1. NAME OF THE MEDICINAL PRODUCT
TANGITARE (Regorafenib film-coated tablets 40mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains:
41.49 mg Regorafenib Monohydrate (Equivalent to 40mg Regorafenib)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.

Light pink oval, biconvex, film-coated tablet debossed with “40” on one side and plain on other.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Colorectal Cancer
TANGITARE 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
TANGITARE 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
TANGITARE is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

4.2 Posology and method of administration
Recommended Dose
The recommended dose is 160 mg TANGITARE (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.
Take TANGITARE at the same time each day. Swallow tablet whole with water after a low-fat meal that contains less than 600 calories and less than 30% fat [see Clinical Pharmacology (11.3)]. Do not take two doses of TANGITARE 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 TANGITARE is 80 mg daily.

Interrupt TANGITARE 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 TANGITARE 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 TANGITARE 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 TANGITARE 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

Route of Administration: Oral

4.3 Contraindications
TANGITARE is contraindicated in patients who are hypersensitive to regorafenib, sorafenib, drugs in the same class or any ingredient in the formulation. For a complete listing, [see section 6.1]

4.4 Special warnings and precautions for use
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.
In the CORRECT study, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and in 0.4% of patients in the placebo arm. In the GRID study, fatal hepatic failure occurred in 0.8% of patients in the regorafenib arm. In the RESORCE study, there was no increase in the incidence of fatal hepatic failure as compared to placebo.
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 regorafenibtreated 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 a 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 [see Adverse Reactions(6.1)]. 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 (RPLS)
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.

Thrombotic microangiopathy (TMA)
Thrombotic microangiopathy (TMA), including thrombotic thrombocytopaenic purpura (TTP), have been associated with the use of regorafenib (see section 4.8). The diagnosis of TMA should be considered in patients presenting with haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment, and fever. Regorafenib therapy should be discontinued in patients who develop TMA and prompt treatment is required. Reversal of the effects of TMA has been observed after treatment discontinuation.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction
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 [see Section 5.2] and may lead to decreased efficacy. Avoid concomitant use of TANGITARE 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 plasma concentrations of the active metabolites M-2 and M-5 [see Section 5.2], 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 [see Section 5.2]. 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.

4.6 Fertility, pregnancy and lactation
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 [see Data]. 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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 % and 15 to 20%, respectively.

Data
Animal Data
In embryo-fetal development studies, a total loss of pregnancy (100% resorption of litter) was observed in rats at doses as low as 1 mg/kg (approximately 6% of the recommended human dose, based on body surface area) and in rabbits at doses as low as 1.6 mg/kg (approximately 25% of the human exposure at the clinically recommended dose measured by AUC).

In a single dose distribution study in pregnant rats, there was increased penetration of regorafenib across the blood-brain barrier in fetuses compared to dams. Daily administration of regorafenib to pregnant rats during

organogenesis resulted in fetal findings of delayed ossification at doses > 0.8 mg/kg (approximately 5% of the recommended human dose based on body surface area) and dose-dependent increases in skeletal malformations including cleft palate and enlarged fontanelle at doses ≥ 1 mg/kg (approximately 10% of the clinical exposure based on AUC). At doses ≥ 1.6 mg/kg (approximately 11% of the recommended human dose based on body surface area), there were dose-dependent increases in the incidence of cardiovascular malformations, external abnormalities, diaphragmatic hernia, and dilation of the renal pelvis.

In pregnant rabbits administered regorafenib daily during organogenesis, there were findings of ventricular septal defects evident at the lowest tested dose of 0.4 mg/kg (approximately 7% of the AUC in patients at the recommended dose). At doses of ≥ 0.8 mg/kg (approximately 15% of the human exposure at the recommended human dose based on AUC), administration of regorafenib resulted in dose-dependent increases in the incidence of additional cardiovascular malformations and skeletal anomalies as well as significant adverse effects on the urinary system including missing kidney/ureter; small, deformed and malpositioned kidney; and hydronephrosis. The proportion of viable fetuses that were male decreased with increasing dose in two rabbit embryo-fetal toxicity studies.

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 breastfed infants from regorafenib, do not breastfeed during treatment with regorafenib and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Contraception

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.

Animal Data

In 28-day repeat dose studies in rats there were dose-dependent findings of dentin alteration and angiectasis. These findings occurred at regorafenib doses as low as 4 mg/kg (approximately 25% of the AUC in humans at the recommended dose). In 13-week repeat dose studies in dogs there were similar findings of dentin alteration at doses as low as 20 mg/kg (approximately 43% of the AUC in humans at the recommended dose). Administration of regorafenib in these animals also led to persistent growth and thickening of the femoral epiphyseal growth plate.

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 see. Closely monitor patients with hepatic impairment for adverse reactions [see Warnings and Precautions].

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 (CORRECT, GRID and CONCUR), a higher incidence of HFSR and liver function test abnormalities occurred in Asian patients treated with REGORAFENIB as comp

4.7 Effects on ability to drive and use machines
No studies on the effects of Regorafenib on the ability to drive or use machines have been performed. If patients experience symptoms affecting their ability to concentrate and react during treatment with Regorafenib, it is recommended that they do not drive or use machines until the effect subsides.

4.8 Undesirable effects
The following serious adverse reactions are discussed elsewhere in the labeling:
- Hepatotoxicity [See Section 4.4]
- Infections [see Section 4.4]
- Hemorrhage [See Section 4.4]
- Gastrointestinal Perforation or Fistula [see Section 4.4]
- Dermatological Toxicity [See Section 4.4]
- Hypertension [See Section 4.4]
- Cardiac Ischemia and Infarction [See Section 4.4]
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [See Section 4.4]

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rate observed in practice.

The data described in the SPECIAL WARNINGS AND PRECAUTIONS FOR USE section reflect exposure to Regorafenib in more than 4800 patients who were enrolled in four randomized, placebo-controlled trials (n=1142), an expanded access program (CONSIGN, n=2864), or single arm clinical trials (single agent or in combination with other agents). There were 4518 patients who received Regorafenib as a single agent; the distribution of underlying malignancies was 80% CRC, 4% GIST, 10% HCC, 6% other solid tumors; and 74% were White, 11% Asian, and 15% race not known. Among these 4518 patients, 83% received Regorafenib for at least 21 days and 20% received Regorafenib for 6 months or longer.

In randomized placebo-controlled trials (CORRECT, GRID, RESORCE and CONCUR), the most frequently observed adverse drug reactions (≥20%) in patients receiving Regorafenib 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.

Colorectal Cancer
The safety data described below, except where noted, are derived from a randomized (2:1), double-blind, placebo-controlled trial (CORRECT) in which 500 patients (median age 61 years; 61% men) with previously treated metastatic colorectal cancer (CRC) received Regorafenib as a single agent at the dose of 160 mg daily for the first 3 weeks of each 4 week treatment cycle and 253 patients (median age 61 years; 60% men) received placebo. The median duration of therapy was 1.7.months (range 2 days, 10.8 months) for patients receiving Regorafenib. Due to adverse reactions, 61% of the patients receiving Regorafenib required a dose interruption and 38% of the patients had their dose reduced. Adverse reactions that resulted in treatment discontinuation occurred in 8.2% of

Regorafenib-treated patients compared to 1.2% of patients who received placebo. Hand-foot skin reaction (HFSR) and rash were the most common reasons for permanent discontinuation of Regorafenib.
Table 1 provides the incidence of adverse reactions (≥10%) in patients in CORRECT.

Table 1 Adverse drug reactions reported in ≥10% of patients treated with Regorafenib in CORRECT and reported more commonly than in patients receiving placebo[a]

Adverse Reactions	**Regorafenib (N=500)**		**Placebo (N=253)**	
	Grade		**Grade**	
	All%	**≥ 3 %**	**All %**	**≥ 3 %**
General disorders and administration site conditions				
Asthenia/fatigue	64	15	46	9
Pain	59	9	48	7
Fever	28	2	15	0
Metabolism and nutrition disorders				
Decreased appetite and food intake	47	5	28	4
Skin and subcutaneous tissue disorders				
HFSR/PPES	45	17	7	0
Rash[b]	26	6	4	<1
Gastrointestinal disorders				
Diarrhea	43	8	17	2
Mucositis	33	4	5	0
Investigations				
Weight loss	32	<1	10	0
Infections and infestations				
Infection[c]	31	9	17	6
Vascular disorders				
Hypertension	30	8	8	<1
Hemorrhage[c]	21	2	8	<1
Respiratory, thoracic and mediastinal disorders				
Dysphonia	30	0	6	0
Nervous system disorders				
Headache	10	<1	7	0

[a]Adverse reactions graded according to National Cancer Institute Common Toxicity for Adverse Events version 3.0 (NCI CTCAE v3.0).
[b]The term rash represents reports of events of drug eruption, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, papular rash, and pruritic rash.
[c]Fatal outcomes observed.

Table 2 provides laboratory abnormalities observed in CORRECT.

Table 2 Laboratory test abnormalities reported in CORRECT

Laboratory Parameter	**Regorafenib (N=500[a])**			**Placebo (N=253[a])**		
	Grade[b]			**Grade[b]**		
	All %	**3 %**	**4 %**	**All %**	**3 %**	**4 %**
Blood and lymphatic system disorders						

Anemia	79	5	1	66	3	0
Thrombocytopenia	41	2	<1	17	<1	0
Neutropenia	3	1	0	0	0	0
Lymphopenia	54	9	0	35	4	<1
Metabolism and nutrition disorders						
Hypocalcemia	59	1	<1	18	1	0
Hypokalemia	26	4	0	8	<1	0
Hyponatremia	30	7	1	22	4	0
Hypophosphatemia	57	31	1	11	4	0
Hepatobiliary disorders						
Hyperbilirubinemia	45	10	3	17	5	3
Increased AST	65	5	1	46	4	1
Increased ALT	45	5	1	30	3	<1
Renal and urinary disorders						
Proteinuria[c]	84	2	0	61	1	0
Investigations						
Increased INR[d]	24	4	N/A	17	2	N/A
Increased Lipase	46	9	2	19	3	2
Increased Amylase	26	2	<1	17	2	<1

[a] % based on number of patients with post-baseline samples which may be less than 500 (regorafenib) or 253 (placebo).
[b]NCI CTCAE v3.0.
[c]Based on urine protein-creatinine ratio data.
[d]International normalized ratio: No Grade 4 denoted in NCI CTCAE, v3.0.

Gastrointestinal Stromal Tumors
The safety data described below are derived from a randomized (2:1), double-blind, placebo-controlled trial (GRID) in which 132 patients (median age 60 years; 64% men) with previously treated GIST received Regorafenib as a single agent at a dose of 160 mg daily for the first 3 weeks of each 4 week treatment cycle and 66 patients (median age 61 years; 64% men) received placebo. The median duration of therapy was 5.7 months (range 1 day, 11.7 months)for patients receiving Regorafenib. Dose interruptions for adverse events were required in 58% of patients receiving Regorafenib and 50% of patients had their dose reduced. Adverse reactions that resulted in treatment discontinuation were reported in 2.3% of Regorafenib treated patients compared to 1.5% of patients who received placebo.

Table 3 provides the incidence of adverse reactions (≥10%) in patients in GRID.

Table 3 Adverse reactions reported in ≥10% patients treated with Regorafenib in GRID and reported more commonly than in patients receiving placebo[a]

Adverse Reactions	**Regorafenib (N=132)**		**Placebo (N=66)**	
	Grade		**Grade**	
	All %	**≥ 3 %**	**All %**	**≥ 3 %**
Skin and subcutaneous tissue disorders				
HFSR/PPE	67	22	12	2
Rash[b]	30	7	3	0
Alopecia	24	2	2	0

General disorders and administration site conditions				
Asthenia/Fatigue	52	4	39	2
Fever	21	0	11	2
Vascular disorders				
Hypertension	59	28	27	5
Hemorrhage	11	4	3	0
Gastrointestinal disorders				
Pain	60	8	55	14
Diarrhea	47	8	9	0
Mucositis	40	2	8	2
Nausea	20	2	12	2
Vomiting	17	<1	8	0
Respiratory, thoracic and mediastinal disorders				
Dysphonia	39	0	9	0
Infections and infestations				
Infection[c]	32	5	5	0
Metabolism and nutrition disorders				
Decreased appetite and food intake	31	<1	21	3
Hypothyroidism[d]	18	0	6	0
Nervous system disorders				
Headache	16	0	9	0
Investigations				
Weight loss	14	0	8	0
Musculoskeletal and connective tissue disorders				
Muscle spasms	14	0	3	0

[a]Adverse reactions graded according to NCI CTCAE v4.0.
[b]The term rash represents reports of events of rash, erythematous rash, macular rash, maculo-papular rash, papular rash and pruritic rash.
[c]Fatal outcomes observed
[d]Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

Table 4 provides laboratory abnormalities observed in GRID.

Table 4 Laboratory test abnormalities reported in GRID.

Laboratory Parameter	**Regorafenib (N=132[a])**			**Placebo (N=66[a])**		
	Grade[b]			**Grade[b]**		
	All %	**3 %**	**4 %**	**All %**	**3 %**	**4 %**
Blood and lymphatic system disorders						
Thrombocytopenia	13	1	0	2	0	2
Neutropenia	16	2	1	12	3	0
Lymphopenia	30	8	0	24	3	0

Metabolismand nutrition disorders						
Hypocalcemia	17	2	0	5	0	0
Hypokalemia	21	3	0	3	0	0
Hypophosphatemia	55	20	2	3	2	0
Hepatobiliary disorders						
Hyperbilirubinemia	33	3	1	12	2	0
Increased AST	58	3	1	47	3	0
Increased ALT	39	4	1	39	2	0
Renal and urinary disorders						
Proteinuria[c]	59	3	-[d]	53	3	-[d]
Investigations						
Increased Lipase	14	0	1	5	0	0

[a]Percent based on number of patients with post-baseline samples which may be less than 132 (regorafenib) or 66 (placebo).
[b]NCI CTCAE v4.0.
[c]Based on urine protein-creatinine ratio data.
[d]No Grade 4 denoted in NCI CTCAE v4.0.

Hepatocellular Carcinoma

The safety data described below are derived from a randomized (2:1), double-blind, placebo-controlled trial (RESORCE) in which patients with previously-treated HCC received either Regorafenib (n=374) 160 mg orally on days 1-21 of each 4 week treatment cycle or placebo (n=193). The median age was 63 years, 88% were men, 98% had Child-Pugh A cirrhosis, 66% had an ECOG performance status (PS) of 0 and 34% had PS of 1. The median duration of therapy was 3.5 months (range 1 day to 29.4 months) for patients receiving Regorafenib. Of the patients receiving Regorafenib, 33% were exposed to Regorafenib for greater than or equal to 6 months and 14% were exposed to Regorafenib for greater than or equal to 12 months. Dose interruptions for adverse events were required in 58.3% of patients receiving Regorafenib and 48% of patients had their dose reduced. The most common adverse reactions requiring dose modification (interruption or dose reduction) were HFSR/PPES (20.6%), blood bilirubin increase (5.9%), fatigue (5.1%) and diarrhea (5.3%). Adverse reactions that resulted in treatment discontinuation were reported in 10.4% of Regorafenib-treated patients compared to 3.6% of patients who received placebo; the most common adverse reactions requiring discontinuation of Regorafenib were HFSR/PPES (1.9%) and AST increased (1.6%).

Table 5 provides the incidence of adverse reactions (≥10%) in patients in RESORCE.

Table 5: Adverse reactions reported in ≥10% of patients treated with TANGITARE in RESORCE and reported more commonly than in patients receiving placebo[a]

Adverse Reactions	**Regorafenib (N=374)**		**Placebo (N=193)**	
	Grade		**Grade**	
	All %	**≥ 3 %**	**All %**	**≥ 3 %**
Skin and subcutaneous tissue disorders				
HFSR/PPE	51	12	7	<1
General disorders and administration site conditions				
Pain	55	9	44	8
Asthenia/Fatigue	42	10	33	5
Fever	20	0	7	0

Vascular disorders				
Hypertension	31	15	6	5
Hemorrhage[b]	18	5	16	8
Gastrointestinal disorders				
Diarrhea	41	3	15	0
Nausea	17	<1	13	0
Vomiting	13	<1	7	<1
Mucositis	13	1	2	≤1
Respiratory, thoracic and mediastinal disorders				
Dysphonia	18	0	2	0
Infections and infestations				
Infection[b]	31	8	18	6
Metabolism and nutrition disorders				
Decreased appetite and food intake	31	3	15	2
Investigations				
Weight loss	13	2	4	0
Musculoskeletal and connective tissue disorders				
Muscle spasms	10	0	2	0

[a]Adverse reactions graded according to NCI CTCAE v4.0.
[b]Fatal outcomes observed.

Other clinically significant adverse reactions observed in less than 10% of Regorafenib -treated patients were: alopecia (7%), hypothyroidism (6.4%), pancreatitis (1.6%), exfoliative rash (1.3%), tremor (1.3%), erythema multiforme (0.8%), myocardial ischemia (0.8%), gastrointestinal fistula (0.3%), and myocardial infarction (0.3%).

Table 6 provides laboratory abnormalities observed in RESORCE.

Table 6: Laboratory test abnormalities reported in RESORCE

Laboratory Parameter	**Regorafenib (N=374[a])**			**Placebo (N=193[a])**		
	Grade[b]			**Grade[b]**		
	All %	**3 %**	**4 %**	**All %**	**3 %**	**4 %**
Blood and lymphatic system disorders						
Thrombocytopenia	63	5	<1	50	0	0
Neutropenia	14	3	0	15	<1	<1
Lymphopenia	68	16	2	59	11	<1
Metabolism and nutrition disorders						
Hypocalcemia	23	<1	0	10	0	0
Hypokalemia	31	4	<1	9	2	0
Hypophosphatemia	70	32	2	31	7	0
Hepatobiliary disorders						
Hyperbilirubinemia	78	13	3	55	11	5
Increased AST	93	16	2	84	17	3
Increased ALT	70	6	<1	59	5	0

Renal and urinary disorders						
Proteinuria[c]	51	17	-[d]	37	3	-[d]
Investigations						
Increased INR	44	<1	-[d]	35	2	-[d]
Increased Lipase	41	11	3	27	8	1
Increased Amylase	23	3	<1	19	2	<1

[a]Percent based on number of patients with post-baseline samples which may be less than 374 (regorafenib) or 193 (placebo).
[b]NCI CTCAE v4.0.
[c]Based on dipstick data.
[d]No Grade 4 denoted in NCI CTCAE v4.0.

Post marketing Experience
The following adverse reaction has been identified during post approval use of regorafenib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- hypersensitivity reaction
- nephrotic syndrome
- cardiac failure
- arterial (including aortic) aneurysms, dissections, and rupture

4.9 Overdose
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.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
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, TrkA, Eph2A, RAF-1, BRAF, $BRAF^{V600E}$, SAPK2, PTK5, Abl and CSF1R 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 in the study.

Clinical efficacy and safety
Colorectal cancer (CRC)
The clinical efficacy and safety of Regorafenib were evaluated in an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial [Study "Patients with metastatic COloRectal cancer treated with REgorafenib or plaCebo after failure of standard Therapy" (CORRECT); NCT 01103323)] in 760 patients with previously- treated metastatic colorectal cancer. The major efficacy outcome measure was overall survival (OS); additional efficacy outcome measures included progression-free survival (PFS) and overall tumor response rate.

Patients were randomized to receive 160 mg regorafenib orally once daily (N=505) plus Best Supportive Care (BSC) or placebo (N=255) plus BSC for the first 21 days of each 28-day cycle. Regorafenib was administered with a low-fat breakfast that contains less than 30% fat *[see Section 4.2].* Treatment continued until disease progression or unacceptable toxicity.

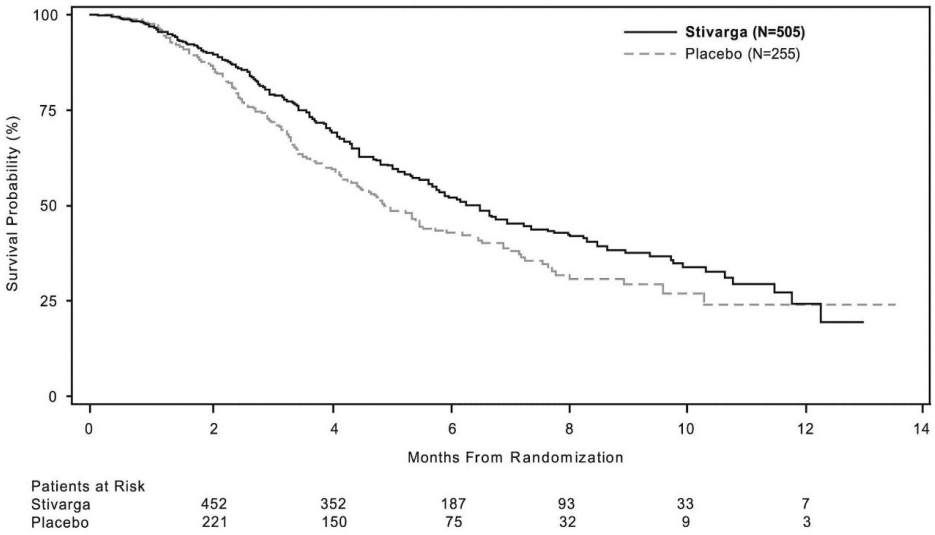
Baseline demographics were: median age 61 years, 61% men, 78% White, and all patients had an ECOG performance status of 0 or 1. The primary site of disease were colon (65%), rectum (29%), or both (6%). History of KRAS evaluation was reported for 729 (96%) patients; 430 (59%) of these patients were reported to have KRAS mutation. The median number of prior lines of therapy for metastatic disease was 3. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and with bevacizumab. All but one patient with KRAS mutation- negative tumors received panitumumab or cetuximab.
The addition of Regorafenib to BSC resulted in a statistically significant improvement in survival compared to placebo plus BSC (see Table 7 and Figure 1).

Table 7 Efficacy Results from CORRECT

	Regorafenib (N=505)	**Placebo (N=255)**
Overall Survival		
Number of Deaths (%)	275 (55%)	157 (62%)
Median Overall Survival (months)	6.4	5.0
95% CI[a]	(5.8, 7.3)	(4.4, 5.8)
Hazard Ratio (HR) (95% CI)	0.77 (0.64, 0.94)	
Stratified log-Rank Test P-value [b,c]	0.0102	
Progression-free Survival		
Number of Deaths or Progressions (%)	417 (83%)	231 (91%)
Median Progression-Free Survival (months)	2.0	1.7
95% CI	(1.9, 2.3)	(1.7, 1.8)
HR (95% CI)	0.49 (0.42, 0.58)	
Stratified log-Rank Test P-value[c]	<0.0001	
Overall Response Rate		
Overall response, N (%)	5 (1%)	1 (0.4%)
95% CI	0.3%, 2.3%	0%, 2.2%

[a]CI=confidence interval.
[b]Stratified by geographic region and time from diagnosis of metastatic disease.
[c]Crossed the O'Brien-Fleming boundary (two-sided p-value < 0.018) at second interim analysis.

Figure 1 Kaplan-Meier Curves of Overall Survival



Gastrointestinal stromal tumours (GIST)
The efficacy and safety of Regorafenib were evaluated in an international, multicenter, randomized (2:1), double-blind, placebo-controlled trial [Study "GIST Regorafenib In progressive Disease" (GRID); NCT 01271712] inpatients with unresectable, locally advanced or metastatic gastrointestinal stromal tumor (GIST), who had been previously treated with imatinib mesylate and sunitinib malate. Randomization was stratified by line of therapy (third vs. four or more) and geographic region (Asia vs. rest of the world).

The major efficacy outcome measure of GRID was progression-free survival (PFS) based on disease assessment by independent radiological review using modified RECIST 1.1 criteria, in which lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodule within a pre-existing tumor mass was progression. The key secondary outcome measure was overall survival.
Patients were randomized to receive 160 mg regorafenib orally once daily (N=133) plus best supportive care (BSC) or placebo (N=66) plus BSC for the first 21 days of each 28-day cycle. Treatment continued until disease progression or unacceptable toxicity. In GRID, the median age of patients was 60 years, 64% were men, 68% were White, and all patients had baseline ECOG performance status of 0 (55%) or 1 (45%). At the time of disease progression as assessed by central review, the study blind was broken and all patients were offered the opportunity to take Regorafenib at the investigator's discretion.

A statistically significant improvement in PFS was demonstrated among patients treated with Regorafenib compared to placebo (see Table 8 and Figure 2).

There was no statistically significant difference in overall survival at the final OS analysis, conducted at 162 OS events (Table 8). Cross-over to open label Regorafenib occurred in 58 (88%) placebo-treated patients after disease progression.

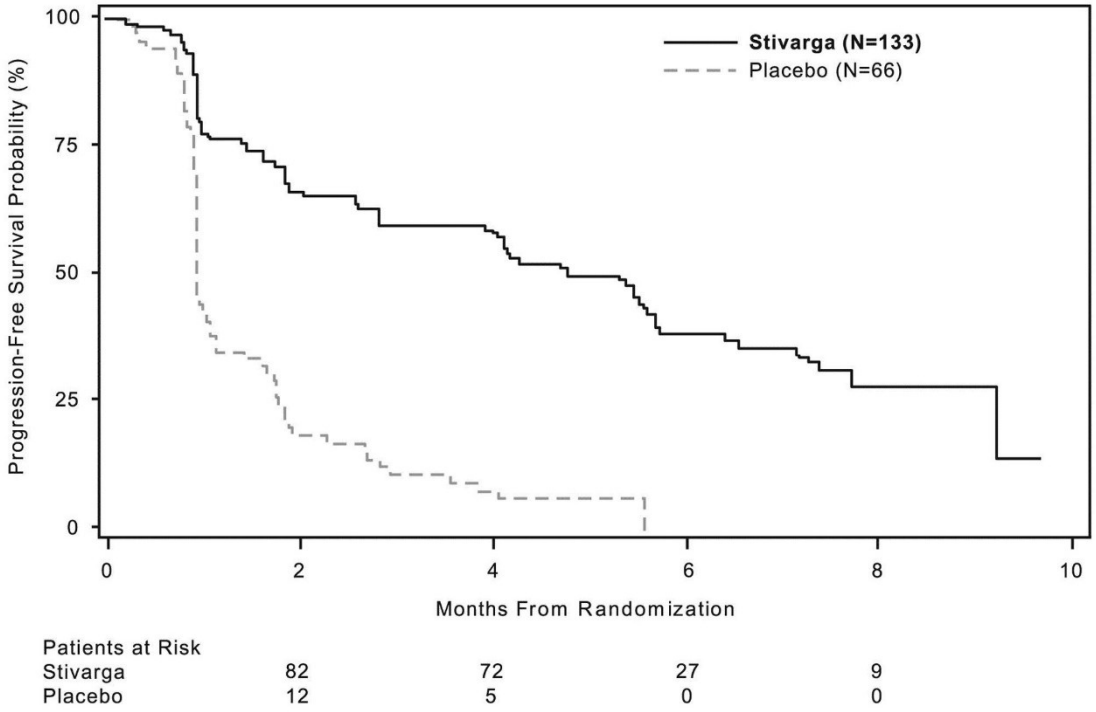
Table 8: Efficacy results from the GRID study

	Regorafenib (N=133)	**Placebo (N=66)**
Progression-free Survival		
Number of Death or Progressions (%)	82 (62%)	63 (96%)
Median PFS in months (95% CI)	4.8 (3.9, 5.7)	0.9 (0.9, 1.1)
HR (95% CI)	0.27 (0.19, 0.39)	

P-value[a]	<0.0001	
Overall Survival		
Number of Deaths (%)	109 (82%)	53 (80.3%)
Median OS in Months (95% CI)	17.4 (14.9, 20.2)	17.4 (12.3, 21.0)
HR (95% CI)	0.91 (0.65, 1.27)	
P-value [a]	0.5716	

[a]2-sided p-value by log-rank test stratified by line of treatment and geographical region.

Figure 2: Kaplan-Meier Curves of Progression-free Survival for GRID



Hepatocellular Carcinoma (HCC)

The clinical efficacy and safety of Regorafenib were evaluated in an international, multicenter, randomized (2:1), double- blind, placebo-controlled trial [Study "REgorafenib after SORafenib in patients with hepatoCEllular carcinoma" (RESORCE); NCT 01774344]. The study enrolled adults with Child-Pugh A and Barcelona Clinic Liver Cancer Stage Category B or C hepatocellular carcinoma, with documented disease progression following sorafenib. The median duration of previous sorafenib treatment was 7.8 months; patients who permanently discontinued sorafenib due to toxicity or were unable to tolerate sorafenib doses of 400 mg once daily were ineligible.

Patients were randomized to receive 160 mg regorafenib orally once daily plus best supportive care (BSC) or matching placebo plus BSC for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity.

Randomization was stratified by geographical region (Asia vs rest of world), ECOG performance status (0 vs 1), alpha- fetoprotein levels (<400 ng/mL vs ≥400 ng/mL), extrahepatic disease (presence vs absence), and macrovascular invasion (presence vs absence). The major efficacy outcome measure was overall survival (OS).

Additional outcome measures were progression-free survival (PFS), overall tumor response rate (ORR) and duration of response as assessed by investigators using RECIST 1.1 and using modified RECIST (mRECIST) for HCC. Patients continued therapy with Regorafenib until clinical or radiological disease progression or unacceptable toxicity.

The characteristics of the study population were a median age of 63 years (range 19 to 85 years); 88% male; 41% Asian, 36% White, and 21% not reported; 66% had ECOG performance status (PS) of 0 and 34% had ECOG PS of 1; 98% had Child-Pugh A and 2% had Child-Pugh B. Risk factors for underlying cirrhosis included hepatitis B (38%), alcohol use (25%), hepatitis C (21%), and non-alcoholic steato hepatitis (7%). Macroscopic vascular invasion or extra-hepatic tumor spread was present in 81% of patients. Barcelona Clinic Liver Cancer (BCLC) was stage C in 87% and stage B in 13% of patients. All patients received prior sorafenib and 61% received prior loco-regional transarterial embolization or chemoinfusion procedures.

Efficacy results are summarized in Table 9 and Figure 3 below.

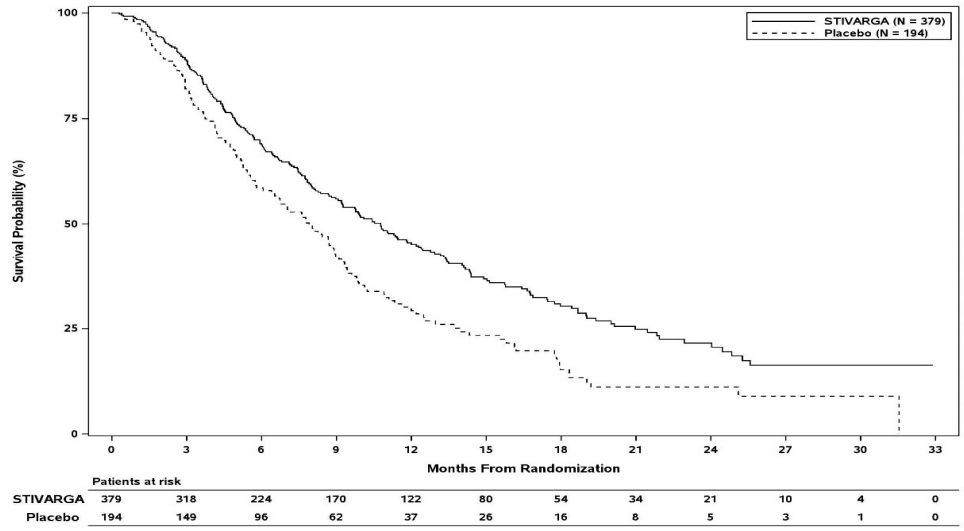
Table 9: Efficacy Results from Study RESORCE

	Regorafenib n=379	**Placebo n=194**
Overall Survival		
Number of Deaths (%)	233 (62)	140 (72)
Median OS in months (95% CI[a])	10.6 (9.1, 12.1)	7.8 (6.3, 8.8)
Hazard Ratio[b] (95% CI[a])	0.63 (0.50, 0.79)	
P-value[c]	<0.0001	
Progression-free Survival (mRECIST)		
Number of Events (%)	293 (77)	181(93)
Progressive Disease	274 (72)	173 (89)
Death	19 (5)	8 (4)
Median PFS in months (95% CI[a])	3.1 (2.8, 4.2)	1.5 (1.4, 1.6)
Hazard Ratio[b] (95% CI[a])	0.46 (0.37, 0.56)	
P-value[c]	<0.0001	
Progression-free Survival (RECIST 1.1)		
Number of Events (%)	288 (76)	184 (95)
Progressive Disease	270 (71)	175 (90)
Death	18 (5)	9 (5)
Median PFS in months (95% CI[a])	3.4 (2.9, 4.2)	1.5 (1.4, 1.5)
Hazard Ratio[b] (95% CI[a])	0.43 (0.35, 0.52)	
Overall Response (mRECIST)		
Overall Response Rate	11%	4%
95% CI[a]	(8%, 14%)	(2%, 8%)
Complete Response	0.5%	0
Partial Response	10%	4%
Overall Response (RECIST 1.1)		
Overall Response Rate	7%	3%
95% CI[a]	(4%, 10%)	(1%, 6%)
Complete Response	0	0
Partial Response	7%	3%

[a]CI=confidence interval.

[b]Estimated with Cox proportional hazard model stratified by geographic region, ECOG performance status, Alpha-fetoprotein level, presence versus absence of extrahepatic disease, and presence versus absence of macrovascular invasion.
[c]Lo grank test stratified by geographic region, ECOG performance status, Alpha-fetoprotein level, presence versus absence of extrahepatic disease, and presence versus absence of macrovascular invasion.

Figure 3: Kaplan-Meier Curve of Overall Survival from Study RESORCE



5.2 Pharmacokinetic properties

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 in the CORRECT and GRID studies *[see Section 4.2 & 5.1]*.

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 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).

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.

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≥ 60mL/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 Interaction Studies
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-5is 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 TANGITARE 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% *[see Section 4.4].*

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 *[see Section 4.5)]*.

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% *[see Section 4.5]*.

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} *[see Section 4.5]*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Croscarmellose sodium, Povidone, Ethanol Anhydrous, Acetone, Magnesium stearate, Colloidal Silicon Dioxide, Opadry Pink 20B540009-CN

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.
Store in the original package in order to protect from moisture.
Keep the bottle tightly closed after first opening. Once the bottle is opened the medicinal product has shown to be stable for 4 weeks below 30 °C. Thereafter, the product is to be discarded

6.5 Nature and contents of container

28’s HDPE Bottle

7. PRODUCT REGISTRATON HOLDER

Dr. Reddy`s Laboratories Malaysia Sdn. Bhd.
UNIT NO. SO-29-07 AND SO-29-08,
MENARA 1, STRATA OFFICE, NO. 3,
JALAN BANGSAR, KL ECO CITY,
59200 KUALA LUMPUR
MALAYSIA

8. MANUFACTURER

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Hyderabad, 500100, India

9. DATE OF REVISION OF THE TEXT

August 2025