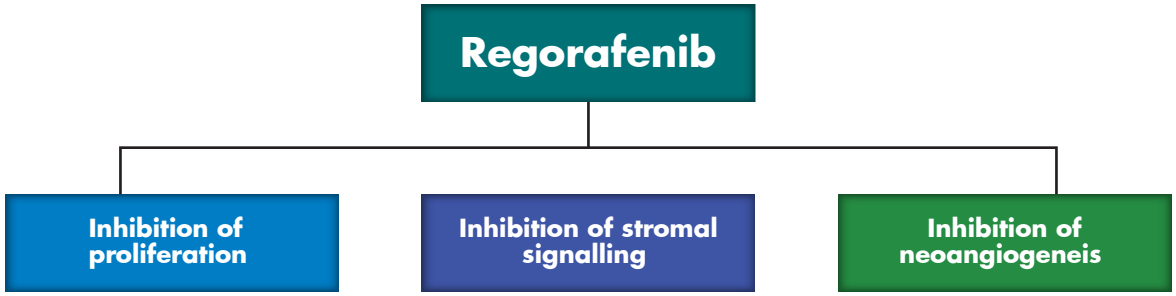

A novel
multikinase
inhibitor
REGONIX
Regorafenib INN 40 mg tablet

Regorafenib a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent antitumor activity.[3]



BEACON Pharma introduces,

REGONIX

Regorafenib INN 40 mg tablet

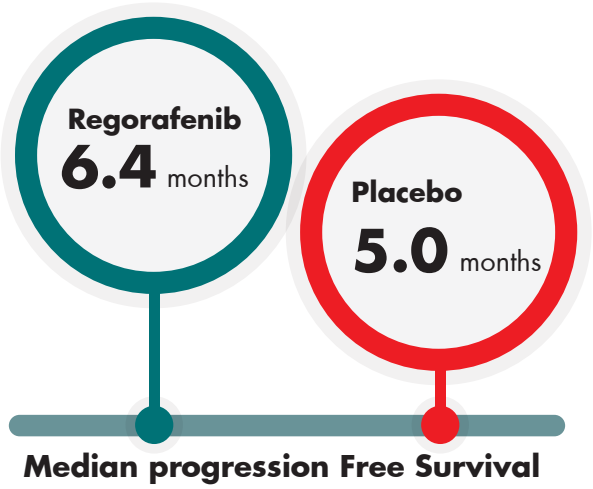
A novel multikinase inhibitor

Significantly improves PFS in metastatic colorectal cancer (mCRC)[1]

Regorafenib is the first small-molecule mutikinase inhibitor with survival benefits in metastatic colorectal cancer which has progressed after all standerd therapies.

In phase 3 trial: 760 patients were randomized to receive Regorafenib or Placebo.

Result:



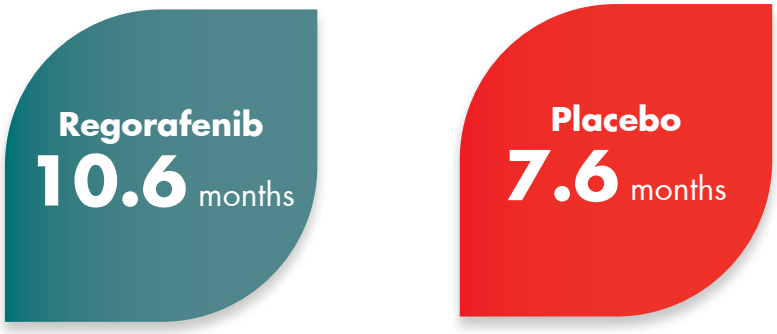
REGONIX

Regorafenib INN 40 mg tablet

Shown better outcome in Hepatotcellular carcinoma (HCC)[4]

In phase 3 trial which is done at 152 sites in 21 countries, patients with HCC tolerated Sorafenib, progressed with on Sorafenib and had child pugh were enrolled.

Result:



Median progression Free Survival

Ensures greater survival benefit

Remarkable improvement in Gastrointestinal stromal tumours (GIST)[3]

In phase 3 trial in 17 countries, patients with metastatic or unresectable GIST with failure of atleast previous Imatinib and Sunitinib were randomised

Result:

Median progression Free Survival

Ensures significant benefits

REGONIX

Regorafenib INN 40 mg tablet

A novel multikinase inhibitor

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NEW POTENT THERAPY FOR mCRC

EFFECTIVE RESULT IN HCC AND GIST

CONVENIENT ORAL DOSE

Prescribing Information

COMPOSITION: ***Regonix 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. **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-day cycle. Continue treatment until disease progression or unacceptable toxicity. Discard any unused tablets 7 weeks after opening the bottle. Take Regorafenib at the same time each day. Swallow tablet whole with water after a low-fat meal that contains less 600 caloris 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) increments; 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. **ADVERSE REACTIONS:** The most common adverse reactions (20%) are pain (includinggastrointestinal and abdominal pain), HFSR, asthenia/fatigue, diarrhea, decreased appetite/food intake, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, rash, and nausea. **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: Regonix Tablet:*** Each commercial bottle contains 28 film coated tablets.

BEACON® Pharmaceuticals Limited

Light for life

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