PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]REZUROCK™

Belumosudil Tablets

Tablets, 200 mg belumosudil (as belumosudil mesylate), oral

Protein Kinase Inhibitor

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Sections or subsections that are not applicable at the time of authorization are not listed

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS AND CLINICAL USE

REZUROCK is indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (GVHD) after failure of at least two prior lines of systemic therapy.

Efficacy in patients with chronic GVHD was based on objective response rate and duration of response in a single-arm study (see 14 CLINICAL TRIALS).

1.1 Pediatrics < 18 years:

Pediatrics (≥ 12-18 years of age): No patients under the age of 18 were enrolled in the clinical development program. Use of REZUROCK in pediatric patients 12 years and older is supported by evidence from studies in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of drug substance, that the exposure of drug substance is expected to be similar between adults and pediatric patients age 12 years and older, and that the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to these pediatric patients.

Pediatrics (< 12 years of age): The safety and efficacy of REZUROCK in pediatric patients younger than 12 years of age have not been established.

1.2 Geriatrics ≥ 65 years:

Geriatrics (≥ 65 years): Evidence from clinical experience/studies suggests that the use in the geriatric population is not associated with any overall differences in safety or effectiveness in older patients versus younger patients (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

2 CONTRAINDICATIONS

REZUROCK is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing considerations

- Treatment with REZUROCK has not been studied in patients with pre-existing severe renal or hepatic impairment. For patients with pre-existing severe renal or hepatic

impairment, consider the risks and potential benefits before initiating treatment with REZUROCK (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

- A complete blood count (CBC), renal function (creatinine) and liver function tests (LFTs) should be performed prior to starting REZUROCK.
- Coadministration of rifampin, a strong CYP3A inducer, decreased plasma belumosudil concentrations. Avoid coadministration of REZUROCK with strong CYP3A inducers. If coadministration cannot be avoided, increase the dose of REZUROCK to 200 mg twice daily (see 9 DRUG INTERACTIONS).
- Coadministration of rabeprazole and omeprazole decreased plasma belumosudil concentrations. Coadministration of REZUROCK with proton pump inhibitors may decrease belumosudil exposure. Increase the dose of REZUROCK to 200 mg twice daily when coadministered with a proton pump inhibitor (see 9 DRUG INTERACTIONS).
- Pregnancy testing is recommended for women of childbearing potential prior to initiating REZUROCK.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of REZUROCK is 200 mg given orally once daily, with food, at approximately the same time each day. Treatment should continue until progression of chronic GVHD that requires a new systemic therapy or occurrence of unacceptable toxicity.

Pediatrics ≤ 18 years:

Health Canada has not authorized an indication for pediatric use in patients under the age of 12 years.

No dosing adjustments are required in adolescents aged ≥ 12-18 years (see 1 INDICATIONS AND CLINICAL USE, 1.1 Pediatrics < 18 years:).

Geriatrics (≥ 65 years):

No dose adjustment is required in patients ≥ 65 years of age (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Recommended Dose Modifications for Adverse Reactions

The recommended REZUROCK dosage modifications for adverse reactions are provided in Error! Reference source not found..

Table 1 Recommended Dosage Modifications for REZUROCK for Adverse Reactions

Adverse Reaction	Severity	REZUROCK Dosage Modifications
Hepatotoxicity (see 8 ADVERSE REACTIONS)	Grade 3 ALT or AST (> 5 to 20 x ULN) or Grade 2 bilirubin (> 1.5 to 3 x ULN)	Hold REZUROCK until recovery to ≤ Grade 1, then resume REZUROCK at the recommended dose at physician's discretion.

Table 1 Recommended Dosage Modifications for REZUROCK for Adverse Reactions

Adverse Reaction	Severity	REZUROCK Dosage Modifications
	Grade 4 ALT or AST (> 20 x ULN) or Grade ≥3 bilirubin (> 3 x ULN)	Permanently discontinue REZUROCK.
Other adverse reactions (see 8 ADVERSE REACTIONS)	Grade 3	Hold REZUROCK until recovery to ≤ Grade 1, then resume REZUROCK at the recommended dose level at the physician's discretion.
	Grade 4	Permanently discontinue REZUROCK.

4.4 Administration

The recommended dose of REZUROCK is 200 mg given orally once daily until progression of chronic GVHD that requires new systemic therapy.

Instruct the patient on the following:

- Swallow REZUROCK tablets whole. Do not cut, crush, or chew tablets.
- Take REZUROCK with a meal at approximately the same time each day (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

Treatment with REZUROCK has not been studied in patients with pre-existing severe renal or hepatic impairment. For patients with pre-existing severe renal or hepatic impairment, consider the risks and potential benefits before initiating treatment with REZUROCK (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

4.5 Missed Dose

In the event of a missed daily dose of REZUROCK, the missed dose should be taken as soon as possible on the same day. Resume the regular daily dose schedule for REZUROCK the next day. Patients should not take extra doses to make up for the missed dose.

5 OVERDOSAGE

There is limited experience with overdose in clinical trials with REZUROCK. There is no known antidote for overdoses with REZUROCK. In the event of suspected overdose, undertake general supportive measures, and observe until clinical stabilization.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablets 200 mg belumosudil (as belumosudil mesylate)	Colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and yellow iron oxide.

REZUROCK is available as 200 mg pale yellow, oblong tablets, debossed with "KDM" on one side and "200" on the other side. Each tablet contains 200 mg belumosudil (equivalent to 242.5 mg belumosudil mesylate).

REZUROCK is packaged in 60 cc high density polyethylene (HDPE) bottles each containing 30 tablets.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Hypertension
Of the 83 patients with chronic GVHD who received the recommended dose of 200 mg once daily, hypertension occurred in 21% of patients, including Grade 3-4 hypertension in 6% of patients. Of note, 52.7% of patients had a concomitant medical condition of hypertension. Optimize blood pressure prior to initiating REZUROCK. Consider monitoring blood pressure monthly and/or as clinically indicated. Withhold or permanently discontinue REZUROCK based on severity (see
4 DOSAGE AND ADMINISTRATION).

Hypotension
Based on the on-target effect of pan-ROCK inhibitors and the observed lowering of blood pressure in nonclinical studies, hypotension is a potential risk with belumosudil treatment. Of the 83 patients with chronic GVHD who received 200 mg once daily, 4.8% and 7.2% of subjects experienced at least one TEAE of hypotension or systolic blood pressure < 90 mm Hg respectively. Of these, grade ≥ 3 TEAEs of hypotension was reported in 2.4% and systolic blood pressure < 90 mm Hg in 4.8% of subjects with 2.4% of subjects requiring dose interruption. Optimize blood pressure prior to initiating REZUROCK. Consider monitoring blood pressure monthly and/or as clinically indicated. Withhold or permanently discontinue REZUROCK based on severity (see
4 DOSAGE AND ADMINISTRATION).

Gastrointestinal

Diarrhea
Of the 83 patients with chronic GVHD who received the recommended dose of 200 mg once daily, diarrhea occurred in 32.5%, with Grade ≥ 3 diarrhea in 5% of patients. A fatal adverse reaction was reported in one patient with severe nausea, vomiting, diarrhea and multi-organ failure; relevant medical history included acute myeloid leukemia, chronic kidney disease, cardiac disorder, and hypertension (see 8 ADVERSE REACTIONS). To prevent dehydration, administer fluid and electrolyte replacement and antidiarrheal medications as needed. Withhold or permanently discontinue REZUROCK based on severity (see 4 DOSAGE AND ADMINISTRATION).

Hematologic

Cytopenias
Of the 83 patients with chronic GVHD who received the recommended dose of 200 mg once daily, cytopenias, including lymphocyte count decreased (2.4%), white blood cell count decreased (3.6%; Grade ≥ 3 in 2.4%), neutrophil count decreased (1.2%), platelet count decreased (4.8%) and anemia (12%) were reported. Grade ≥ 3 leukopenia on laboratory tests was reported in 2.4% of patients, 2 patients experienced on-treatment shifts from Grade 0 to Grade 4 (see 8 ADVERSE REACTIONS). Patients should have their complete blood counts monitored monthly. Withhold or permanently discontinue REZUROCK based on severity (see 4 DOSAGE AND ADMINISTRATION).

Hemorrhage
Of the 83 patients with chronic GVHD who received the recommended dose of 200 mg once daily, Grade ≥ 3 hemorrhagic events, mainly contusion and hematoma, occurred in 5% of patients treated with REZUROCK. Withhold or permanently discontinue REZUROCK based on severity (see 4 DOSAGE AND ADMINISTRATION).

Hepatic

Of the 83 patients with chronic GVHD who received the recommended dose of 200 mg once daily, hepatotoxicity events occurred (see 8 ADVERSE REACTIONS). Liver function test (LFT) elevations, including elevations in ALT, AST, GGT, blood alkaline phosphatase, and increased bilirubin levels were frequently reported in belumosudil clinical studies. Grade ≥ 3 LFT elevations were uncommon, with grade ≥ 3 AST/ALT elevations occurring in 1.2% and GGT in 4.8% of patients. Liver function (ALT, AST, GGT and total bilirubin) should be monitored prior to the start of REZUROCK, and then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin. Withhold or permanently discontinue REZUROCK based on severity (see 4 DOSAGE AND ADMINISTRATION).

Immune

Infection
Of the 83 patients with chronic GVHD who received the recommended dose of 200 mg once daily, infection occurred in 53% of patients, with Grade 3 or 4 infections in 16% of patients. The majority of infections were mild or moderate and non-serious. The number of subjects discontinuing or interrupting treatment due to infection events was low. Most infections were viral, followed in frequency by bacterial infections. Respiratory infections were most common and included upper respiratory tract (28.9%), pneumonia (10.8%), sinusitis (4.8%), influenza (3.6%), and respiratory tract infection (3.6%). Fungal and opportunistic infections were uncommon. Patients should be monitored for fever, neutropenia, and infection, and appropriate anti-infective therapy should be initiated as indicated. Withhold or permanently discontinue REZUROCK based on severity (See
4 DOSAGE AND ADMINISTRATION, Recommended Dose Modifications for Adverse Reactions).

Reproductive Health: Female and Male Potential

Fertility
No human data on the effects of REZUROCK on fertility are available. In non-clinical fertility studies in rats, changes in male reproductive organs and sperm, as well as reductions in implantation sites and the number of viable embryos were observed (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Teratogenic Risk
Based on findings in animals and its mechanism of action, REZUROCK can cause fetal harm (embryofetal mortality and embryofetal malformations) when administered to pregnant women and should not be used during pregnancy (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). Pregnancy testing is recommended for women of childbearing potential prior to initiating REZUROCK.

Women of childbearing potential should be advised to avoid becoming pregnant and use highly effective contraceptive measures while receiving REZUROCK and for 1 week after ending treatment.

Men with female partners of reproductive potential should be advised to use effective contraception during treatment with REZUROCK and for 3 months after the final dose.

Skin

Photosensitivity
REZUROCK absorbs UV light and shows affinity for melanin. REZUROCK demonstrated phototoxicity in an *in vitro* assay using Balb/c 3T3 mouse fibroblast cells (see 16 NON-CLINICAL

TOXICOLOGY). While phototoxicity has not been observed in clinical studies, patients should be advised that skin reactions due to phototoxicity could potentially occur with REZUROCK.

7.1 Special Populations

7.1.1 Pregnant Women

There are no clinical data on the use of REZUROCK in pregnant women. Based on findings in animals and its mechanism of action, REZUROCK can cause fetal harm when administered to pregnant women. Administration of belumosudil to pregnant rabbits during organogenesis was associated with embryofetal mortality and embryofetal malformations at maternal exposures (AUC) lower than exposures in patients at the recommended dose (see 16 NON-CLINICAL TOXICOLOGY and 10 CLINICAL PHARMACOLOGY).

REZUROCK should not be used during pregnancy, unless clearly necessary and after a careful consideration of the need of the mother and the risk to the fetus. Verify pregnancy status of females of reproductive potential prior to initiating REZUROCK. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy. If REZUROCK is used during pregnancy or if the patient becomes pregnant while taking REZUROCK, the patient should be apprised of the potential hazard to the fetus.

7.1.2 Breast Feeding

There are no data regarding the presence of belumosudil in human milk, the effects of belumosudil on the breastfed infant, or its effects on milk production. It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk, precaution should be exercised. Advise lactating women not to breast feed during treatment with REZUROCK and for 1 week following the final dose.

7.1.3 Pediatrics (< 18 years of age)

Pediatrics (≥ 12-18 years of age): No patients under the age of 18 years were enrolled in the clinical development program. Use of REZUROCK in pediatric patients 12 years and older is supported by evidence from studies in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of drug substance, that the exposure of drug substance is expected to be similar between adults and pediatric patients age 12 years and older, and that the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients.

REZUROCK may impair fertility in male and female adolescents of reproductive potential (see 16 NON-CLINICAL TOXICOLOGY, **Reproductive and Developmental Toxicology**).

The safety of long-term use of REZUROCK in adolescent patients has not been evaluated.
No dose adjustments in this population are required.

Pediatrics (< 12 years of age): The safety and efficacy of REZUROCK in pediatric patients younger than 12 years of age have not been established.

7.1.4 Geriatrics (≥ 65 years of age)

Of the 65 patients with chronic GVHD who were evaluated for efficacy of REZUROCK, 26% were 65 years and older. Of the 186 patients with chronic GVHD receiving all doses and who were evaluated for safety of REZUROCK, 26% were 65 years and older. No clinically meaningful differences in safety or effectiveness of REZUROCK were observed in patients over the age of 65 years in comparison to younger patients.

No dose adjustments in this population are required.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of REZUROCK reflects exposure to REZUROCK 200 mg once daily in patients with chronic GVHD receiving corticosteroid or other immunosuppressive treatments after failure of at least one line of prior systemic therapy.

The most frequently observed adverse reactions with the 200 mg/day dose (≥ 20%), including laboratory abnormalities, were infections, fatigue, nausea, diarrhea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension.

Permanent discontinuation of REZUROCK due to adverse events occurred in 18% of patients. The most frequent reasons for treatment interruption in patients receiving the 200 mg/day dose were progression of chronic GVHD (13%) and recurrence of the underlying malignancy (8%). Adverse events leading to dose interruption occurred in 29% of patients. The adverse events leading to dose interruption in ≥ 2% were infections (11%), diarrhea (4%), and asthenia, dyspnea, hemorrhage, hypotension, liver function test abnormal, nausea, pyrexia, edema, and renal failure (2% each).

A fatal adverse reaction was reported in one patient with severe nausea, vomiting, diarrhea and multi-organ failure.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of REZUROCK in adult patients with chronic GVHD was evaluated in two clinical trials (KD025-213 and KD025-208) in which chronic GVHD patients were treated with 200 mg once

daily (N=83), 200 mg twice daily (N=82) or 400 mg once daily (N=21) (see 14 CLINICAL TRIALS, 14.1 Clinical Trials by Indication).

Study KD025-213 was a randomized, open-label, multicenter two arm, phase 2 study examining belumosudil in the treatment of patients with chronic GVHD who had failed two to five prior lines of systemic therapy (N=66 200 mg once daily). Study KD025-208 was a phase 2A dose-escalation trial evaluating the activity of belumosudil in subjects with active, steroid-dependent chronic GVHD who had failed 1-3 previous lines of treatment (N=17 200 mg once daily). The median duration of treatment in the 83 patients receiving 200 mg/day was 6.9 months (range: 0.5 to 38.7 months).

Of all belumosudil-treated subjects with chronic GVHD, 109 (58.6%) of the 186 subjects were male and 77 (41.4%) were female. Median age was 54.5 years (range: 20-77 years). Most subjects were White (159 subjects, 85.5%) and not Hispanic or Latino (157 subjects, 84.4%). The median number of organs affected by chronic GVHD was 3.5 and 4.0 for belumosudil-treated subjects in Studies KD025-208 and KD025-213, respectively, with > 50% of subjects having 4 or more organs involved. All subjects with chronic GVHD were taking a concomitant systemic corticosteroid at study initiation. The median duration of treatment with belumosudil in the 186 subjects with chronic GVHD was 6.83 months (range: 0.39-38.74 months), with 84 subjects (45.2%) having been exposed to belumosudil for ≥ 6 to 12 months and 31 subjects (16.7%) treated for ≥ 12 months.

Table 2 Adverse Reactions Occurring with a Frequency of ≥ 10% in Clinical Trials with REZUROCK

System Organ Class	REZUROCK 200 mg once daily (N=83)	
	All Grades[a] (%)	Grade 3-4[a] (%)
Gastrointestinal		
Nausea[b]	42	4
Diarrhea	35	5
Abdominal pain[c]	22	1
Dysphagia	15	0
General disorders and administration site conditions		
Asthenia[d]	46	4
Oedema[e]	27	1
Pyrexia	18	1
Infections and infestations		
Infection (pathogen not specified)[f]	53	16
Viral infection[g]	19	4
Bacterial infection[h]	16	4
Investigations		

Table 2 Adverse Reactions Occurring with a Frequency of ≥ 10% in Clinical Trials with REZUROCK

System Organ Class	REZUROCK 200 mg once daily (N=83)	
	All Grades[a] (%)	Grade 3-4[a] (%)
Alanine aminotransferase increased	12	1
Aspartate aminotransferase increased	12	1
Gamma-glutamyltransferase increased	11	5
Metabolism and nutrition		
Decreased appetite	17	1
Musculoskeletal and connective tissue		
Musculoskeletal pain[i]	22	4
Muscle spasm	17	0
Arthralgia	15	2
Nervous system		
Headache[j]	21	0
Respiratory, thoracic and mediastinal		
Dyspnea[k]	33	5
Cough[l]	30	0
Nasal congestion	12	0
Skin and subcutaneous		
Rash[m]	12	0
Pruritus[n]	11	0
Vascular		
Hemorrhage[o]	23	5
Hypertension	21	7

[a] Adverse events were coded according to MedDRA Version 20.0

[b] includes nausea, vomiting.

[c] includes abdominal pain, abdominal pain upper, abdominal pain lower.

[d] includes fatigue, asthenia, malaise.

[e] includes oedema peripheral, generalized oedema, face oedema, localized oedema, oedema.

[f] infection with an unspecified pathogen includes acute sinusitis, device related infection, ear infection, folliculitis, gastroenteritis, gastrointestinal infection, hordeolum, infectious colitis, lung infection, skin infection, tooth infection, urinary tract infection, wound infection, upper respiratory tract infection, pneumonia, conjunctivitis, sinusitis, respiratory tract infection, bronchitis, sepsis, septic shock.

[g] includes influenza, rhinovirus infection, gastroenteritis viral, viral upper respiratory tract infection, bronchitis viral, Epstein-Barr viremia, Epstein-Barr virus infection, parainfluenzae virus infection, Varicella zoster virus infection, viral infection.

[h] includes cellulitis, Helicobacter infection, Staphylococcal bacteremia, catheter site cellulitis, Clostridium difficile colitis, Escherichia urinary tract infection, gastroenteritis Escherichia coli, Pseudomonas infection, urinary tract infection bacterial.

[i] includes pain in extremity, back pain, flank pain, limb discomfort, musculoskeletal chest pain, neck pain, musculoskeletal pain.

[j] includes headache, migraine.

[k] includes dyspnea, dyspnea exertional, apnea, orthopnea, sleep apnea syndrome.

[l] includes cough, productive cough.

[m] includes rash, rash maculo-papular, rash erythematous, rash generalized, dermatitis exfoliative.

Table 2 Adverse Reactions Occurring with a Frequency of ≥ 10% in Clinical Trials with REZUROCK

System Organ Class	REZUROCK 200 mg once daily (N=83)	
	All Grades[a] (%)	Grade 3-4[a] (%)

[n] includes pruritus, pruritus generalized.
[o] includes contusion, hematoma, epistaxis, increased tendency to bruise, conjunctival hemorrhage, hematochezia, mouth hemorrhage, catheter site hemorrhage, hematuria, hemothorax, purpura.

8.3 Less Common Clinical Trial Adverse Reactions

The following less common adverse reactions were reported in clinical trials KD025-213 and KD025-208 with a frequency > 2% in adult patients with chronic GVHD receiving REZUROCK.

Gastrointestinal disorders: nausea, diarrhea, vomiting, constipation

General disorders and administration site conditions: fatigue, peripheral oedema, pyrexia

Infections and infestations: upper respiratory tract infection

Investigation: increased aspartate aminotransferase, increased alanine aminotransferase, increased gamma glutamyl transferase, increased blood alkaline phosphatase, decreased platelet count, decreased lymphocyte count, decreased weight

Metabolism and nutrition disorders: hyperglycaemia, decreased appetite

Musculoskeletal and connective tissue disorders: muscle spasm, arthralgia

Nervous system disorders: headache, peripheral neuropathy

Respiratory, thoracic and mediastinal disorders: dyspnea, cough

Vascular disorders: hypertension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Error! Reference source not found.**3** below lists the laboratory abnormalities which worsened from baseline in patients with chronic GVHD who received REZUROCK in the two clinical trials.

Table 3 Select Laboratory Abnormalities Worsening from Baseline in Chronic GVHD

	REZUROCK 200 mg once daily (N=83)		
	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post
Parameter	**(N)**	**(%)**	**(%)**
Chemistry			
Phosphate decreased	76	28	7
Gamma glutamyl transferase increased	47	21	11
Calcium decreased	82	12	1
Alkaline phosphatase increased	80	9	0
Potassium increased	82	7	1
Alanine aminotransferase increased	83	7	2
Creatinine increased	83	4	0
Hematology			
Lymphocytes decreased	62	29	13
Hemoglobin decreased	79	11	1
Platelets decreased	82	10	5
Neutrophil count decreased	83	8	4

Elevations of ALT and AST were reported in patients receiving 200 mg REZUROCK once daily in chronic GVHD trials. The majority (90%) of these were mild in severity (Grade 1) and resolved with few drug interruptions (1.2%) and no dose reductions or drug discontinuations.

Cytopenia, mainly anemia and decreased hemoglobin, was reported in 14.5% of patients treated with REZUROCK 200 mg once daily in chronic GVHD trials. Most patients recovered and no drug interruptions, discontinuations or dose reductions were required. Grade 3 cytopenias were often associated with relapse of the underlying malignancy.

9 DRUG INTERACTIONS

9.2 Drug Interaction Overview

Effects of Other Drugs on Belumosudil

Strong CYP3A inducers: Coadministration of REZUROCK with strong CYP3A inducers decreases belumosudil exposure, which may reduce the efficacy of REZUROCK. Avoid coadministration of

REZUROCK with strong CYP3A inducers. If coadministration cannot be avoided, increase the dose of REZUROCK as recommended (see 9.4 Drug-Drug Interactions).

Moderate CYP3A inducers: Coadministration of REZUROCK with a moderate CYP3A inducer efavirenz is predicted to decrease belumosudil C_{max} by 32% and AUC by 35% in healthy subjects. No REZUROCK dose adjustment is necessary.

Strong CYP3A inhibitors: Coadministration of REZUROCK with a strong CYP3A inhibitor itraconazole did not have clinically meaning effects on belumosudil exposure.

Proton pump inhibitors: Coadministration of REZUROCK with proton pump inhibitors decreases belumosudil exposure, which may reduce the efficacy of REZUROCK. Increase the dose of REZUROCK when coadministered with proton pump inhibitors (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions).

Effects of Belumosudil on Other Drugs

CYP3A Substrates: Coadministration of REZUROCK is predicted to increase midazolam (a sensitive CYP3A substrate) C_{max} and AUC approximately 1.3- and 1.5-fold in healthy subjects, respectively.

CYP2C9 Substrates: Coadministration of REZUROCK is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin).

CYP2C8 Substrates: Coadministration of REZUROCK is not expected to have clinically meaningful effect on the exposure of CYP2C8 substrates that are not an OATP1B1 substrate.

***In vitro* studies**

Enzymes: In vitro, belumosudil is an inhibitor of CYP2C8, CYP2C9, CYP2C19, CYP3A, UGT1A1, UGT1A3, and UGT1A9.

Transporters: Belumosudil is a substrate of P-gp.

Belumosudil inhibits BCRP, P-gp, OATP1B1, MATE1, and MATE2-K *in vitro*. The co-administration of oral BCRP, P-gp, OATP1B1, MATE1 or MATE2-K substrates with REZUROCK may increase the concentrations of the substrate drugs.

9.4 Drug-Drug Interactions

The drugs listed in Table 4 are based on either drug interactions case reports or studies or potential interactions due to the expected magnitude and seriousness of the interactions.

Table 4 Established or Potential Drug-Drug Interactions with REZUROCK

Drug Name or Group	Source of Evidence	Effect	Clinical Comment
Strong CYP3A Inducers	Clinical trial	Coadministration of multiple doses of rifampin decreased belumosudil C_{max} by 59% and AUC by 72%	Avoid coadministration of REZUROCK with strong CYP3A inducers. If coadministration cannot be avoided, increase the dose of REZUROCK to 200 mg twice daily
Proton Pump Inhibitors	Clinical trial	Coadministration of multiple doses of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80% Coadministration of multiple doses of omeprazole decreased belumosudil C_{max} by 68% and AUC by 47%	Increase the dose of REZUROCK to 200 mg twice daily when coadministered with proton pump inhibitors

9.5 Drug-Food Interactions

Administration of belumosudil with a high-fat and high-calorie meal was found to delay absorption and increase exposure of belumosudil in healthy subjects. REZUROCK should be taken with food (see
4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

9.6 Drug-Herb Interactions

Interactions of belumosudil with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions of belumosudil with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Belumosudil is an inhibitor of Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) and ROCK1, with IC_{50} values of approximately 100 nM and 3 µM, respectively. Belumosudil downregulated proinflammatory responses via modulation of CD4+ T-cell activity and STAT3/STAT5 phosphorylation in *ex vivo* or *in vitro* human T cell assays. Belumosudil also

inhibited pro-fibrotic signaling *in vitro*. *In vivo*, REZUROCK demonstrated activity in animal models of chronic GVHD.

10.2 Pharmacodynamics

Cardiac Electrophysiology

A dedicated QT study has not been conducted with REZUROCK.

10.3 Pharmacokinetics

The belumosudil pharmacokinetic parameters are presented following administration of the approved recommended dosage in patients with chronic GVHD, unless otherwise specified.

Exposure to belumosudil (C_{max} and AUC) increased approximately dose proportionally over a dosage range of 200 and 400 mg (1 to 2 times once daily recommended dosage). With once daily administration, steady-state concentrations of belumosudil were achieved with an accumulation ratio of 1.4.

Table 5 Summary of Steady State Pharmacokinetic Parameters of Belumosudil following 200 mg Once Daily Dose in Patients with Chronic GVHD Given a High-Fat Meal

PK Parameter	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-24} (h•ng/mL)	CL/F (L/h)	V/F (L)
Mean (CV%)	2390 (44%)	1.98 to 2.53	19.0 (39.0%)	22700 (48%)	9.83 (46%)	184 (67.6%)

C_{max} = maximum concentration; T_{max} = time of maximum concentration; $T_{1/2}$ = elimination half-life; AUC_{0-24} = area under the concentration-time curve calculated from time 0 to 24 h; CL/F = apparent oral clearance; V/F apparent oral volume of distribution

[a]Data presented as mean (coefficient of variation %), except for T_{max} which is presented as range of medians observed in patients with chronic GVHD patients and V/F which is presented as the geometric mean (geometric CV%) in healthy subjects following a single dose.

Absorption

The median T_{max} of belumosudil across studies in patients with chronic GVHD following administration of 200 mg QD was 1.98 to 2.53 h. Following a single oral dose of belumosudil 200 mg, the mean (%CV) bioavailability was 64% (17%) in healthy subjects.

Effect of Food:

In healthy subjects, the administration of a single 200 mg dose of belumosudil with a high-fat, high-calorie meal (800 to 1,000 calories with approximately 50% of the total caloric content of the meal from fat) increased belumosudil C_{max} to 2.2 times that following fasted administration and AUC to 2 times that following fasted administration. Median T_{max} was delayed 0.5 hour.

Distribution

The geometric mean volume of distribution after a single dose of belumosudil in healthy subjects was 184 L (geo CV% 67.7%). In *in vitro* preparations, binding to human serum albumin was 99.9% and binding to α_1-acid glycoprotein was 98.6%.

Metabolism

In vitro, belumosudil is primarily metabolized by CYP3A4, and to a lesser extent by CYP2D6, CYP2C8, and UGT1A9.

Elimination

Following a single oral dose of radiolabeled belumosudil in healthy subjects, 85% of radioactivity was recovered in feces (30% as unchanged) and less than 5% was recovered in urine. The mean (%CV) elimination half-life of belumosudil was 19.0 h (39%). The mean (%CV) clearance of belumosudil was 9.83 L/h (46%).

Special Populations and Conditions

Based on the population pharmacokinetic analysis in adult patients with chronic GVHD, body weight (38.6 kg to 143 kg) has no clinically meaningful effect on belumosudil pharmacokinetics.

- **Pediatrics:** Belumosudil pharmacokinetics have not been studied in a pediatric population**.**
- **Geriatrics:** In the population pharmacokinetic analysis**,** no clinically meaningful differences in belumosudil pharmacokinetics were observed based on age (18 to 77 years).
- **Sex:** In the population pharmacokinetic analysis, no clinically significant differences in belumosudil pharmacokinetics were observed based on sex.
- **Renal Insufficiency:** Belumosudil pharmacokinetics are not expected to be affected by mild (eGFR ≥ 60 and < 90 mL/min/1.72m^2) to moderate (eGFR ≥ 30 and < 60 mL/min/1.72m^2) renal impairment. The effect of severe renal impairment on belumosudil pharmacokinetics has not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Temperature
Store at room temperature, 15°C to 30°C.

Moisture
Store in the original container only to protect from moisture. Replace cap securely each time after opening. Do not discard desiccant.

Others

Keep this and all medicines out of the reach and view of children.

Unused tablets should be disposed in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling requirements

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

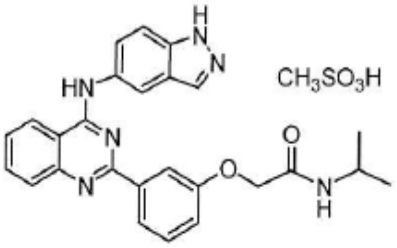
Proper/Common name: belumosudil mesylate

CAS Registry Number: 2109704-99-4 (mesylate salt); 911417-87-3 (free base)

Chemical Name: 2-{3-[4-(1*H*-indazol-5-ylamino)quinazolin-2-yl]phenoxy}-*N*-(propan-2-yl) acetamide-methane sulfonate (1:1)

Molecular formula and molecular mass: $C_{26}H_{24}N_6O_2 \cdot CH_3SO_3H$ (salt); 548.62 g/mol

Structural Formula (mesylate salt):



Physicochemical properties:
Belumosudil mesylate is a yellow crystalline solid. It is very slightly hygroscopic. There is one known stable crystal form and no known polymorph.

It is soluble in dimethylsulfoxide (DMSO), slightly soluble in dimethylformamide (DMF) and methanol, very slightly soluble in 2.0 pH (PBS buffer), and practically insoluble in water, acetonitrile, toluene, ethyl acetate, dichloromethane (DCM), acetone, isopropyl alcohol, n-heptane and in 2.0, 4.5, and 6.8 pH (PBS buffers).

Melting point range: 255 – 275°C

pH: 3.075 (in 1% w/v suspension in water)

pKa: 1.57 and 5.33

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Indication 1

Table 6 Summary of Patient Demographics for Clinical Trials in Chronic GVHD

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N)	Mean Age (yrs) (Range)	Sex
KD025-208 (NCT02841995)	Phase 2a, dose-escalation, open label, multicentre study in patients with chronic GVHD, who had received 1 to 3 prior lines of systemic therapy	200 mg QD or 200 mg BID or 400 mg QD orally. Median duration: 8.4 months*	54	Median age: 51.5 (20-75)	Male: 34 (63%) Female: 20 (37%)
KD025-213 (ongoing) (NCT03640481)	Phase 2, randomized, open-label multicentre study in patients with chronic GVHD who had received 2 to 5 prior lines of systemic therapy.	200 mg QD or 200 mg BID orally. Median duration: 6.7 months*	132	Median age: 55.5 (21-77)	Male: 75 (56.8%) Female: 57 (43.2)

*Patients were treated in 28-day cycles until clinically significant progression of chronic GVHD requiring new systemic therapy, recurrence of malignancy or unacceptable toxicity.

Study KD025-213 was a randomised, open-label, multicentre study of REZUROCK for treatment of patients with chronic GVHD who had received 2 to 5 prior lines of systemic therapy and required additional treatment. Patients were randomised to receive 200 mg once daily (N=66) or 200 mg twice daily (N=66) of REZUROCK. Patients were excluded from the studies if platelets were < 50 × 109/L; absolute neutrophil count < 1.5 × 109/L; AST or ALT> 3 × ULN; total bilirubin > 1.5 × ULN; QTc(F) > 480 ms; eGFR < 30 mL/min/1.73 m2; or FEV1 ≤39%. There were 66 patients treated with REZUROCK 200 mg taken orally once daily. Concomitant treatment with supportive care therapies for chronic GVHD was permitted. Concomitant treatment with GVHD prophylaxis and standard care systemic chronic GVHD therapies was permitted as long as the subject has been on a stable dose for at least 2 weeks prior to study. Initiation of new systemic chronic GVHD therapy while on study was not permitted.

The primary endpoint was Overall Response Rate (ORR), defined as the proportion of patients whose best overall response met the criteria for Partial Response (PR) and Complete Response

(CR) (per the 2014 NIH Consensus Development Project for Clinical trials in chronic GVHD criteria) through Cycle 7 Day 1 (C7D1).

Table 7 Overall Response Rate through Cycle 7 Day 1 for Patients with Chronic GVHD in Study KD025-213

	REZUROCK 200 mg once daily (N=65)
Overall Response Rate (ORR)	49 (75%)
95% Confidence Interval [a]	(63%, 85%)
Complete Response	4 (6%)
Partial Response	45 (69%)

[a] Estimated using Clopper-Pearson method

Complete response (CR) was achieved in 4 patients. The median time to response was 8 weeks (range, 4 to 41 weeks). Responses, including complete responses, were achieved across all organs involved (skin, eyes, joints/fascia, mouth, lung, esophagus, upper GI, lower GI and liver).

The duration of response (DOR) was calculated from first response by C7D1 to death or new systemic therapies for chronic GVHD. Median DOR was not reached in the 200 mg once daily group. Durability of response was longer than 12 months in 62% (95% CI: 46, 74) of patients in the 200 mg once daily group. The median duration of response calculated from first response to first documentation of deterioration from best ORR, initiation of new systemic therapy for chronic GVHD, or death was 3.7 months (95% CI: 1.9, 8.3). The median duration of response, calculated from first response to progression from nadir in any organ, death, or new systemic therapies for chronic GVHD, was 1.9 months (95% CI: 1.2, 2.9). The median time to first response was 1.8 months (95% CI: 1.0, 1.9). The median (range) duration of follow-up for efficacy was 13.5 months (0.6, 21.9).

ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in the Lee Symptom Scale summary score through Cycle 7 Day 1 in 52% (95% CI: 40, 65) of patients.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Repeated dose studies with belumosudil of up to 26 weeks in rats and 39 weeks in dogs were conducted. In the 26-week rat study, belumosudil was administered orally at 50, 125, and 275 mg/kg/day. The NOAEL was 125 mg/kg/day (~3 to 7-fold the AUC at the human recommended dose of 200 mg daily). In a 3-month dog study, belumusodil was administered orally at 35, 70, and 125 mg/kg/day. In a separate 39-week dog study, belumusodil was administered orally at 5, 20, and 40 mg/kg/day. The NOAEL in the 3-month and 9-month dog study was 35 and 40 mg/kg/day, respectively, which is comparable to human exposures at the recommended dose (~1-fold AUC). Adverse effects observed in one or both species included toxicities in the gastrointestinal (GI) tract (emesis, loose stools, and/or abnormal black contents, increase in salivation), liver (elevated liver enzymes, hypertrophy/increased organ weight, and cholestasis/inflammation), kidney (increased blood urea nitrogen [BUN], tubular changes, pigmentation, intracellular protein droplets in the epithelium), hemolymphoid system (regenerative anemia), and reproductive system. In females, changes included lower uterine weights that correlated with uterine/cervical hypoplasia and decreased follicular development; findings were reversible. In males, toxicities included lower epididymis and testes weights associated with multifocal bilateral spermatozoan degeneration in the epididymis and testes, and multinucleated spermatids in the testes, and the changes were partially or fully reversible.

Carcinogenicity

Carcinogenicity studies have not been conducted with belumosudil.

Genotoxicity

Belumosudil was not mutagenic in an *in vitro* bacterial mutagenicity (Ames) assay and was not clastogenic in either an *in vitro* chromosome aberration assay in mammalian (CHO) cells or an *in vivo* mouse bone marrow micronucleus assay.

Reproductive and Developmental Toxicology

In a combined male and female rat fertility study, belumosudil-treated animals were mated with untreated animals. Belumosudil (50, 150, or 275 mg/kg/day) was administered orally to male rats 70 days prior to and throughout the mating period, and to female rats 14 days prior to mating and up to gestation day 7. In female rats at 275 mg/kg/day, adverse findings included pre- and post-implantation loss, and decreased number of viable embryos. In male rats at 275 mg/kg/day, adverse effects on sperm (low motility, reduced number, and increased abnormal sperm) and reproductive organs (reduced testicular and epididymal weights, testicular atrophy) were observed, along with decreased fertility. The exposure (AUC) at the dose of 275 mg/kg/day was approximately 8-9 times the exposure (AUC) in patients receiving the recommended dose of 200 mg daily.

In embryo-fetal developmental studies in pregnant female rats receiving belumosudil (15, 50, or 150 mg/kg/day), belumosudil administered at 150 mg/kg/day during the period of organogenesis was associated with decreased fetal weight (approximately 4 times the exposure

[AUC] in patients receiving the recommended dose). In embryo-fetal studies in pregnant rabbits receiving belumosudil (50, 125, or 225 mg/kg/day), embryofetal death was noted at maternal exposures lower than human exposure (0.4-fold of human AUC), and skeletal malformations were noted at maternal exposures comparable to human exposures at the recommended dose of belumosudil (~1-fold of human AUC).

Special Toxicology

Phototoxicity

In-vitro belumosudil has demonstrated photo-absorbance between 290 and 370 nm and positive phototoxic potential in the *in vitro* 3T3 Neutral Red Uptake Assay. No phototoxicity studies have been performed in animals.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrREZUROCK™
Belumosudil tablets

Read this carefully before you start taking **REZUROCK** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **REZUROCK**.

What is REZUROCK used for?
REZUROCK is used to treat patients, 12 years of age and older, with chronic graft-versus-host disease (GVHD) after two or more prior treatments that did not work.

How does REZUROCK work?

- REZUROCK blocks a specific protein in the body that is involved in inflammation and fibrosis. This may help to decrease symptoms of chronic GVHD like inflammation and scarring.

What are the ingredients in REZUROCK?

- Medicinal ingredient: belumosudil (as belumosudil mesylate)
- Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and yellow iron oxide.

REZUROCK comes in the following dosage forms:
Tablets: 200 mg belumosudil (as belumosudil mesylate)

Do not use REZUROCK if:

- you are allergic to belumosudil or to any ingredient in this medicine or container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REZUROCK. Talk about any health conditions or problems you may have, including if you have:

- a gastrointestinal infection

- liver or kidney problems

Other warnings you should know about:

Hypertension and hypotension (high and low blood pressure): REZUROCK can infrequently cause high or low blood pressure. Your healthcare professional will check your blood pressure before and during treatment.

Gastrointestinal problems: REZUROCK can cause diarrhea, severe nausea, vomiting and dehydration. Your healthcare professional will treat these problems as needed.

Blood and bleeding problems: REZUROCK may infrequently cause blood problems like lymphopenia and neutropenia (low white blood cells), **thrombocytopenia** (low blood platelets), and **anemia** (low red blood cells). Your healthcare professional will do blood tests monthly. REZUROCK can also cause bleeding problems.

Infections: REZUROCK can cause mainly bacterial or viral infections, which most often affect the organs involved in breathing (called respiratory system) such as lungs and the upper respiratory system. Your healthcare professional will treat these infections as needed.

Liver problems: REZUROCK can cause an increase in liver function tests. You will have regular blood tests done before starting your treatment and while you are taking REZUROCK. These blood tests will tell your healthcare professional how your liver is working.

Photosensitivity (sensitivity to sunlight)**:** REZUROCK might cause you to become more sensitive to sunlight. If you have a reaction from the sun, talk to your healthcare professional.

See the "Serious side effects and what to do about them" table, below, for more information on these and other serious side effects.

Pregnancy and breastfeeding:

Female patients

- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- You should not take REZUROCK if you are pregnant. It may harm your unborn baby.
- If you are able to become pregnant:
    - Your healthcare professional will do a pregnancy test before you start taking REZUROCK. This test must show that you are not pregnant.

- Avoid becoming pregnant while you are taking REZUROCK. Use effective birth control during your treatment and for at least 1 week after your last dose. Ask your healthcare professional about methods of birth control available to you.
- Tell your healthcare professional right away if you become pregnant or think you may be pregnant during your treatment with REZUROCK.

- Do not breastfeed while you are taking REZUROCK and for at least 1 week after your last dose.

Male patients

- Avoid fathering a child while you are taking REZUROCK.
- During your treatment with REZUROCK, use effective birth control each time you have sex with a woman who is pregnant, may be pregnant or could get pregnant. Continue using birth control for at least 3 months after your last dose.
- If, during your treatment with REZUROCK, your sexual partner becomes pregnant or thinks she may be pregnant, tell your healthcare professional right away.

Fertility in female and male patients:

REZUROCK may affect your fertility. Talk to your healthcare practitioner if you are planning on having children.

Tell your healthcare professional about all medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with REZUROCK:

- Medicines for bacterial infections such as rifampin
- Medicines for excess stomach acid or ulcers, such as omeprazole and rabeprazole
- Medicines for HIV treatment such as efavirenz
- Medicines for sedation such as midazolam

How to take REZUROCK:

- Take exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take with food at the same time each day.
- Swallow REZUROCK tablets whole with a glass of water.
- Do not cut, crush, or chew REZUROCK tablets.

Usual dose:

Adults and children 12 years and over: Take one tablet (200 mg) per day.

Your healthcare professional may stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you:

- experience serious side effects
- your disease gets worse
- are taking other medicines.

Overdose:

If you think you, or a person you are caring for, have taken too much REZUROCK, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

- If you miss a dose, take the missed tablet as soon as possible on the same day. Take the next dose at your usual time.
- Do not take an extra dose to make up for the missed dose.

What are the possible side effects from using REZUROCK?

These are not all the possible side effects you may feel when taking REZUROCK. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Infections
- Tiredness or weakness
- Nausea or vomiting
- Difficulty swallowing
- Diarrhea or constipation
- Cough
- Shortness of breath
- Cold symptoms
- Swelling
- Bleeding
- Stomach pain
- Muscle, bone or joint pain
- Muscle spasms
- Headache
- High blood pressure
- Itchy skin, rash

Your healthcare professional will do some tests before, during and after your treatment. These include blood tests to check your blood, kidney and liver health. More frequent tests might be needed.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Infections: fever and chills, fatigue, generally feeling unwell		√	
COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		√	
Gastrointestinal problems: stomach pain, decreased appetite, diarrhoea, nausea, vomiting		√	
Hypertension (high blood pressure): headache, shortness of breath, nosebleeds		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, tiredness (may occur when you stand up from lying or sitting)		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, tiredness, itchy skin		√	
Pneumonia (infection in the lungs): high fever with chills, fast breathing, chest pain when you cough, cough which may produce phlegm, fatigue, nausea, vomiting or diarrhea, shortness of breath		√	
Thrombocytopenia (low blood platelets): bleeding gums, nosebleeds, bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		√	
UNKNOWN			
Photosensitivity (sensitivity to sunlight): itchy, red skin when exposed to sunlight		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the sue of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/healthcanada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

Note: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at 15°C to 30°C in the original container. Protect from moisture.
- Replace cap securely each time after opening. Do not remove desiccant (a small pack inside the bottle which protects the pills from moisture damage) from bottle.
- Keep out of the reach and sight of children.
- Ask your healthcare professional on how to throw away drugs you no longer use.

If you want more information about REZUROCK:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drugproduct-database.html); the manufacturer's website (www.sanofi.ca) or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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