ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

REZUROCK 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains belumosudil mesylate equivalent to 200 mg belumosudil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Pale yellow to yellow, oval shaped tablet, with "KDM" on one side and "200" on the other side, with dimensions of 7.4 x 14.8 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REZUROCK is indicated for the treatment of adults and paediatric patients (12 years and older with a body weight of at least 40 kg) with chronic graft-versus-host disease (cGVHD) when other treatment options provide limited clinical benefit, are not suitable or have been exhausted.

4.2 Posology and method of administration

Treatment should be initiated and supervised by physicians experienced in the management of cGVHD.

Posology

The recommended dose is 200 mg given orally once daily with a meal.

Treatment is recommended until disease progression or unacceptable toxicity.

A complete blood cell counts and liver function tests must be performed before initiating therapy (see section 4.4). Initiation of belumosudil in patients with platelets < 50×10^9/L or absolute neutrophil count < 1.5×10^9/L should be based on close monitoring of laboratory values and clinical assessment.

Dose modifications due to adverse reactions
Liver function tests must be performed at least monthly throughout treatment (see section 4.4).

The recommended dose modifications in case of adverse reactions are provided in Table 1.

Table 1: Recommended dose modifications in case of adverse reactions

Adverse reaction	Severity*	Dose modification
Hepatotoxicity	Grade 3 ALT or AST (> 5 to 20 × ULN) or Grade 2 bilirubin (> 1.5 to 3 × ULN)	Hold treatment until recovery to ≤ Grade 1, then resume belumosudil recommended dose and monitor laboratory tests for toxicity.
	Grade 4 ALT or AST (> 20 × ULN) or Grade ≥ 3 bilirubin (> 3 × ULN)	Permanently discontinue treatment.
Other adverse reactions (see section 4.8)	Grade 3	Hold treatment until recovery to ≤ Grade 1, then resume belumosudil recommended dose and monitor for toxicity.
	Grade 4	Permanently discontinue treatment.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal
*Grade 1 is mild, Grade2 is moderate, Grade 3 is severe, Grade 4 is life-threatening. Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

Dose modifications due to drug interactions
Strong CYP3A4 inducers and proton pump inhibitors decrease the exposure of belumosudil (see section 4.5).

Strong CYP3A inducers
The recommended dose is 200 mg twice daily with a meal when co-administered with strong CYP3A inducers.

Proton pump inhibitors
The recommended dose is 200 mg twice daily with a meal when co-administered with proton pump inhibitors.

Delayed or missed dose

In the event of a delayed or missed dose:

A dose should be taken as soon as possible on the same day if:
- a 200 mg dose is missed less than or equal to 12 hours ago for once daily dosing OR
- a 200 mg dose is missed less than or equal to 6 hours ago for twice daily dosing (see section 4.5)

For the next dose, the usual schedule should be resumed.

A dose should not be taken if:
- a dose is missed longer than 12 hours ago for once daily dosing OR
- a dose is missed longer than 6 hours ago for twice daily dosing (see section 4.5)

For the next dose, the usual schedule should be resumed.

If a patient vomits following the intake of a dose, the next dose should be taken at the usual time.

In case of missed dose, the patient should be instructed not to take extra doses to make up the missed dose.

Special populations

Hepatic impairment
Use in patients with severe hepatic impairment (Child-Pugh C) without liver GVHD is contraindicated (see section 4.3). Use in patients with moderate hepatic impairment (Child-Pugh B) without liver GVHD is not recommended (see section 5.2).

No dose adjustment is recommended when administering belumosudil to patients with mild hepatic impairment (Child-Pugh A) (see section 5.2).

Renal impairment
No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min).

No data are available for patients with severe renal impairment (creatinine clearance < 30 mL/min) or for patients with end-stage renal disease on dialysis (see section 5.2). Patients should be carefully monitored with regard to safety and efficacy during belumosudil treatment.

Elderly patients (≥65 years)
No additional dose adjustments are recommended for elderly patients (see sections 5.1 and 5.2).

Paediatric population
The safety and efficacy of REZUROCK in paediatric patients aged less than 12 years and with a bodyweight of less than 40 kg have not been established. No data are available.

Method of administration

For oral use.

Film-coated tablets are to be swallowed whole with water at approximately the same time every day with a meal (see section 5.2).

4.3 Contraindications

Pregnancy and breast-feeding (see section 4.6).

Patients with severe hepatic impairment (Child-Pugh C) without liver GVHD (see section 5.2).

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Women of childbearing potential

Women of childbearing potential must have their pregnancy status verified prior to initiating treatment with belumosudil and must use highly effective contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil.

In case pregnancy should occur during treatment with belumosudil, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus (see section 4.6). Patient must be informed of the potential hazard to the foetus.

Male patients with female partners of childbearing potential

While taking belumosudil, male patients with female partners of childbearing potential must be advised that their female partners should avoid becoming pregnant and of the potential risks to a foetus.

Male patients with female partners of childbearing potential must use highly effective contraception during treatment with belumosudil and for one week after the last dose of belumosudil (see section 4.6).

Breast-feeding

Breast-feeding should be discontinued during treatment and for at least one week after the last dose of belumosudil (see section 4.6).

Fertility

Based on testicular findings and effects on sperm observed in animal studies from rats and dogs, belumosudil may impair male fertility (see section 4.6).

Hepatotoxicity

Increases in liver function tests were observed in clinical studies with belumosudil and generally occurred early during treatment with the incidence decreasing thereafter (see section 4.8). Liver function tests must be performed prior to the initiation of treatment and monitored at least monthly during treatment, and the dose must be adjusted for Grade ≥ 2 toxicities (see section 4.2).

CYP3A4 and P-gp substrates

Belumosudil is an inhibitor of both CYP3A4 and P-gp. Co-administration of belumosudil with medicinal products that are substrates of both CYP3A4 and P-gp (e.g., tacrolimus, sirolimus) may result in an increase in their concentrations (see section 4.5). As a result, dose adjustments may be required in accordance with the respective prescribing information. Close therapeutic drug monitoring until steady state is achieved is recommended.

Excipients

This medicinal product 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 CYP3A inducers on belumosudil

The co-administration of multiple doses of rifampicin (a strong CYP3A4 inducer) decreased belumosudil C_{max} by 59% and AUC by 72%. The co-administration of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampin [rifampicin], St. John's wort [*Hypericum perforatum*]) with belumosudil may decrease belumosudil exposure, which may reduce the efficacy. Co-administration of strong CYP3A4 inducers is not recommended. However, if co-administration is required, the dose of belumosudil should be increased to 200 mg twice daily. It is recommended to resume the belumosudil 200 mg once daily dose within 1 day after the last administration of the strong CYP3A inducer.

The co-administration of moderate CYP3A4 inducers e.g. efavirenz is expected to have a reduced effect on belumosudil as compared to strong CYP3A4 inducers. The co-administration of moderate CYP3A4 inducers with belumosudil may decrease belumosudil exposure. No dose adjustment is recommended.

Effect of proton pump inhibitors on belumosudil

The co-administration of multiple doses of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80%. The co-administration of multiple doses of omeprazole decreased belumosudil C_{max} by 68% and AUC by 47%. The co-administration of proton pump inhibitors with belumosudil may decrease

belumosudil exposure, which may reduce the efficacy. Therefore, the dose of belumosudil should be increased to 200 mg twice daily.

Effect of other gastric acid reducing agents on belumosudil

The co-administration of belumosudil with gastric acid reducing agents (e.g. H2 antagonist and antacids) other than proton pump inhibitors may decrease belumosudil exposure. No dose adjustment is recommended. It is recommended to take belumosudil 2 hours before or 12 hours after the gastric acid reducing agent.

Effect of belumosudil on other medicinal products

Belumosudil is an inhibitor of OATP1B1 and BCRP. Co-administration of belumosudil (200 mg once daily) increased the AUC and C_{max} of rosuvastatin (substrate of OATP1B1 and BCRP) by 4.4-fold and 3.6-fold, respectively. Co-administration of belumosudil with substrates of OATP1B1 and BCRP, for which concentration changes may lead to serious toxicities, is not recommended. If co-administration cannot be avoided, the OATP1B1 and BCRP substrate dose(s) should be decreased in accordance with the respective product information.

Belumosudil is an inhibitor of P-gp. Co-administration of belumosudil (200 mg once daily) increased the AUC and C_{max} of dabigatran (substrate of P-gp) by 2.1-fold and 2.4-fold, respectively. Co-administration of belumosudil with substrates of P-gp, for which small concentration changes may lead to serious toxicities, is not recommended. If co-administration cannot be avoided, the P-gp substrate dose(s) should be decreased in accordance with the respective product information.

Belumosudil is an inhibitor of UGT1A1. Co-administration of belumosudil (200 mg once daily) with raltegravir (substrate of UGT1A1) decreased exposure to raltegravir glucuronide by 40%. Co-administration of belumosudil with sensitive substrates of UGT1A1, for which small concentration changes may lead to serious toxicities, is not recommended. If co-administration cannot be avoided, the UGT1A1 substrate dose(s) should be decreased in accordance with the respective product information.

CYP1A2, CYP2C19 and CYP3A4 substrates
In vitro findings have demonstrated that belumosudil is a reversible and time-dependent inhibitor of CYP1A2 and CYP3A4/5 and a time-dependent inhibitor of CYP2C19.

Clinical inhibition of these CYP enzymes in presence of belumosudil cannot be excluded at the recommended dose of 200 mg once daily. Co-administration of belumosudil with sensitive substrates of these enzymes, for which small concentration changes may lead to serious toxicities, is not recommended. If co-administration cannot be avoided, the substrate dose(s) should be decreased in accordance with the respective product information.

Tacrolimus and sirolimus
Belumosudil is an inhibitor of both CYP3A4 and P-gp. Co-administration of belumosudil with medicinal products that are substrates of both CYP3A4 and P-gp (e.g., tacrolimus, sirolimus) may result in a significant increase in their concentrations. Close therapeutic drug monitoring until steady state is achieved is recommended (see section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Women of childbearing potential should use highly effective contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil (see sections 4.4 and 5.3).

Male patients with female partners of childbearing potential must use highly effective contraception during treatment with belumosudil and for one week after the last dose of belumosudil (see section 4.4).

Pregnancy

There are no data from the use of belumosudil in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). REZUROCK is contraindicated during pregnancy (see section 4.3). REZUROCK is not recommended in women of childbearing potential not using highly effective contraception.

Breast-feeding

It is unknown whether belumosudil/metabolites are secreted in animal or human milk. A risk to the suckling child cannot be excluded. Breast-feeding is contraindicated (see section 4.3) during treatment with REZUROCK and for at least one week after the last dose (see section 4.4).

Fertility

No human data are available to determine potential effects of belumosudil on fertility in females and males.

Belumosudil repeat dose toxicity studies in rats demonstrated adverse effects of general toxicity manifesting in low body weight that may lead to impairment of female fertility (see section 5.3).

Based on testicular findings and effects on sperm observed in animal studies, belumosudil may impair male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

REZUROCK has a minor influence on the ability to drive and use machines. It may cause fatigue or dizziness (see section 4.8). If patients experience related symptoms, driving or operating machines is not recommended.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were fatigue (20.2%), diarrhoea (12.8%), nausea (11.7%), headache (10.6%), vomiting (8.5%), and aspartate aminotransferase (AST) increased (7.4%), alanine aminotransferase (ALT) increased (5.3%), and gamma-glutamyltransferase (GGT) increased (4.3%).

The most common Grade 3 or 4 adverse reaction was pneumonia, hypoxia and diarrhoea (2.1% each).

Serious adverse reactions were pneumonia (2.1%) and cellulitis, large intestine infection, periorbital cellulitis, staphylococcal bacteraemia, upper respiratory tract infection, hypoxia, pulmonary embolism, diarrhoea, nausea, tongue dysplasia, vomiting, and multiple organ dysfunction syndrome (1.1% each).

The most common adverse reaction leading to discontinuation of treatment was nausea (2.1%).

Adverse reactions leading to dose interruption occurred in 14.9% of patients and were nausea (2.1%) and gastroenteritis, large intestine infection, periorbital cellulitis, pneumonia, ALT increased, blood creatine phosphokinase increased, GGT increased, procalcitonin increased, diarrhoea, vomiting,

fatigue, pulmonary embolism, neutropenia, arthralgia, neuropathy peripheral, and dermatitis bullous (1.1% each).

Long-term safety data beyond 12 months demonstrated that 13.8% of patients in the 200 mg once daily group experienced at least one related adverse reaction. The most frequent observed related adverse reactions were diarrhoea (4.3%), upper respiratory infections (2.1%), nausea (2.1%) and weight decreased (2.1%).

Tabulated list of adverse reactions

Table 2 presents the frequency category for adverse reactions reported in all open-label clinical trials with belumosudil 200 mg once daily in 94 patients. The median duration of treatment was 9.18 months (range 0.46 to 83.75 months).

Their frequency is defined using the following conventions: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions

Adverse reactions	All severity grades frequency category	All grades (%)	Grade 3-4 (%)
Infections and infestations			
Upper respiratory tract infection	Common	4 (4.3)	0
Pneumonia	Common	2 (2.1)	2 (2.1)
Cellulitis	Common	2 (2.1)	1 (1.1)
Gastroenteritis	Common	1 (1.1)	0
Large intestine infection	Common	1 (1.1)	0
Nasopharyngitis	Common	1 (1.1)	0
Periorbital cellulitis	Common	1 (1.1)	0
Sinusitis	Common	1 (1.1)	1 (1.1)
Staphylococcal bacteremia	Common	1 (1.1)	0
Blood and lymphatic system disorders			
Anaemia	Common	3 (3.2)	0
Neutropenia	Common	1 (1.1)	1 (1.1)
Endocrine disorders			
Hypothyroidism	Common	2 (2.1)	0
Metabolism and nutrition disorders			
Decreased appetite	Common	6 (6.4)	1 (1.1)
Hyperglycaemia	Common	4 (4.3)	0
Hypophosphataemia	Common	2 (2.1)	0
Hyperlipidaemia	Common	2 (2.1)	0
Nervous system disorders			
Headache	Very common	10 (10.6)	0
Neuropathy peripheral	Common	4 (4.3)	0
Dizziness	Common	2 (2.1)	0
Paraesthesia	Common	2 (2.1)	0
Migraine	Common	1 (1.1)	0
Vascular disorders			

Hypertension	Common	2 (2.1)	1 (1.1)
Hypotension	Common	1 (1.1)	1 (1.1)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Common	6 (6.4)	1 (1.1)
Cough	Common	2 (2.1)	0
Hypoxia	Common	2 (2.1)	2 (2.1)
Pulmonary embolism	Common	2 (2.1)	1 (1.1)
Gastrointestinal disorders			
Nausea	Very common	11 (11.7)	1 (1.1)
Diarrhoea	Very common	12 (12.8)	2 (2.1)
Vomiting	Common	8 (8.5)	1 (1.1)
Constipation	Common	5 (5.3)	1 (1.1)
Abdominal pain	Common	2 (2.1)	0
Abdominal distension	Common	2 (2.1)	0
Abdominal discomfort	Common	2 (2.1)	0
Tongue dysplasia	Common	1 (1.1)	0
Skin and subcutaneous tissue disorders			
Pruritus	Common	1 (1.1)	0
Rash	Common	1 (1.1)	0
Dermatitis bullous	Common	1 (1.1)	0
Musculoskeletal and connective tissue disorders			
Back pain	Common	3 (3.2)	0
Muscle spasms	Common	2 (2.1)	0
Arthralgia	Common	2 (2.1)	0
General disorders and administration site conditions			
Fatigue	Very common	19 (20.2)	1 (1.1)
Oedema peripheral	Common	3 (3.2)	0
Pyrexia	Common	2 (2.1)	0
Malaise	Common	1 (1.1)	0
Localized oedema	Common	1 (1.1)	0
Multiorgan dysfunction syndrome	Common	1 (1.1)	1 (1.1)
Swelling	Common	1 (1.1)	0
Investigations			
Aspartate aminotransferase increased	Common	7 (7.4)	1 (1.1)
Alanine aminotransferase increased	Common	5 (5.3)	1 (1.1)
Gamma-glutamyltransferase increased	Common	4 (4.3)	1 (1.1)
Weight decreased	Common	3 (3.2)	0
Blood alkaline phosphatase increased	Common	3 (3.2)	0
Blood creatine phosphokinase increased	Common	3 (3.2)	1 (1.1)
Platelet count decreased	Common	2 (2.1)	0
Blood creatinine increased	Common	2 (2.1)	0
Lymphocyte count decreased	Common	2 (2.1)	0
White blood cell count decreased	Common	2 (2.1)	1 (1.1)
Bilirubin conjugated increased	Common	1 (1.1)	0
Procalcitonin increase	Common	1 (1.1)	0

Description of selected adverse reactions

Liver enzyme increase
AST, ALT and GGT increased within the first month of belumosudil treatment with the incidence decreasing thereafter. For recommended dose modifications following elevations of liver enzymes, see section 4.2. For recommended monitoring of liver enzymes, see section 4.4.

Haematologic reactions
Anaemia (all severity grade) occurred in 12.5% of patients and grade ≥ 3 anaemia occurred in 4.2% of patients. There were no consistent differences in the time to first occurrence of anaemia across dose groups in the pooled analysis. The highest incidence of anaemia was between 3 and < 6 months. The single event of severe neutropenia occurred on day 253, i.e. approximately 8 months after initiating treatment with belumosudil. See modifications in case of adverse reactions, section 4.2.

Renal impairment

There were no differences in adverse reaction frequency for mild and moderate cGVHD patients when evaluated based on normal renal function, mild and moderate renal impairment. For severe cGVHD patients, a higher frequency of adverse reactions was observed in patients with moderate renal impairment compared to mild impairment and normal renal function.

Paediatric population

There is limited experience in adolescents. A total of three adolescent patients (2 in the 200 mg once daily group and 1 in the 200 mg twice daily group) received belumosudil in study KD025-213. From the post- marketing setting and compassionate use 112 adolescents have received treatment with belumosudil and reported safety information. The most frequently reported adverse reactions were nausea (4.6%) and headache (2.8%). The safety profile of belumosudil in paediatric patients (aged ≥ 12 years) with cGVHD was consistent in type, nature, and severity with the known safety profile in adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for overdoses with belumosudil. Single doses up to 1 000 mg have been administered with acceptable tolerability in healthy volunteers. In the event of an overdose, the patient must be monitored for signs or symptoms of adverse reactions and all appropriate supportive measures must be taken immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA48

Mechanism of action

Belumosudil is a selective Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) inhibitor that mediates signalling in immune cellular function and fibrotic pathways.

Pharmacodynamic effects

Cardiac electrophysiology
At 2.2 times the maximum exposure of the approved recommended dose, belumosudil does not prolong the QT interval to any clinically relevant extent.

Clinical efficacy and safety

Study KD025-213
Study KD025-213 was a phase 2, open-label, multicentre study of belumosudil for the treatment of patients with cGVHD. The intent-to-treat (ITT) adult population included 156 patients. Patients 12 years of age or older were eligible for the study if they had received 2 to 5 prior lines of systemic therapy and required additional therapy. Eligible patients received a stable dose of corticosteroids for two weeks prior to entry into the study. Patients were randomised 1:1 to receive belumosudil dosed orally at 200 mg once daily or 200 mg twice daily. Patients were excluded from the study 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 ≤ 39%.

Belumosudil was added to continued use of standard cGVHD therapies such as corticosteroids, calcineurin inhibitors (CNIs, cyclosporine or tacrolimus), sirolimus, ECP and/or topical or inhaled therapies per institutional guidelines if a stable dose/schedule was in place at study entry. Transient increases in corticosteroids dosing (up to 1 mg/kg/day prednisone equivalent) for up to 6 weeks were permitted for cGVHD flare. An elevated corticosteroids dose for > 6 weeks, or more than 2 cGVHD flare episodes during the first 6 months of belumosudil treatment were considered as treatment failures, as was the initiation of a new systemic therapy for cGVHD.

Of adult patients enrolled in the 200 mg once daily arm (N=78), the median age was 53 years (range 21 to 77 years), 63% were male, and 85% were white. The majority (73%) of patients had severe cGVHD disease with 81% of patients were refractory to their last systemic therapy prior to study enrollment. The organs involved at baseline were skin (82%), joints/fascia (77%), eyes (73%), lung (35%), mouth (53%), oesophagus (30%), upper gastrointestinal tract (GI) (18%), lower GI (9%) and liver (13%). Fifty-one percent of patients had four or more organs involved. The most frequently used systemic concomitant treatments that the patients taking on Cycle 1 Day 1 in study KD025-213 were corticosteroids, CNIs (tacrolimus or cyclosporin), sirolimus, MMF, and ECP. The median number of prior lines of systemic cGVHD therapy was 3.0. The study also enrolled 2 adolescent patients, ages 12 and 13 years, to the 200 mg once daily arm.

The primary efficacy endpoint of overall response rate (ORR) was defined as the proportion of subjects who achieved either a complete response (CR [resolution of all manifestations in each organ or site]) or a partial response (PR [improvement in at least one organ or site without progression in any other organ or site]) at any post-baseline response assessment according to the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD. Secondary endpoints included duration of response and time to response. Responses, including complete responses, were achieved across all organs involved (skin, eyes, mouth, oesophagus, upper GI, lower GI, liver, lungs, and joints/fascia). ORR and key secondary endpoints results are presented in Table 3.

Table 3: Best overall response rate and other efficacy results, ITT adult population

Variable	**Belumosudil 200 mg once daily (N = 78)**
Overall response rate (%)	73.1
95% CI of ORR (%)	61.8, 82.5
Complete response (%)	5.1

Variable	Belumosudil 200 mg once daily (N = 78)
Partial response (%)	67.9
ORR at 6 months (%)	43.6
95% CI of ORR at 6 months	32.4, 55.3
[#]K-M duration of response (primary), median, weeks (95% CI)	23.9 (11.43, 50.43)
Time to response, median, weeks (range)	4.43 (3.7, 80.1)

Abbreviations: CI = confidence interval; ORR = overall response rate; K M = Kaplan-Meier; NR= not reached; ITT = intent-to-treat

Note: Data cut-off: 02 September 2022

Note: 2-sided, exact CI of ORR was calculated using the Clopper Pearson method.

Note: Responder population was used for duration of response and time to response. The percentages are calculated based on the number of ITT population.

[#]Duration of response (primary) is defined as the time from first response to deterioration from best response (e.g., CR to PR, or PR-LR), the initiation of new systemic treatment or death.

ORR- defined as the proportion of subjects who achieved a complete response (CR) or a partial response (PR) at any time in the absence of new systemic treatment for cGVHD according to the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD, and as assessed by investigators.

Paediatric population

A total of 3 adolescent patients were treated with belumosudil 200 mg once daily in the interventional clinical studies and belumosudil responses were observed in these patients. The safety and efficacy of belumosudil in adolescents aged 12 to 18 years are supported by evidence from study KD025-213.

In study KD025-213, two adolescent patients were treated with belumosudil 200 mg once daily. One of them achieved a PR. The responder showed a time to response (TTR) of 53 days and duration of response (DOR) of 820 days.

Based on PK model predictions, the efficacy and safety are expected to be similar in adolescents and adult patients.

The European Medicines Agency has deferred the obligation to submit the results of studies with belumosudil in one or more subsets of the paediatric population in treatment of chronic graft versus host disease (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Median T_{max} of belumosudil across studies was approximately 3 hours. Following a single oral dose of belumosudil 200 mg, mean absolute bioavailability (% coefficient of variation) was 64% (17%).

Effects of food

In healthy subjects, the administration of a single 200 mg dose of belumosudil with a high-fat and high-calorie meal (800 to 1 000 kilocalories with approximately 50% of total caloric content of the

meal from fat) increased belumosudil C_{max} to 2.25 times that following fasted administration and AUC to 2 times that following fasted administration. Median T_{max} was delayed 0.5 hour.

Based on population PK modelling, the mean steady-state AUC (% coefficient of variation) in patients with cGVHD receiving 200 mg once daily administered with food was 18 800 (33%) h•ng/mL; mean steady-state C_{max} was 2 230 (31%) ng/mL. With once daily administration, steady-state concentrations of belumosudil were achieved with an accumulation ratio of 1.2.

Distribution

Based on population PK modelling, pharmacokinetics were described by a two compartmental model with a mean distribution half-life of 1.57 h (78%). Belumosudil mean (% coefficient of variation, CV) apparent volume of distribution of the central compartment was 35.8 L (93%). In *in vitro* preparations, binding to human serum albumin was 99.9% and binding to human α1-acid glycoprotein was 98.6%.

Biotransformation

Based on *in vitro* assessment, CYP3A4 was the predominant CYP isoform responsible for the metabolism of belumosudil, although CYP2C8, CYP2D6 and UGT1A9 contributed to a lesser extent.

Elimination

Population PK modelling results in cGVHD patients showed that belumosudil elimination mean (% coefficient of variation, CV) elimination half-life was 32.9 h (15%). Belumosudil mean (% CV) apparent clearance in patients (%CV) was 12.5 L/h (38%).

The Human Mass Balance study results indicated that faecal excretion is the major route of excretion (85% of the dose). Of the dose recovered in faeces, 30% was parent belumosudil. Less than 5% of the dose was recovered in urine.

Linearity/non-linearity

Exposure to belumosudil (C_{max} and AUC) appears to be slightly greater than dose proportional over the 20 to 500 mg once daily dose range, but less than dose-proportional for doses above 500 mg in healthy subjects. In subjects with cGVHD, the exposure increase between 200 and 400 mg is approximately proportional.

Special populations

Based on population PK analysis no clinically relevant differences in belumosudil pharmacokinetics were observed with regard to age (20 to 77 years), race, gender, or weight (38.6 to 143 kg).

Renal impairment
Based on population PK analysis, no clinically relevant differences in belumosudil pharmacokinetics were observed in patients with mild or moderate renal impairment. Severe renal impairment has not been studied.

Hepatic impairment
Following a single 200 mg dose of belumosudil, changes in belumosudil exposure in subjects with varying degrees of hepatic impairment based on Child-Pugh score without liver GVHD relative to subjects with normal hepatic function is shown in Table 4.

Table 4: Effect of varying degrees of hepatic impairment on belumosudil exposure

Hepatic impairment category	Changes in belumosudil exposure in subjects with hepatic impairment compared to subjects with normal hepatic function

	Total (Free + Bound) concentrations		Free concentrations	
	C_{max}	AUC	C_{max}	AUC
Mild (Child-Pugh A)	1.2-fold increase	1.4-fold increase	14% decrease	19% decrease
Moderate (Child-Pugh B)	6% decrease	1.5-fold increase	12% decrease	1.4-fold increase
Severe (Child-Pugh C)	1.3-fold increase	4.2-fold increase	5.4-fold increase	16-fold increase

Paediatric population
No signs of PK dissimilarity were observed in three adolescent patients from whom sparse PK data were available.

5.3 Preclinical safety data

In repeated dose studies, toxicity was observed at belumosudil average plasma concentration levels below or similar to the expected human exposure and in the studies of toxicity to reproduction, the toxicity was observed below the expected human exposure.

No evidence of special hazard for humans on safety pharmacology or genotoxicity was identified *in vitro* and *in vivo* studies.

Repeated dose toxicity

In repeated oral dose studies in rats and dogs the adverse effects observed in one or both species included toxicities in the gastrointestinal 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, tubular changes, pigmentation, intracellular protein droplets in the epithelium), hemolymphoid system (regenerative anaemia, lymphocyte depletion in spleen and thymus), and reproductive system.

Impairment of fertility

In male rats and dogs, toxicities included lower epididymis and testes weights associated with abnormal sperm findings such as multifocal bilateral spermatozoan degeneration in the epididymis and testes, and multinucleated spermatids in the testes, reduced motility and count of sperm; in the repeat dose studies the changes were reversible in dogs but not fully reversible in rats.

In female rats, lower uterine weights that correlated with uterine/cervical hypoplasia and decreased follicular development in ovaries related to adverse body weight reduction was observed. These changes were reversible.

Toxicity to reproductive and development

Adverse effects in female rats (treated with belumosudil or untreated but mated with treated males) included increased pre- or post-implantation loss, decreased number of viable embryos and foetal malformations including absence of anus and tail, omphalocele, and dome shaped head.

In rabbits, maternal toxicity and embryo-foetal developmental effects (including spontaneous abortion, increased post-implantation loss, decreased percentage of live foetuses, and decreased foetal body weight and skeletal/external malformations) were observed.

Carcinogenicity

No carcinogenic effects were reported in transgenic mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline
Hypromellose
Croscarmellose sodium
Magnesium stearate
Silica, colloidal anhydrous

Tablet coating

Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with polypropylene child-resistant closure and a silica gel desiccant.

Pack size: 28 or 30 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2015/001
EU/1/26/2015/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Sanofi Winthrop Industrie
30-36 Avenue Gustave Eiffel
37100 Tours
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of the Union reference dates (EURD list) provided for under Article 107c(7) of Directive 201/83/EC and any subsequent updates published on the European medicines web portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of Rezurock in adult and paediatric patients (12 years and older with a body weight of at least 40 kg) with cGVHD when other medicinal products approved for use in cGVHD provide limited clinical benefit or are not suitable, the MAH shall submit the final results of Study EFC22965, a Phase III, randomised, open-label, multi-center study of belumosudil versus best available therapy according to an agreed protocol.	Q4 2029

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

REZUROCK 200 mg film-coated tablets
belumosudil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains belumosudil mesylate equivalent to 200 mg belumosudil.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2015/001 28 tablets
EU/1/26/2015/002 30 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rezurock 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

REZUROCK 200 mg film-coated tablets
belumosudil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains belumosudil mesylate equivalent to 200 mg belumosudil.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2015/001 28 tablets
EU/1/26/2015/002 30 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rezurock 200 mg film-coated tablets
belumosudil

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rezurock is and what it is used for

Rezurock contains the active substance belumosudil which belongs to a group of medicines called immunosuppressants.

Rezurock is used to treat adults and paediatric patients (12 years and older with a body weight of at least 40 kg) with chronic graft-versus-host disease (GVHD) when other treatment options provide limited clinical benefit, are not suitable, or have been exhausted.

Chronic GVHD can happen weeks to months after you have undergone a bone marrow or stem cell (blood-forming cells) transplantation., the cells transplanted from the donor (the graft) attack the body (the host) causing inflammation and damage to many organs like the skin, liver or digestive system.

The active substance in Rezurock, belumosudil, works by blocking an enzyme (protein) called ROCK2 that is involved in how your immune system (the body's natural defences) works. This reduces inflammation and further damage to organs.

2. What you need to know before you take Rezurock

Do not take Rezurock
- if you are allergic to belumosudil or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or breast-feeding
- if you have severe liver problems without liver GVHD

If you are uncertain whether the conditions above apply to you, talk to your doctor or pharmacist before taking Rezurock.

Warnings and precautions
Talk to your doctor or pharmacist before taking Rezurock if you:
- are pregnant or plan to become pregnant, since Rezurock can harm your unborn baby (see section “Pregnancy, breast-feeding, fertility and contraception”).
- are breast-feeding or plan to breast-feed, since Rezurock may potentially cause serious side effects in a breast-fed child (see section “Pregnancy, breast-feeding, fertility and contraception”).
- have any liver problems. You must have blood tests before and during treatment with Rezurock including tests to monitor how well your liver is working.
- are taking other medicines (see section “Other medicines and Rezurock”).

Children
Do not give Rezurock to children under 12 years old or with a bodyweight of less than 40 kg, because Rezurock has not been studied in this age group.

Other medicines and Rezurock
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. Rezurock may affect the way other medicines work, and other medicines may affect the way Rezurock works.

Especially tell your doctor if you are taking any of the following medicines, as your doctor may need to change the dose of these medicines or the dose of Rezurock.

The following medicines might decrease the effectiveness of Rezurock by decreasing the amount of Rezurock in the blood:
- Rifampin (used for tuberculosis).
- Proton pump inhibitors like omeprazole or rabeprazole (used to lower acid production in the stomach).
- Other gastric acid reducing agents (used to lower acid production in the stomach).

Rezurock might increase the risk of side effects with these medicines by increasing the amounts of these medicines in the blood:
- Statins like rosuvastatin (used to lower cholesterol).
- Dabigatran (used to prevent blood clots from forming in the body).
- Raltegravir (for HIV).
- Sirolimus or tacrolimus (used to prevent graft-versus-host disease).

If you are not sure if any of the above apply to you, talk to your doctor before taking Rezurock.

While you are taking Rezurock, you should never start a new medicine without checking first with your doctor. This includes prescription medicines, non-prescription medicines (over-the-counter medicines) and herbal or alternative medicines.

Keep a list of all the medicines you take to show your doctor and pharmacist when you get a new medicine.

Rezurock with food
Rezurock must be taken with food. See section 3.

Pregnancy, breast-feeding, fertility and contraception
Tell your doctor immediately if you are pregnant, think you may be pregnant, or if you are breast-feeding. If you are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy

Do not take Rezurock during pregnancy because Rezurock can harm your unborn baby. Your doctor will check if you are pregnant before starting the treatment. If you become pregnant while taking Rezurock, speak to your doctor immediately.

Contraception

If you are a woman who is able to become pregnant, your doctor will check if you are pregnant before starting treatment with Rezurock. This is because Rezurock can harm an unborn baby. You must use a reliable and highly effective method of contraception (birth control) during your treatment with Rezurock and for at least one week after the last dose.

If you are a man with a partner who is able to become pregnant, your partner should avoid pregnancy while you are taking Rezurock. You must use an effective method of contraception during your treatment with Rezurock and for at least one week after the last dose.

Talk to your doctor about which methods of contraception are appropriate for you during your treatment with Rezurock.

Breast-feeding

Do not breast-feed during treatment with Rezurock and for at least one week after the last dose. Rezurock may be harmful to a breast-fed child.

Fertility

Based on animal studies, Rezurock may cause temporary infertility.

Driving and using machines
If you experience tiredness or dizziness after taking Rezurock, do not drive or use machines.

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

3. How to take Rezurock

Always take Rezurock exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose for adults and adolescents (12 years of age or over and weighing at least 40 kg) is one tablet (containing 200 mg of belumosudil) taken once daily orally (by mouth) the same time each day.

Swallow the tablet whole with a glass of water and with a meal.

Your doctor may increase your dose of Rezurock if you are also taking certain other medicines that can affect how belumosudil works.

Your doctor may tell you to stop taking Rezurock for a while or permanently, depending on how well you tolerate the treatment.

Duration of treatment
You should continue treatment until your doctor tells you to stop.

If you take more Rezurock than you should
If you take too much Rezurock, tell your doctor or go to the nearest hospital right away. Take the medicine pack with you.

If you forget to take Rezurock
If you miss a dose of Rezurock you should take it as soon as you remember on the same day, only if:
- you take Rezurock once a day and it has been less than 12 hours since your dose was due
- you take Rezurock twice a day and it has been less than 6 hours since your dose was due

After taking the missed dose, take your next dose of Rezurock at your usual time.

If you miss a dose of Rezurock you should not take it if:
- you take Rezurock once a day and it has been more than 12 hours since your dose was due
- you take Rezurock twice a day and it has been more than 6 hours since your dose was due

In these cases, skip the missed dose, and take your next dose of Rezurock at the usual time.

Do not take a double dose to make up for a forgotten dose.

If you are sick after taking Rezurock
If you are sick (vomit) after taking Rezurock, do not take another dose of Rezurock. Take your next dose of Rezurock at the usual time.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some side effects can be serious.

Serious side effects
Tell your doctor straight away if you experience any of the following common serious side effects (may affect up to 1 in 10 people):

- Cough, chest pain, shortness of breath, fever. These could be symptoms of pneumonia.
- Feeling of not being able to breath or think properly. These could be symptoms of hypoxia (low oxygen).
- Inflammation of the deep skin tissue. These could be symptoms of cellulitis.
- Belly pain, diarrhoea, fever. These could be symptoms of a large intestine infection.
- Inflammation that affects the eyelids and surrounding skin. These could be symptoms of periorbital cellulitis.
- Fever, chills and low blood pressure. These could be symptoms of staphylococcal bacteraemia (infection in your bloodstream).
- Common cold, nose or throat (upper respiratory tract) infection.
- Feeling shortness of breath and chest pain. These could be symptoms of a pulmonary embolism (clot in a blood vessel in the lungs).
- Diarrhoea
- Feeling sick (nausea)
- Sores in your tongue that do not heal could be a sign of a presence of abnormal cells (which may become cancerous). These could be symptoms of tongue dysplasia.
- Vomiting
- Feeling very weak, vomiting, fever, chills, confusion, fast heartbeat. These could be symptoms of two to more of your organ systems that are failing to support your body's needs (multiple organ dysfunction syndrome).

Other side effects
Other possible side effects include the following listed below. If these side effects become severe, tell your doctor.

Very common (may affect more than 1 in 10 people)
- Headache
- Extreme tiredness

Common (may affect up to 1 in 10 people)
- Low red blood cell count (anaemia)
- An underactive thyroid gland (hypothyroidism)
- Decreased appetite
- High blood sugar levels (hyperglycaemia)
- Low blood phosphate levels (hypophosphataemia)
- High levels of fat in the blood (hyperlipidaemia)
- Nerve damage in the arms and legs (peripheral neuropathy)
- Dizziness
- Sensations like numbness, tingling, pins and needles (paraesthesia)
- High blood pressure (hypertension)
- Sudden shortness of breath or difficulty breathing (dyspnoea)
- Cough
- Constipation
- Belly (abdominal) pain
- Abdominal swelling
- Abdominal discomfort
- Back pain
- Muscle spasms
- Joint pain (arthralgia)
- Swelling especially of the ankles and feet (oedema peripheral)
- Fever
- Abnormal liver function test
- Weight loss
- Increase of levels of creatine phosphokinase, an enzyme (protein) that is released into the blood when muscle is damaged
- Decrease blood levels of platelets, components that help the blood to clot
- Increased levels of creatinine, a sign of worsening kidney problems
- Decreased blood count of lymphocytes, a type of white blood cell
- White blood cell count decreased
- Belly pain, diarrhoea, fever. These could be symptoms of gastroenteritis.
- Inflammation of the nose and throat
- Sinus infection
- Headache (migraine)
- Low blood pressure
- Itching
- Rash
- Inflammation of the skin with large blisters (dermatitis bullous)
- Feeling generally unwell (malaise)
- Local swelling
- Yellowing of the skin and eyes (bilirubin conjugated increased)
- Increased levels of procalcitonin, a protein in the blood that is a marker for infection

Your doctor may change your dose of Rezurock, temporarily stop, or permanently stop treatment with Rezurock if you have certain side effects.

Reporting of side effects
If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Rezurock

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after “EXP”. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rezurock contains
The active substance is belumosudil (as mesylate). Each tablet contains 200 mg belumosudil.

The other ingredients are:
Tablet core: cellulose microcrystalline, hypromellose, croscarmellose sodium, magnesium stearate, silica colloidal anhydrous.

Tablet coating: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide yellow (E172).

What Rezurock looks like and contents of the pack

Rezurock film-coated tablets are pale yellow to yellow, oval shaped tablets with "KDM" on one side and "200" on the other side.

Rezurock is available in a plastic bottle with a child-resistant closure in a pack-size of 28 or 30 film-coated tablets. The bottle contains a desiccant packet.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Sanofi Winthrop Industrie, 82 Avenue Raspail, 94250 Gentilly, France

Manufacturer
Sanofi Winthrop Industrie, 30-36 Avenue Gustave Eiffel, 37100 Tours, France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Annex IV

Conclusions on the granting of the conditional marketing authorisation presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.