SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Regonix 40 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sl. No.	Name of Materials	Specification	Quantity per Capsule	Quantity per Batch
01	Regorafenib Monohydrate	INN	*41.491 mg (eqv to Regorafenib 40 mg)	*829.820 g
Excipients:				
02	Copovidone (Kollidon VA 64)	BP	15.000 mg	300.000g
03	Sodium Starch Glycolate(Primojel)	BP	15.000 mg	300.000 g
04	Sodium Lauryl Sulphate	BP	3.000 mg	60.000 g
05	Purified Talc	BP	6.000 mg	120.000 g
06	Ludipress	Ph.Grade	**215.009 mg	**4300.18g
07	Magnesium Stearate	BP	3.000 mg	60.000 g
08	Colloidal Anhydrous Silica (Aerosil 200)	BP	1.500 mg	30.000 g
Coating Materials				
09	Opadry II White (85G68918)	P.Grade	9.600 mg	192.000 g
10	Opadry II Pink (85G84846)	P.Grade	2.400 mg	48.000 g
10	Purified Water	USP	60.000 mg	1200.000 g
* Based on 100% potency ** Calculated amount of material				

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS 4.1

Therapeutic indications

Regonix is indicated for the treatment of adult patients with

- metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy .

- unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

4.2 Posology and method of administration

Regonix should be prescribed by physicians experienced in the administration of anticancer therapy.

Posology

The recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle.

If a dose is missed, then it should be taken on the same day as soon as the patient remembers. The patient should not take two doses on the same day to make up for a missed dose. In case of vomiting after regorafenib administration, the patient should not take additional tablets.

Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs.

Posology adjustments
Dose interruptions and/or dose reductions may be required based on individual safety and tolerability. Dose modifications are to be applied in 40 mg (one tablet) steps. The lowest recommended daily dose is 80 mg. The maximum daily dose is 160 mg.

For recommended dose modifications and measures in case of hand-foot skin reaction (HFSR) / palmar-plantar erythrodysesthesia syndrome see Table 1.

Table 1: Recommended dose modifications and measures for HFSR

Skin toxicity grade	Occurrence	Recommended dose modification and measures
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2	1st occurrence	Decrease dose by 40 mg (one tablet) and immediately institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1. A dose re-escalation is permitted at the discretion of the physician.
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	4th occurrence	Discontinue treatment with Regonix permanently.
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet).
	3rd occurrence	Discontinue treatment with Regonix permanently.

For recommended measures and dose modifications in case of worsening of liver function tests considered related to treatment with Regonix see Table 2 (see also section 4.4).

Table 2: Recommended measures and dose modifications in case of drug-related liver function test abnormalities

Observed elevations of ALT and/or AST	Occurrence	Recommended measures and dose modification
≤5 times upper limit of normal (ULN) (maximum Grade 2)	Any occurrence	Continue Regonix treatment. Monitor liver function weekly until transaminases return to <3 times ULN (Grade 1) or baseline.
>5 times ULN ≤20 times ULN (Grade 3)	1st occurrence	Interrupt Regonix treatment. Monitor transaminases weekly until return to <3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start Regonix treatment, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks.
	Re-occurrence	Discontinue treatment with Regonix permanently.
>20 times ULN (Grade 4)	Any occurrence	Discontinue treatment with Regonix permanently.
>3 times ULN (Grade 2 or higher) with concurrent bilirubin >2 times ULN	Any occurrence	Discontinue treatment with Regonix permanently. Monitor liver function weekly until resolution or return to baseline. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

Hepatic impairment
Regorafenib is eliminated mainly via the hepatic route. No dose adjustment is required in patients with mild hepatic impairment. Close monitoring of overall safety is recommended in these patients.

Renal impairment
No dose adjustment is required in patients with mild, moderate or severe renal impairment.

Elderly population
In clinical studies, no relevant differences in exposure, safety or efficacy were observed between elderly (aged 65 years and above) and younger patients.

Gender
In clinical studies, no relevant differences in exposure, safety or efficacy were observed between male and female patients. No dose adjustment is necessary based on gender.

Ethnic differences
No dose adjustment is necessary based on ethnicity.

Paediatric population
There is no relevant use of Regonix in the paediatric population in the indication of metastatic colorectal cancer.

Method of administration
Regonix is for oral use. Regonix should be taken at the same time each day. The tablets should be swallowed whole with water after a light meal that contains less than 30% fat. An example of a light (low-fat) meal would include 1 portion of cereal (about 30 g), 1 glass of skimmed milk, 1 slice of toast with jam, 1 glass of apple juice, and 1 cup of coffee or tea (520 calories, 2 g fat).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 2.

4.4 Special warnings and precautions for use

Hepatic effects
It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of treatment with Regonix and monitor closely (at least every two weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated.

Haemorrhage
Regonix has been associated with an increased incidence of haemorrhagic events, some of which were fatal. Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation of Regonix should be considered.

Cardiac ischaemia and infarction
Patients with a history of ischaemic heart disease should be monitored for clinical signs and symptoms of myocardial ischaemia. In patients who develop cardiac ischaemia and/or infarction, interruption of Regonix is recommended until resolution. The decision to re-start Regonix therapy should be based on careful consideration of the potential benefits and risks of the individual patient. Regonix should be permanently discontinued if there is no resolution.

Posterior reversible encephalopathy syndrome (PRES)
In patients developing PRES, discontinuation of Regonix, along with control of hypertension and supportive medical management of other symptoms is recommended.

Gastrointestinal perforation and fistula
Discontinuation of Regonix is recommended in patients developing gastrointestinal perforation or fistula.

Arterial hypertension
Regonix has been associated with an increased incidence of arterial hypertension. Blood pressure should be controlled prior to initiation of treatment with Regonix. It is recommended to monitor blood pressure and to treat hypertension in accordance with standard medical practice. In case of hypertensive crisis, Regonix should be discontinued.

Wound healing complications
As medicinal products with anti-angiogenic properties may suppress or interfere with wound healing, temporary interruption of Regonix is recommended for precautionary reasons in patients undergoing major surgical procedures.

Dermatological toxicity
Hand-foot skin reaction (HFSR) or palmar-plantar erythrodysesthesia syndrome and rash represent the most frequently observed dermatological adverse reactions with Regonix.

Biochemical and metabolic laboratory test abnormalities
Regonix has been associated with an increased incidence of electrolyte abnormalities (including hypophosphatemia, hypocalcaemia, hyponatraemia and hypokalaemia) and metabolic abnormalities (including increases in thyroid stimulating hormone, lipase and amylase. It is recommended to monitor biochemical and metabolic parameters during Regonix treatment and to institute appropriate replacement therapy according to standard clinical practice if required.

Important information about some of the ingredients

Each daily dose of 160 mg contains 2.427 mmol (or 55.8 mg) of sodium. To be taken into consideration by patients on a controlled sodium diet. Each daily dose of 160 mg contains 1.68 mg of lecithin (derived from soya).

4.5 Interaction with other medicinal products and other forms of interaction Inhibitors

of CYP3A4 and UGT1A9 / inducers of CYP3A4

Administration of ketoconazole (400 mg for 18 days), a strong CYP3A4 inhibitor, with a single dose of regorafenib (160 mg on day 5) resulted in an increase in mean exposure (AUC) of regorafenib of approximately 33%, and a decrease in mean exposure of the active metabolites, M-2 (N-oxide) and M -5 (N-oxide and N-desmethyl), of approximately 90%. It is recommended to avoid concomitant use of strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin and voriconazole) as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.

Co-administration of a strong UGT1A9 inhibitor (e.g. mefenamic acid, diflunisal, and niflumic acid) during regorafenib treatment should be avoided, Administration of rifampicin (600 mg for 9 days), a strong CYP3A4 inducer, with a single dose of regorafenib (160 mg on day 7) resulted in a reduction in AUC of regorafenib of approximately 50%, a 3- to 4 -fold increase in mean exposure of the active metabolite M-5, and no change in exposure of active metabolite M-2. Other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital and St. John's wort) may also increase metabolism of regorafenib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

Breast cancer resistance protein (BCRP) and P-glycoprotein substrates
Co-administration of regorafenib may increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin). Therefore, it is recommended to monitor patients closely for signs and symptoms of increased exposure to BCRP substrates.

Antibiotics

Pharmacokinetic interactions of other antibiotics have not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential must be informed that regorafenib may cause foetal harm.
Women of childbearing potential and men should ensure effective contraception during treatment and up to 8 weeks after completion of therapy.

Pregnancy
Regonix should not be used during pregnancy unless clearly necessary and after careful consideration of the benefits for the mother and the risk to the foetus.

Breast-feeding
Breast-feeding must be discontinued during treatment with Regonix.

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

4.7 Effects on ability to drive and use machines

No studies on the effects of Regonix on the ability to drive or use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

The **most serious** adverse drug reactions in patients receiving Regonix are severe liver injury, haemorrhage and gastrointestinal perforation.

The **most frequently** observed adverse drug reactions (≥30%) in patients receiving Regonix are asthenia/fatigue, hand foot skin reaction, diarrhoea, decreased appetite and food intake, hypertension, dysphonia and infection.

Tabulated list of adverse reactions

The adverse drug reactions reported in clinical trials in patients treated with Regonix are shown in Table 3. They are classified according to System Organ Class and the most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions are grouped according to their frequencies. Frequency groups are defined.

Table 3: Adverse drug reactions (ADRs) reported in clinical trials in patients treated with Regonix

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare
Infections and infestations	Infection			
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Keratoacanthoma/ Squamous cell carcinoma of the skin
Blood and lymphatic system disorders	Thrombocytopenia Anaemia	Leucopenia		
Immune system disorders			Hypersensitivity reaction	
Endocrine disorders		Hypothyroidism		
Metabolism and nutrition disorders	Decreased appetite and food intake	Hypokalaemia Hypophosphatemia Hypocalcaemia Hyponatraemia Hypomagnesaemia Hyperuricaemia Dehydration		
Nervous system disorders	Headache	Tremor		Posterior reversible encephalopathy syndrome (PRES)
Cardiac disorders			Myocardial infarction Myocardial ischaemia	
Vascular disorders	Haemorrhage* Hypertension		Hypertensive crisis	

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare
Respiratory, thoracic and mediastinal disorders	Dysphonia			
Gastrointestinal disorders	Diarrhoea Stomatitis Vomiting Nausea	Taste disorders Dry mouth Gastro-oesophageal reflux Gastroenteritis	Gastrointestinal perforation* Gastrointestinal fistula	
Hepatobiliary disorders	Hyperbilirubin-aemia	Increase in transaminases	Severe liver injury*#	
Skin and subcutaneous tissue disorders	Hand-foot skin reaction** Rash Alopecia	Dry skin Exfoliative rash	Nail disorder Erythema multiforme	Stevens-Johnson syndrome Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders		Musculoskeletal stiffness		
Renal and urinary disorders		Proteinuria		
General disorders and administration site conditions	Asthenia/fatigue Pain Fever Mucosal inflammation			
Investigations	Weight loss	Increase in amylase Increase in lipase Abnormal International normalised ratio		

* fatal cases have been reported

** palmar-plantar erythrodysesthesia syndrome in MedDRA terminology

according to drug-induced liver injury (DILI) criteria of the international DILI expert working group

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.

4.9 Overdose

The highest dose of Regonix studied clinically was 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhoea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue.

There is no specific antidote for Regonix overdose. In the event of suspected overdose, Regonix should be discontinued immediately.

PHARMACOLOGICAL PROPERTIES 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor;
ATC Code: L01XE21

Mechanism of action and pharmacodynamic effects
Regorafenib is an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, $BRAF^{V600E}$), and the tumour microenvironment (PDGFR, FGFR). In particular, regorafenib inhibits mutated KIT, a major oncogenic driver in gastrointestinal stromal tumors, and thereby blocks tumor cell proliferation. In preclinical studies regorafenib has demonstrated potent antitumour activity in a broad spectrum of tumour models including colorectal and gastrointestinal stromal tumour models which is mediated by its anti-angiogenic and anti-proliferative effects.

Clinical efficacy and safety

Metastatic colorectal cancer (CRC)

The clinical efficacy and safety of Regonix have been evaluated in an international, multi-centre, randomised, double-blind, placebo-controlled phase III study (CORRECT) in patients with metastatic colorectal cancer who have progressed after failure of standard therapy.

Table 4: Efficacy results from the CORRECT study

Efficacy parameter	**Hazard ratio* (95% CI)**	**P-value (one-sided)**	**Median (95% CI)**	
			Regonix plus BSC§ (N=505)	**Placebo plus BSC§ (N=255)**
Overall Survival	0.774 (0.636, 0.942)	0.005178	6.4 months (5.9, 7.3)	5.0 months (4.4, 5.8)
Progression Free Survival**	0.494 (0.419, 0.582)	<0.000001	1.9 months (1.9, 2.1)	1.7 months (1.7, 1.7)

§ Best Supportive Care
* Hazard ratio < 1 favours Regonix
** based on investigator's assessment of tumour response

Gastrointestinal stromal tumours (GIST)

The clinical efficacy and safety of Regonix have been evaluated in an international, multi-center, randomized, double-blind, placebo-controlled phase III study (GRID) in patients with gastrointestinal stromal tumors (GIST) previously treated with 2 tyrosine kinase inhibitors (imatinib and sunitinib).

Table 5: Efficacy Results from the GRID study

Efficacy parameter	**Hazard Ratio* (95% CI)**	**P-value (one-sided)**	**Median (95% CI)**	
			Regonix plus BSC§ (N=133)	**Placebo plus BSC§ (N=66)**
Progression-Free Survival	0.268 (0.185, 0.388)	<0.000001	4.8 months (4.0, 5.7)	0.9 months (0.9, 1.1)
Time To Progression	0.248 (0.170,0.364)	<0.000001	5.4 months (4.1, 5.7)	0.9 months (0.9, 1.1)
Overall Survival	0.772 (0.423, 1.408)	0.199	NR**	NR**

§ Best Supportive Care
* Hazard ratio < 1 favors
Regonix ** NR: not reached

5.2 Pharmacokinetic properties

Absorption
Regorafenib reaches mean peak plasma levels of about 2.5 mg/l at about 3 to 4 hours after a single oral dose of 160 mg given as 4 tablets each containing 40 mg. Following single doses of 60 mg or 100 mg, the average relative bioavailability of tablets compared to an oral solution was 69% and 83%, respectively.
The exposure of metabolites M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl) is higher when regorafenib is given with a low fat breakfast as compared to fasting condition and lower when given with a high fat meal as compared to fasting condition.

Distribution
Plasma concentration-time profiles for regorafenib as well as for the major circulating metabolites showed multiple peaks across the 24-hour dosing interval, which are attributed to enterohepatic circulation.

Biotransformation
Two major and six minor metabolites of regorafenib have been identified in plasma. Metabolites may be reduced or hydrolysed in the gastrointestinal tract by microbial flora, allowing reabsorption of the unconjugated active substance and metabolites (enterohepatic circulation).

Elimination
Following oral administration, mean elimination half-life for regorafenib and its metabolite M-2 in plasma ranges from 20 to 30 hours in different studies. The mean elimination half-life for the metabolite M-5 is approximately 60 hours (range from 40 to 100 hours).
Approximately 90% of the radioactive dose was recovered within 12 days after administration, with about 71% of the dose excreted in faeces (47% as parent compound, 24% as metabolites), and about 19% of the dose excreted in urine as glucuronides.

Hepatic impairment

Regorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population.

Renal impairment
In patients with severe renal impairment compared to patients with normal renal function, regorafenib exposure was similar while exposure to M-2 and M-5 was decreased by about 30% under steady-state conditions, which is not considered relevant.

Elderly
Age did not affect the regorafenib pharmacokinetics over the studied age range (29 – 85 years).

Gender
The pharmacokinetics of regorafenib is not influenced by gender.

Ethnic differences
The exposure of regorafenib in various Asian populations (Chinese, Japanese, Korean) is within the same range as seen in Caucasians.

Cardiac electrophysiology/QT prolongation
No QTc prolonging effects were observed after administration of 160 mg regorafenib at steady state in a dedicated QT study in male and female cancer patients.

5.3 Preclinical safety data

Systemic toxicity
After repeated dosing to mice, rats and dogs, adverse effects were observed in a number of organs, primarily in the kidneys, liver, digestive tract, thyroid gland, lympho-/haematopoietic system, endocrine system, reproductive system and skin. A slightly increased incidence of thickening of the atrioventricular valves of the heart was seen in the 26 week repeat-dose toxicity study in rats. This may be due to acceleration of an age-related physiological process. These effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison). Alterations of teeth and bones and adverse effects in the reproductive system were more pronounced in young and growing animals as well as in juvenile rats and indicate a potential risk for children and adolescents.

Reproductive and developmental toxicity
Specific studies on fertility have not been performed. However, a potential of regorafenib to adversely affect male and female reproduction has to be considered based on morphological changes in the testes, ovaries, and the uterus observed after repeated dosing in rats and dogs at exposures below the anticipated human exposure (based on AUC comparison). The observed changes were only partially reversible.

An effect of regorafenib on intrauterine development was shown in rabbits at exposures below the anticipated human exposure (based on AUC comparison). Main findings consisted of malformations of the urinary system, the heart and major vessels, and the skeleton.

Genotoxicity and carcinogenicity

Studies on the carcinogenic potential of regorafenib have not been performed.

Environmental Risk Assessment (ERA)
Environmental risk assessment studies have shown that regorafenib has the potential to be persistent, bioaccumulative and toxic to the environment and may pose a risk to the surface water and to the sediment compartment.

6. PHARMACEUTICAL

PARTICULARS 6.1

List of excipients

On Section 2

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1.8 Months.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.
Keep the bottle tightly closed and keep the desiccant in the bottle.

6.5 Nature and contents of container

White opaque HDPE bottle closed with a PP/PP (polypropylene) screw cap with sealing insert and a molecular sieve desiccant.

Each bottle contains 28 film-coated tablets.

Pack sizes
Pack of 28 film-coated tablets.

6.6 Special precautions for disposal and other handling

This medicinal product may pose a risk to the environment.

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

7. MARKETING AUTHORISATION HOLDER

Beacon Pharmaceuticals Limited
Motijeel, Dhaka
Bangladesh

8. MARKETING AUTHORISATION NUMBER(S)

341-310-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30.01.2017/29.01.2022

10. DATE OF REVISION OF THE TEXT

10.12.2021