin (CYP2C9) or 4 mg of Rosiglitazone (CYP2C8) one week before and two weeks after Regorafenib at a dose of 160 mg once daily. No clinically meaningful effect was observed in the mean AUC of Rosiglitazone (N=12) or the mean Omeprazole (N=11) plasma concentrations measured 6 hours after dosing or the mean AUC of Midazolam (N=15). The mean AUC of Warfarin (N=8) increased by 25%.

Effect of CYP3A4 Strong Inducers on Regorafenib: Twenty-two healthy men received a single 160 mg dose of Regorafenib alone and then 7 days after starting Rifampin. Rifampin, a strong CYP3A4 inducer, was administered at a dose of 600 mg daily for 9 days. The mean AUC of Regorafenib decreased by 50% and mean AUC of M-5 increased by 264%. No change in the mean AUC of M-2 was observed.

Effect of CYP3A4 Strong Inhibitors on Regorafenib: Eighteen healthy men received a single 160 mg dose of Regorafenib alone and then 5 days after starting Ketoconazole. Ketoconazole, a strong CYP3A4 inhibitor, was administered at a dose of 400 mg daily for 18 days. The mean AUC of Regorafenib increased by 33% and the mean AUC of M-2 and M-5 both decreased by 93%.

Effect of Neomycin on Regorafenib: Twenty-seven healthy men received a single 160 mg dose of Regorafenib and then 5 days after starting Neomycin. Neomycin, a non-absorbable antibiotic, was administered at a dose of 1 gram three times daily for 5 days. No clinically meaningful effect on the mean AUC of Regorafenib was observed; however, the mean AUC of M-2 decreased by 76% and the mean AUC of M-5 decreased by 86%. The decreased exposure of M-2 and M-5 may result in a decreased efficacy of Regorafenib. The effects of other antibiotics on the exposure of Regorafenib and its active metabolites have not been studied.

Effect of Regorafenib on UGT1A1 Substrates: In vitro studies showed that Regorafenib, M-2, and M-5 competitively inhibit UGT1A9 and UGT1A1 at therapeutically relevant concentrations. Eleven patients received Irinotecan-containing combination chemotherapy with Regorafenib at a dose of 160 mg. The mean AUC of Irinotecan increased by 28% and the mean AUC of SN-38 increased by 44% when Irinotecan was administered 5 days after the last of 7 daily doses of Regorafenib.

Effect of Regorafenib on BCRP Substrates: Administration of Regorafenib (160 mg for 14 days) prior to administration of a single dose of Rosuvastatin (5 mg), a BCRP substrate, resulted in a 3.8-fold increase in mean exposure (AUC) of Rosuvastatin and a 4.6-fold increase in C_{max}.

INDICATIONS

Colorectal Cancer

Regorafenib 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 wildtype, an anti-EGFR therapy.

Gastrointestinal Stromal Tumors

Regorafenib 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

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

DOSAGE & ADMINISTRATION

Recommended Dose

The recommended dose is 160 mg Regorafenib (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-days cycle. Continue treatment until disease progression or unacceptable toxicity.

Take Regorafenib at the same time each day. Swallow tablet whole with water after a low-fat meal that contains less 600 caloris and less than 30% fat. Do not take two doses of Regorafenib on the same day to make up for a missed dose from the previous day.

DOSE MODIFICATIONS

If dose modifications are required, reduce the dose in 40 mg (one tablet) decrements; the lowest recommended daily dose of Regorafenib is 80 mg daily.

Interrupt Regorafenib for the following

- Grade 2 hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia syndrome (PPES)] that is recurrent or does not improve within 7 days despite dose reduction; interrupt therapy for a minimum of 7 days for Grade 3 HFSR
- Symptomatic Grade 2 hypertension
- Any Grade 3 or 4 adverse reaction
- Worsening infection of any grade

Reduce the dose of Regorafenib to 120 mg

- For the first occurrence of Grade 2 HFSR of any duration
- After recovery of any Grade 3 or 4 adverse reaction except infection
- For Grade 3 aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) elevation, only resume if the potential benefit outweighs the risk of hepatotoxicity

Reduce the dose of Regorafenib to 80 mg

- For re-occurrence of Grade 2 HFSR at the 120 mg dose
- After recovery of any Grade 3 or 4 adverse reaction at the 120 mg dose (except hepatotoxicity or infection)

Discontinue Regorafenib permanently for the following:

- Failure to tolerate 80 mg dose
- Any occurrence of AST or ALT more than 20 times the upper limit of normal (ULN)
- Any occurrence of AST or ALT more than 3 times ULN with concurrent bilirubin more than 2 times ULN
- Re-occurrence of AST or ALT more than 5 times ULN despite dose reduction to 120 mg
- For any Grade 4 adverse reaction; only resume if the potential benefit outweighs the risks

USE IN SPECIAL POPULATION

Pregnancy

Risk Summary

Based on animal studies and its mechanism of action, Regorafenib can cause fetal harm when administered to a pregnant woman. There are no available data on Regorafenib use in pregnant women. Administration of Regorafenib was embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, genitourinary, and skeletal malformations. Advise pregnant women of the potential hazard to a fetus.The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Lactation

Risk Summary

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. In rats, Regorafenib and its metabolites are excreted in milk. Because of the potential for serious adverse reactions in breastfeed infants from Regorafenib, do not breastfeed during treatment with Regorafenib and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Females

Use effective contraception during treatment and for 2 months after completion of therapy.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 months following the final dose of Regorafenib.

Infertility

There are no data on the effect of Regorafenib on human fertility. Results from animal studies indicate that Regorafenib can impair male and female fertility.

Pediatric Use

The safety and efficacy of Regorafenib in pediatric patients less than 18 years of age have not been established.

Geriatric Use

Of the 1142 Regorafenib-treated patients enrolled in randomized, placebo-controlled trials, 40% were 65 years of age and over, while 10% were 75 and over. No overall differences in efficacy were observed between these patients and younger patients. There was an increased incidence of Grade 3 hypertension (18% versus 9%) in the placebo-controlled trials among Regorafenib-treated patients 65 years of age and older as compared to younger patients. In addition, one Grade 4 hypertension event has been reported in the 65 years and older age group and none in the younger age group.

Hepatic Impairment

No dose adjustment is recommended in patients with mild (total bilirubin ≤ULN and AST >ULN, or total bilirubin >ULN to ≤1.5 times ULN) or moderate (total bilirubin >1.5 to ≤3 times ULN and any AST) hepatic impairment. Closely monitor patients with hepatic impairment for adverse reactions.

Regorafenib is not recommended for use in patients with severe hepatic impairment (total bilirubin >3x ULN) as Regorafenib has not been studied in this population.

Renal Impairment

No dose adjustment is recommended for patients with renal impairment. The pharmacokinetics of Regorafenib have not been studied in patients who are on dialysis and there is no recommended dose for this patient population.

Race

Based on pooled data from three placebo-controlled trials, a higher incidence of HFSR and liver function test abnormalities occurred in Asian patients treated with Regorafenib as compared with Whites. No starting dose adjustment is necessary based on race.

CONTRAINDICATION

None

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Severe drug-induced liver injury with fatal outcome occurred in Regorafenib-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.

Obtain liver function tests (ALT, AST, and bilirubin) before initiation of Regorafenib and monitor at least every two weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the ULN or baseline.

Temporarily hold and then reduce or permanently discontinue Regorafenib depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis.

Infections

Regorafenib caused an increased risk of infections. The overall incidence of infection (Grades 1-5) was higher (32% vs.17%) in 1142 Regorafenib-treated patients as compared to the control arm in randomized placebo-controlled trials.The incidence of grade 3 or greater infections in Regorafenib treated patients was 9%. 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 Regorafenib (1.0%) as compared to patients receiving placebo (0.3%); the most common fatal infections were respiratory (0.6% in Regorafenib-treated patients vs 0.2% in patients receiving placebo).

Withhold Regorafenib for Grade 3 or 4 infections, or worsening infection of any grade. Resume Regorafenib at the same dose following resolution of infection.

Hemorrhage

Regorafenib caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) was 18.2% in 1142 patients treated with Regorafenib and 9.5% in patients receiving placebo in randomized, placebo-controlled trials. The incidence of grade 3 or greater hemorrhage in patients treated with Regorafenib was 3.0%. The incidence of fatal hemorrhagic events was 0.7%, involving the central nervous system or the respiratory, gastrointestinal, or genitourinary tracts.

Permanently discontinue Regorafenib in patients with severe or life-threatening hemorrhage. Monitor INR levels more frequently in patients receiving Warfarin.

Gastrointestinal Perforation or Fistula

Gastrointestinal perforation occurred in 0.6% of 4518 patients treated with Regorafenib across all clinical trials of Regorafenib administered as as single agent; this included eight fatal events.

Gastrointestinal fistula occurred in 0.8% of patients treated with Regorafenib and 0.2% of patients in placebo arm across randomized, placebo-controlled trials. Permanently discontinue Regorafenib in patients who develop gastrointestinal perforation or fistula.

Dermatologic Toxicity

In randomized, placebo-controlled trials, adverse skin reactions occurred in 71.9% of patients in the Regorafenib arm and in 25.5% of patients in the placebo arm, including hand-foot skin reaction (HFSR) also known as palmar-plantar erythrodysesthesia syndrome (PPES), and severe rash requiring dose modification.

In the randomized, placebo-controlled trials, the overall incidence of HFSR was higher in 1142 Regorafenib-treated patients (53%) than in the placebo-treated patients (8%). Most cases of HFSR in Regorafenib-treated patients appeared during the first cycle of treatment. The incidences of Grade 3 HFSR (16% versus <1%), Grade 3 rash (3% versus <1%), serious adverse reactions of erythema multiforme (<0.1% vs. 0%) and Stevens-Johnson Syndrome (<0.1% vs. 0%) were also higher in Regorafenib-treated patients. Across all trials, a higher incidence of HFSR was observed in Asian patients treated with Regorafenib (all grades: 72%; Grade 3: 18%).

Toxic epidermal necrolysis occurred in 0.02% of 4518 Regorafenib-treated patients across all clinical trials of Regorafenib administered as a single agent.

Withhold Regorafenib, reduce the dose, or permanently discontinue Regorafenib depending on the severity and persistence of dermatologic toxicity. Institute supportive measures for symptomatic relief.

Hypertension

In randomized, placebo-controlled trials, hypertensive crisis occurred in 0.2% of patients in the Regorafenib arms and in none of the patients in the placebo arms. Regorafenib 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).

Do not initiate Regorafenib unless blood pressure is adequately controlled. Monitor blood pressure weekly for the first 6 weeks of treatment and then every cycle, or more frequently, as clinically indicated. Temporarily or permanently withhold Regorafenib for severe or uncontrolled hypertension.

Cardiac Ischemia and Infarction

Regorafenib increased the incidence of myocardial ischemia and infarction (0.9% vs 0.2%) in randomized placebo controlled trials. Withhold Regorafenib in patients who develop new or acute onset cardiac ischemia or infarction. Resume Regorafenib only after resolution of acute cardiac ischemic events, if the potential benefits outweigh the risks of further cardiac ischemia.

Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one of 4800 Regorafenib-treated patients across all clinical trials. Perform an evaluation for RPLS in any patient presenting with seizures, severe headache, visual disturbances, confusion or altered mental function. Discontinue Regorafenib 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 Regorafenib can impair wound healing, discontinue treatment with Regorafenib at least 2 weeks prior to scheduled surgery. The decision to resume Regorafenib after surgery should be based on clinical judgment of adequate wound healing. Discontinue Regorafenib in patients with wound dehiscence.

Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, Regorafenib can cause fetal harm when administered to a pregnant woman. There are no available data on Regorafenib use in pregnant women. Regorafenib was embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, genitourinary, and skeletal malformations. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with Regorafenib and for 2 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Regorafenib and for 2 months after the final dose.

ADVERSE REACTIONS

The most common adverse reactions (20%) are pain (including gastrointestinal and abdominal pain), HFSR, asthenia/fatigue, diarrhea, decreased appetite/food intake, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, rash, and nausea.

OVERDOSAGE

The highest dose of Regorafenib 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 Regorafenib overdose. In the event of suspected overdose, interrupt Regorafenib, institute supportive care, and observe until clinical stabilization.

DRUG INTERACTIONS

Effect of Strong CYP3A4 Inducers on Regorafenib

Co-administration of a strong CYP3A4 inducer with Regorafenib 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. Avoid concomitant use of Regorafenib with strong CYP3A4 inducers (e.g. Rifampin, Phenytoin, Carbamazepine, Phenobarbital, and St. John's Wort).

Effect of Strong CYP3A4 Inhibitors on Regorafenib

Co-administration of a strong CYP3A4 inhibitor with Regorafenib 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. Avoid concomitant use of Regorafenib with strong CYP3A4 inhibitors (e.g. Clarithromycin, Grapefruit juice, Itraconazole, Ketoconazole, Nefazodone, Posaconazole, Telithromycin, and Voriconazole).

Effect of Regorafenib on Breast Cancer Resistance Protein (BCRP) Substrates

Co-administration of Regorafenib with a BCRP substrate increased the plasma concentrations of the BCRP substrate. Monitor patients closely for signs and symptoms of exposure related toxicity to the BCRP substrate (e.g. Methotrexate, Fluvastatin, Atorvastatin). Consult the concomitant BCRP substrate product information when considering administration of such products together with Regorafenib.

PHARMACEUTICAL INFORMATION

Storage and Handling

Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Regora Tablet: Each commercial box contains 10 film coated tablets in Alu-Alu blister.

Manufactured by-

BEACON® Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

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