Prescribing Information: REZUROCK ▼ (belumosudil) 200 mg film-coated tablets

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each film-coated tablet contains belumosudil mesilate, equivalent to 200 mg belumosudil.
Indication: Rezurock is indicated for the treatment of patients aged 12 years and older with chronic graft-versus-host disease (chronic GVHD) who have received at least two prior lines of systemic therapy.
Dosage and Administration: Therapy should be initiated and supervised by physicians experienced in the management of chronic GVHD. The recommended dose of Rezurock is 200 mg administered orally once daily at approximately the same time each day with a meal. The film-coated tablet should not be broken, crushed or chewed. Treatment should continue until disease progression or unacceptable toxicity. A complete blood cell count and liver function test must be performed before initiating therapy with Rezurock. Perform liver function tests at least monthly throughout treatment. Dose modification due to hepatotoxicity and other adverse reactions: For Grade 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (>5 – 20 × upper limit of normal (ULN)) or Grade 2 bilirubin (>1.5 – 3 × ULN) or other Grade 3 adverse reactions, hold Rezurock until recovery to ≤Grade 1, then resume Rezurock at the recommended dose at physician's discretion. For Grade 4 ALT or AST (>20 × ULN) or Grade ≥3 bilirubin (>3 × ULN) or other Grade 4 adverse reactions, permanently discontinue Rezurock. Dose modification due to drug interactions: Strong CYP3A4 inducers and Proton Pump Inhibitors decrease the exposure of belumosudil. Increase the dosage of Rezurock to 200mg twice daily when co-administered with strong CYP3A inducers or proton pump inhibitors. Delayed or missed dose: If a dose is missed or delayed for <12 hours after the scheduled dose, the dose should be taken as soon as possible on the same day with a return to the normal schedule the following day. If a dose is missed or delayed for >12 hours after the scheduled dose, the dose should be taken at the usual time the following day. If a patient vomits following the intake of a dose, the next dose should be taken at the usual time the following day. Patients should not take extra doses to make up the missed dose.
Special Populations: Hepatic impairment: Use in patients with moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) without liver GVHD is not recommended. Dose modification is not recommended when administering belumosudil to patients with mild hepatic impairment (Child-Pugh A). Monitor patients frequently for adverse reactions. Renal impairment: No dose modification of Rezurock is required in patients with mild or moderate renal impairment (creatinine clearance ≥30mL/min). No data are available for patients with severe renal impairment (creatinine clearance <30mL/min) or for patients with end-stage renal disease on dialysis. Use with caution. Elderly patients (≥65 years): No additional dose adjustments are recommended for elderly patients. Paediatric population: The posology is the same in adults and adolescents aged 12 – 18 years. The safety and efficacy of Rezurock in children and adolescents aged below 12 years of age have not been established. No data are available.
Contraindications: Pregnancy. Hypersensitivity to the active substance or to any of the excipients.
Warnings and Precautions: Female patients of childbearing potential and male patients with female partners of childbearing potential: Women of childbearing potential (WOCBP) should be advised to avoid becoming pregnant while they or their male partner are taking belumosudil and of the potential risk to a fetus. WOCBP should be advised to have a pregnancy test prior to starting treatment with belumosudil. WOCBP and male patients with female partners of childbearing potential must use a highly effective method of contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil. Hepatotoxicity: Increases in liver function tests were observed in clinical studies with belumosudil and generally occurred early during treatment with the incidence decreasing thereafter. Liver function tests should be performed prior to the initiation of treatment with belumosudil and monitored at least monthly during treatment with belumosudil and the dose should be adjusted for ≥Grade 2 toxicities. Excipients of known effect: This product is essentially sodium free.
Interactions: Effect of CYP3A inhibitors on belumosudil: The coadministration of multiple doses of itraconazole did not alter exposure to belumosudil to any clinically relevant extent. Effect of CYP3A inducers on belumosudil: The coadministration of multiple doses of rifampin decreased belumosudil C_{max} by 59% and AUC by 72%. The coadministration of strong CYP3A4 inducers with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200mg twice daily. The coadministration of moderate CYP3A4 inducers e.g., efavirenz is predicted to have a reduced effect on belumosudil as compared to strong CYP3A4 inducers. The coadministration of moderate CYP3A4 inducers with belumosudil may decrease belumosudil exposure. No dose adjustment is recommended. Effect of proton pump inhibitors on belumosudil: The coadministration of multiple doses of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80%. The coadministration of multiple doses of omeprazole decreased belumosudil C_{max} by 68% and AUC by 47%. The coadministration of proton pump inhibitors with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200mg twice daily. Effect of other gastric acid reducing agents on belumosudil: The coadministration of belumosudil with gastric acid reducing agents other than proton pump inhibitors may decrease belumosudil exposure. No dose adjustment is recommended, however belumosudil and the gastric acid reducing agent should be taken 12 hours apart. In vitro studies: *Effect of belumosudil on CYP3A substrates:* The coadministration of belumosudil is predicted to increase midazolam C_{max} and AUC approximately 1.3- and 1.5-fold, respectively. No dose adjustment is recommended. The coadministration of belumosudil may increase exposure of sensitive CYP3A4 substrates with a narrow therapeutic index such as ciclosporin and tacrolimus. No dose adjustment is recommended. *Effect of belumosudil on CYP2C9 substrates*: The coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin). *Effect of belumosudil on 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. *Effect of belumosudil on UGT1A1 substrates*: Belumosudil is a

weak inhibitor of UGT1A1, the clinical consequences are not known. *Transporters*: Avoid co-administration of belumosudil with P-gp (e.g. dabigatran), OATP1B1, and BCRP substrates (e.g. rosuvastatin), for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the P-gp, OATP1B1, and BCRP substrates dosage(s) in accordance with the respective SmPC. Belumosudil is an inhibitor of P-gp, OATP1B1, and BCRP. Co-administration of belumosudil with P-gp, OATP1B1, and BCRP substrates increased their plasma concentrations, which may increase the risk of adverse reactions related to these substrates.

Fertility, pregnancy and lactation: There are no human data on the effect of belumosudil on fertility. Belumosudil repeat dose toxicity studies in rats demonstrated effects of general toxicity manifesting low body weight that may lead to impairment of female fertility. Based on testicular findings from rats and dogs, belumosudil may impair male fertility. There are no data on the use of belumosudil in pregnant women. Belumosudil can cause fetal harm based on findings from animal studies and its mechanism of action. As a precautionary measure, belumosudil is contraindicated in pregnancy. WOCBP must have their pregnancy status verified prior to initiating treatment with belumosudil, and must use a reliable and highly effective method of 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 fetus. It is unknown whether belumosudil or its metabolites are excreted in human milk. No data are available regarding the presence of belumosudil or its metabolites in animal or human milk or its effects on the breast-fed child, or on milk production. A risk to the infant cannot be excluded. Because of the potential for serious adverse reactions in a breast-fed child, breast-feeding should be discontinued during treatment with belumosudil and for at least one week after the last dose. Prescribers should consult the SmPC for more information.

Adverse Reactions: Very common: Nausea, asthenia. Common: upper and lower respiratory tract infections, anaemia, leukopenia, platelet count decreased, decreased appetite, hyperglycaemia, headache, neuropathy peripheral, dizziness, hypertension, dyspnoea, cough, diarrhoea, vomiting, abdominal pain, constipation, AST, ALT and gamma-glutamyltransferase increased, pruritus, musculoskeletal pain, muscle spasms, blood alkaline phosphatase increased, blood creatine phosphokinase and blood creatinine increased, oedema, pyrexia, weight decreased. *Prescribers should consult the SmPC in relation to other adverse reactions.*

Legal Category: POM

List Price: £6708.

Marketing Authorisation Number: PLGB 04425/0902

Marketing Authorisation Holder: Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to the Sanofi drug safety department on Tel: 0800 0902 314. Alternatively, send via email to UK-drugsafety@sanofi.com