AUSTRALIAN PRODUCT INFORMATION
RHOLISTIQ™ Tablets

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

1 NAME OF THE MEDICINE

Belumosudil

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RHOLISTIQ film-coated tablets contain 200 mg of belumosudil (equivalent to 242.5 mg belumosudil mesilate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

RHOLISTIQ 200 mg film-coated tablets are supplied as pale, yellow oblong tablets, debossed with "KDM" on one side and "200" on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RHOLISTIQ is indicated for the treatment of patients with chronic graft-versus-host disease (chronic GVHD) aged 12 years and older who have an inadequate response to corticosteroids.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose of RHOLISTIQ is 200 mg given orally once daily.

Swallow RHOLISTIQ tablets whole. Do not cut, crush, or chew tablets.

Advise patients to take RHOLISTIQ at approximately the same time each day with a meal.

If the patient misses a dose of RHOLISTIQ, instruct the patient not to take extra doses to make up the missed dose.

Monitor total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at least monthly.

Dose Modifications for Adverse Reactions

The recommended RHOLISTIQ dosage modifications for adverse reactions are provided in Table 1.

Table 1: Recommended Dosage Modifications for RHOLISTIQ for Adverse Reactions

Adverse Reaction	Severity	RHOLISTIQ Dosage Modifications
Hepatotoxicity [see Section 4.8 Adverse Effects]	Grade 3 ALT or AST (5x to 20x ULN) or Grade 2 bilirubin (1.5x to 3x ULN)	Hold RHOLISTIQ until recovery of bilirubin, AST and ALT to Grade 0-1, then resume RHOLISTIQ at the recommended dose.
	Grade 4 ALT or AST (more than 20x ULN) or Grade ≥3 bilirubin (more than 3x ULN)	Discontinue RHOLISTIQ permanently.
Other adverse reactions [see Section 4.8 Adverse Effects]	Grade 3	Hold RHOLISTIQ until recovery to Grade 0-1, then resume RHOLISTIQ at the recommended dose level.
	Grade 4	Discontinue RHOLISTIQ permanently.

Dose Modification Due to Drug Interactions

Strong CYP3A Inducers

Increase the dosage of RHOLISTIQ to 200 mg twice daily when coadministered with strong CYP3A inducers [see Section 4.5 Interactions with other medicines and other forms of interaction].

Proton Pump Inhibitors

Increase the dosage of RHOLISTIQ to 200 mg twice daily when coadministered with proton pump inhibitors [see Section 4.5 Interactions with other medicines and other forms of interactions].

Dose Modifications for Renal or Hepatic Impairment

Renal Impairment

Patients with Mild or Moderate Renal Impairment

No dose modification of RHOLISTIQ is required [see Section 5.2 Pharmacokinetic Properties – Pharmacokinetics in Specific Populations].

Patients with Severe Renal Impairment

No data available for patients with severe renal impairment or for patients with end stage renal disease on dialysis [see Section 5.2 Pharmacokinetic Properties – Pharmacokinetics in Specific Populations]. Use with caution.

Hepatic Impairment

Patients with Mild or Moderate Hepatic Impairment

No dose modification of RHOLISTIQ is required.

Patients with Severe Hepatic Impairment

No data available for patients with severe hepatic impairment.

Method of Administration

RHOLISTIQ is dosed orally and should be administered with a meal.

Special patient populations

No dose modification is required for patients aged 65 years and older or for adolescent patients.

4.3 CONTRAINDICATIONS

Hypersensitivity to belumosudil or to any of the excipients listed in Section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Embryofetal Toxicity

Based on findings in animals, RHOLISTIQ can cause embryofetal harm when administered to a pregnant woman. Embryofetal lethality and fetal malformations were observed in pregnant rats and rabbits administered belumosudil at doses yielding clinically relevant exposure levels [see Section 4.6 Fertility, Pregnancy & Lactation]. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Section 4.6 Fertility, Pregnancy & Lactation].

Advise females of reproductive potential to use effective contraception during treatment with RHOLISTIQ and for at least one week after the last dose of RHOLISTIQ. Advise males with female partners of reproductive potential to use effective contraception during treatment with RHOLISTIQ and for at least one week after the last dose of RHOLISTIQ [see Section 4.6 Fertility, Pregnancy & Lactation].

Photosensitivity

RHOLISTIQ absorbs UV light and shows affinity for melanin. RHOLISTIQ demonstrated phototoxicity in an *in vitro* assay using Balb/c 3T3 mouse fibroblast cells. While phototoxicity has not been observed in clinical studies, patients should be advised that skin reactions due to phototoxicity could potentially occur with RHOLISTIQ.

Use in the Elderly

Of the 186 patients with chronic GVHD in clinical studies of RHOLISTIQ, 25.8% were 65 years and older. No overall differences in safety or effectiveness of RHOLISTIQ were observed between these patients and younger patients.

Paediatric Use

Use of RHOLISTIQ in paediatric 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 paediatric

patients age 12 years and older, and that the course of disease is sufficiently similar in adult and paediatric patients to allow extrapolation of data in adults to these paediatric patients.

The safety and effectiveness of RHOLISTIQ in paediatric patients less than 12 years old have not been established.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of strong CYP3A Inducers on RHOLISTIQ

Table 2 summarises drug interactions that affect the pharmacokinetics of belumosudil.

Table 2: Drug Interactions that affect RHOLISTIQ

Strong CYP3A4 Inducers	
Clinical Impact	The coadministration of strong CYP3A4 inducers with RHOLISTIQ may decrease belumosudil exposure
Prevention or Management	Increase the dosage of RHOLISTIQ to 200 mg twice a day when coadministered with strong CYP3A inducers.

Effect of Proton Pump Inhibitors on RHOLISTIQ

Table 3 summarises drug interactions that affect the pharmacokinetics of belumosudil.

Table 3: Drug Interactions that affect RHOLISTIQ

Proton Pump Inhibitors	
Clinical Impact	The coadministration of proton pump inhibitors with RHOLISTIQ may decrease belumosudil exposure
Prevention or Management	Increase the dosage of RHOLISTIQ to 200 mg twice a day when coadministered with proton pump inhibitors.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Based on findings from animal studies, RHOLISTIQ may impair male fertility.

In male rats, belumosudil impaired fertility at an oral dose of 275 mg/kg/day (yielding 8 times the exposure in patients at the maximum recommended human dose of 200 mg/day, based on plasma AUC). This was accompanied by decreased sperm count, reduced sperm motility and increased abnormal sperm, and degenerative changes in the testes and epididymides. Similar degenerative changes in the male reproductive tract were observed in dogs treated with belumosudil at ≥35 mg/kg/day (yielding systemic exposure only marginally above that of patients). Impairment of fertility in male rats was shown to be reversible.

Belumosudil had no effect on the incidence of pregnancy in female rats at oral doses up to 275 mg/kg/day (yielding 9 times the exposure in patients at the maximum recommended human dose). However, embryolethality (as increased post-implantation loss with an associated decrease in the number of viable embryos) was evident at this dose, occurring in conjunction with maternotoxicity.

Females and Males of Reproductive Potential

RHOLISTIQ can cause embryofetal harm when administered to a pregnant woman [see Use in Pregnancy].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with RHOLISTIQ.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with RHOLISTIQ and for at least one week after the last dose of RHOLISTIQ. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with RHOLISTIQ and for at least one week after the last dose of RHOLISTIQ.

Use in Pregnancy – Pregnancy Category D

RHOLISTIQ can cause embryofetal harm based on findings from animal studies and its mechanism of action. There are no available human data on RHOLISTIQ use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage.

If RHOLISTIQ is used during pregnancy or if the patient becomes pregnant while taking RHOLISTIQ, the patient should be apprised of the potential hazard to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown.

In pregnant rats, oral administration of belumosudil reduced fetal weight at ≥150 mg/kg/day and resulted in embryolethality at 300 mg/kg/day (yielding 3–9 times the exposure in patients at the maximum recommended human dose). Fetal malformations were observed at ≥50 mg/kg/day and included absence of anus and tail, whole body oedema, omphalocele and dome-shaped head. In rabbits, abortions, increased post-implantation loss, decreased live litter size, decreased fetal body weight, and fetal malformations at oral doses ≥ 125 mg/kg/day (approximately 0.4 times the human exposure at the recommended dose based on AUC) were observed. Malformations observed in rabbits involved the tail (short), ribs (branched, fused or

misshapen), sternebrae (fused) and thoracic vertebral neural arches (fused, misaligned or misshapen).

Use in lactation

No data are available regarding the presence of belumosudil or its metabolites in animal or human milk or its effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with RHOLISTIQ and for at least one week after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

RHOLISTIQ has no influence on the ability to drive and use machines. The clinical status of the patient should be considered when assessing the patient's ability to perform tasks that require judgment, motor, or cognitive skills.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following clinically significant adverse events are discussed in more detail in other sections of the Product Information.

- Embryofetal toxicity [see Section 4.4 Warnings and Precautions].

Because clinical trials are conducted under widely variable conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Chronic Graft versus Host Disease

In the chronic GVHD program, 186 patients were exposed to belumosudil with a median duration of exposure of 9.9 months (range 0.4 – 44.7). There were 83 patients given the proposed 200 mg/day dose and median duration of exposure for these patients was 9.2 months (range 0.5 – 44.7), with 34 patients having received ≥12 months of treatment.

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

Permanent discontinuation of RHOLISTIQ due to adverse events occurred in 18% of patients. The adverse event which resulted in permanent discontinuation in RHOLISTIQ in >3% of patients included nausea (4%). 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).

The most common (≥20%) adverse events, including laboratory abnormalities, were infections, asthenia, nausea, diarrhea, cough, oedema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension.

Table 4 summarises the nonlaboratory adverse events.

Table 4: Nonlaboratory Adverse Events in ≥10% Patients with Chronic GVHD Treated with RHOLISTIQ

Adverse Event	RHOLISTIQ 200 mg once daily (N=83)	
	All Grades (%)	**Grade 3-4 (%)**
Infections and infestations		
Infection (pathogen not specified)[a]	53	16
Viral infection[b]	19	4
Bacterial infection[c]	16	4
General disorders and administration site conditions		
Asthenia[d]	46	4
Oedema[e]	27	1
Pyrexia	18	1
Gastrointestinal		
Nausea[f]	42	4
Diarrhea	35	5
Abdominal pain[g]	22	1
Dysphagia	16	0
Respiratory, thoracic and mediastinal		
Dyspnea[h]	33	5
Cough[i]	30	0
Nasal congestion	12	0
Vascular		
Hemorrhage[j]	23	5
Hypertension	21	7
Musculoskeletal and connective tissue		
Musculoskeletal pain[k]	22	4
Muscle spasm	17	0
Arthralgia	15	2
Nervous system		
Headache[l]	21	0

Adverse Event	RHOLISTIQ 200 mg once daily (N=83)	
	All Grades (%)	Grade 3-4 (%)
Metabolism and nutrition		
Decreased appetite	17	1
Skin and subcutaneous		
Rash[m]	12	0
Pruritus[n]	11	0

[a] 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.
[b] 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.
[c] 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.
[d] includes fatigue, asthenia, malaise.
[e] includes edema peripheral, generalized edema, face edema, localized edema, edema.
[f] includes nausea, vomiting.
[g] includes abdominal pain, abdominal pain upper, abdominal pain lower.
[h] includes dyspnea, dyspnea exertional, apnea, orthopnea, sleep apnea syndrome.
[i] includes cough, productive cough.
[j] includes contusion, hematoma, epistaxis, increased tendency to bruise, conjunctival hemorrhage, hematochezia, mouth hemorrhage, catheter site hemorrhage, hematuria, hemothorax, purpura.
[k] includes pain in extremity, back pain, flank pain, limb discomfort, musculoskeletal chest pain, neck pain, musculoskeletal pain.
[l] includes headache, migraine.
[m] includes rash, rash maculo-papular, rash erythematous, rash generalized, dermatitis exfoliative.
[n] includes pruritus, pruritus generalized.

Table 5 summarises the laboratory abnormalities in RHOLISTIQ.

Table 5: Select Laboratory Abnormalities in Patients with Chronic GVHD Treated with RHOLISTIQ

	RHOLISTIQ 200 mg once daily		
	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post
Parameter	**N**	**(%)**	**(%)**
Chemistry			
Phosphate Decreased	76	28	7

	RHOLISTIQ 200 mg once daily		
	Grade 0-1 Baseline	**Grade 2-4 Max Post**	**Grade 3-4 Max Post**
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

Description of selected adverse reactions

Increased ALT or AST

Elevations of ALT and AST were reported in patients treated with RHOLISTIQ 200 mg once daily in chronic GVHD trials. The majority were mild in severity (Grade 1) and resolved with few drug discontinuations, drug interruptions or dose reductions.

Cytopenia

Cytopenia was reported in 14.5% of patients treated with RHOLISTIQ 200 mg once daily in chronic GVHD trials, anemia and decreased hemoglobin being the largest group of cytopenias. 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific experience in the management of RHOLISTIQ overdose in patients. There is no known antidote for overdoses with RHOLISTIQ. Single doses up to 1000 mg have been

given with acceptable tolerability in healthy volunteers. Appropriate supportive treatment should be given.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Belumosudil is a potent and selective inhibitor of Rho-associated, coiled-coil containing protein kinase-2 (ROCK2). In chronic GVHD, naïve T cells are skewed to a pro-inflammatory T-cell phenotype, known as Th17, with aberrant activation of ROCK2 promoting the synthesis of the pro-inflammatory cytokines interleukin-17 (IL-17) and IL-21. ROCK2 activation is also recognised to promote pro-fibrotic processes and suppress regulatory T cells. *In vitro*, belumosudil was shown to suppress IL-17 and IL-21 release from human peripheral blood mononuclear cells and to shift the Th17/Treg balance of human T cells (mediated via downregulation of STAT3 phosphorylation and upregulation of STAT5 phosphorylation, respectively). Anti-fibrotic activity was evident for belumosudil in experiments with cultured human lung fibroblasts. *In vivo,* belumosudil demonstrated efficacy in mice models of chronic GVHD.

Clinical trials

Chronic Graft versus Host Disease

Study KD025-213 (NCT03640481) was a randomised, open-label, multicentre study of RHOLISTIQ 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 RHOLISTIQ. Patients were excluded from the studies if platelets were $< 50 \times 10^9$/L; absolute neutrophil count $< 1.5 \times 10^9$/L; AST or ALT $> 3 \times$ ULN; total bilirubin $> 1.5 \times$ ULN; QTc(F) > 480 ms; eGFR < 30 mL/min/1.73 m^2; or FEV1 $\leq$ 39%. There were 66 patients treated with RHOLISTIQ 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.

Demographics and baseline characteristics are summarised in Table 6.

Table 6: Demographics and Baseline Characteristics of Patients with Chronic GVHD

	RHOLISTIQ 200 mg once daily (N=65)[a]
Age, Median, Years (minimum, maximum)	53 (21, 77)
Age ≥ 65 Years, n (%)	17 (26)
Males, n (%)	42 (65)
Race, n (%)	
White	54 (83)
Black	6 (9)
Other or Not Reported	5 (8)
Median (range) time (months) from Chronic GVHD Diagnosis	25.3 (1.9, 162.4)
≥ 4 Organs Involved, n (%)	31 (48)
Median (range) Number of Prior Lines of Therapy	3 (2, 6)
Number of Prior Lines of Therapy, n (%)	
2	23 (35)
3	12 (19)
4	15 (23)
≥5	15 (23)
Prior chronic GVHD treatment with ibrutinib, n (%)	21 (32)
Prior chronic GVHD treatment with ruxolitinib, n (%)	20 (31)
Refractory to Last Therapy, n (%[b])	43/55 (78)
Severe chronic GVHD, n (%)	46 (71)
Median (range) Global Severity Rating	7 (2, 9)
Median (range) Lee Symptom Scale Score at baseline	27 (7, 56)
Median (range) Corticosteroid dose at baseline (PE/kg)[c]	0.19 (0.03, 0.95)

[a] Excludes 1 inevaluable patient from the total of 66 patients treated with RHOLISTIQ 200 mg taken orally once daily

[b] Denominator excludes patients with unknown status

[c] Prednisone equivalents/kilogram

The efficacy of RHOLISTIQ was based on overall response rate (ORR) occurring by Cycle 7 Day 1 (C7D1) where overall response included complete response or partial response according to the 2014 NIH Response Criteria. The ORR results are presented in Table 7. The ORR was 75% (95% CI: 63, 85).

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

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

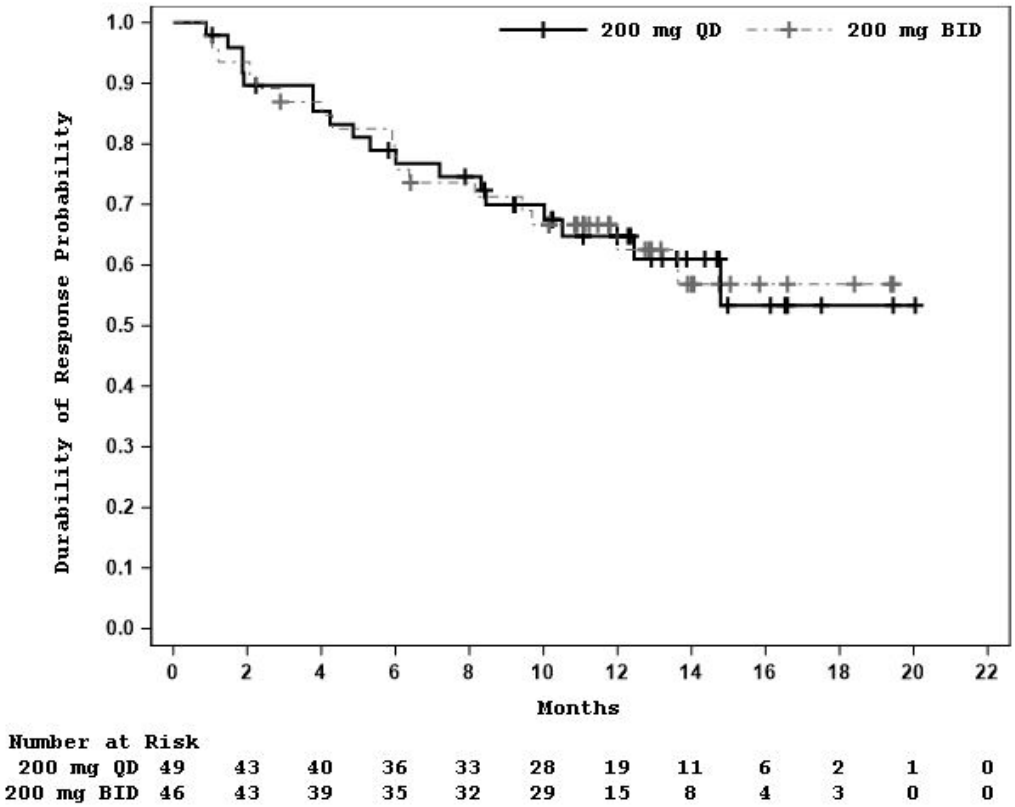
[a] Excludes 1 inevaluable patient from the total of 66 patients treated with RHOLISTIQ 200 mg taken orally once daily

[b]Estimated using Clopper-Pearson method

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.

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 6 months in 79% (95% CI: 64, 88) and 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 Kaplan-Meier curve for DOR is in Figure 1. 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 is 13.5 months (0.6, 21.9).

Figure 1: Kaplan-Meier Curve for Duration of Response in Study KD025-213



5.2 PHARMACOKINETIC PROPERTIES

The following pharmacokinetic parameters are presented for chronic GVHD patients administered belumosudil 200 mg once daily, unless otherwise specified. The mean (% coefficient of variation, %CV) steady-state AUC and C_{max} of belumosudil was 22700 (48%) h•ng/mL and 2390 (44%) ng/mL, respectively. Belumosudil C_{max} and AUC increased in an approximately proportional manner over a dosage range of 200 and 400 mg (1 to 2 times once daily recommended dosage). The accumulation ratio of belumosudil was 1.4.

Absorption

Median T_{max} of belumosudil at steady state was 1.26 to 2.53 hours following administration of 200 mg once daily or twice daily in patients. The mean (%CV) bioavailability was 64% (17%) following a single belumosudil dose in healthy subjects.

Effect of Food

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

Distribution

The geometric mean volume of distribution after a single dose of belumosudil in healthy subjects was 184 L (geo CV% 67.7%).

Belumosudil binding to human serum albumin and human α_1-acid glycoprotein was 99.9% and 98.6%, respectively, in vitro.

The mean (%CV) elimination half-life of belumosudil was 19 hours (39%), and clearance was 9.83 L/hours (46%) in patients.

Metabolism

Belumosudil is primarily metabolised by CYP3A4, and to a lesser extent by CYP2C8, CYP2D6 and UGT1A9, *in vitro*.

Excretion

Following a single oral dose of radiolabeled belumosudil, 85% of radioactivity was recovered in faeces and less than 5% was recovered in urine.

Pharmacokinetics in Specific Populations

No clinically relevant differences in belumosudil pharmacokinetics were observed with regard to age, race, sex, weight, or renal impairment (mild or moderate). Severe renal impairment has not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effects of Other Drugs on Belumosudil

Strong CYP3A Inhibitors: There was no clinically meaningful effect on belumosudil exposure when coadministered with itraconazole (a strong CYP3A inhibitor) in healthy subjects.

Strong CYP3A Inducers: The coadministration of rifampin (a strong CYP3A4 inducer) decreased belumosudil C_{max} by 59% and AUC by 72%.

Moderate CYP3A Inducers: The coadministration of efavirenz is predicted to decrease belumosudil C_{max} by 32% and AUC by 35% in health subjects.

Proton Pump Inhibitors: The coadministration of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80%, and omeprazole decreased belumosudil C_{max} by 68% and AUC by 47% in healthy subjects.

Effects of Belumosudil on Other Drugs

CYP3A Substrates: The coadministration of belumosudil is predicted to increase midazolam (a sensitive CYP3A substrate) C_{max} and AUC approximately 1.3- and 1.5-fold, respectively.

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

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

In Vitro Studies

Effects of Belumosudil on CYP and UGT enzymes

Belumosudil inhibits CYP2C8, CYP2C9, CYP2C19, CYP3A4, UGT1A1 and UGT1A9. RHOLISTIQ may increase the concentrations of co-administered drugs that are substrates of these enzymes.

Transporters

Belumosudil is a substrate of P-gp. Belumosudil inhibits BCRP, P-gp, OATP1B1, MATE1 and MATE2-K. RHOLISTIQ may increase the concentrations of co-administered drugs that are substrates of these transporters.

5.3 PRECLINICAL SAFETY DATA

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 human lymphocytes or an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with belumosudil.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, hypromellose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and OPADRY II complete film coating system 85F32410 YELLOW.

6.2 INCOMPATIBILITIES

Nil.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

200 mg film-coated tablets: 30 tablets in an HDPE bottle with a child-resistant closure and a desiccant canister labelled 'Do not eat'.

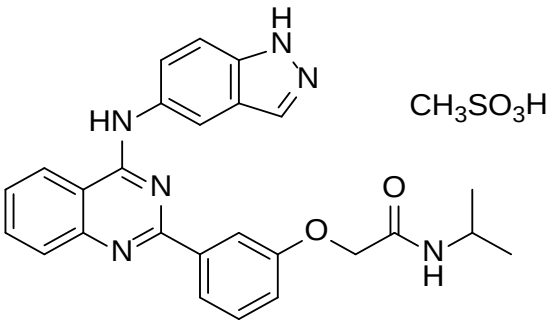
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Belumosudil mesilate is a selective Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) inhibitor. The chemical name is 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide methanesulfonate (1:1). The molecular formula is $C_{27}H_{28}N_6O_5S$ and the molecular weight is 548.62 g/mol.

Chemical structure



CAS number

911417-87-3 (free base)

2109704-99-4 (mesilate salt)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Kadmon Oceania Pty Ltd
Level 13, 77 Castlereagh St
Sydney
NSW 2000

9 DATE OF FIRST APPROVAL

12 November 2021

10 DATE OF REVISION

Not Applicable

Attachment 1: Product information for AusPAR - Rholistiq – belumosudil - Kadmon Oceania Pty Ltd - PM-2020-05433-1-6 FINAL 5 May 2022. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	New Document