Prescribing Information: REZUROCK (belumosudil) ▼ 200mg film-coated tablets (Licence valid in GB only)

Therapy should be initiated and supervised by physicians experienced in the management of chronic GVHD.
Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each film-coated tablet contains belumosudil mesilate, equivalent to 200mg 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: The recommended dose of Rezurock is 200mg administered orally once daily at approximately the same time 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 CYP3A Inducers:* Increase the dosage of Rezurock to 200mg twice daily when co-administered with strong CYP3A inducers. Co-administration of belumosudil with drugs transported by OATP1B1 and BCRP substrates can lead to an increase in exposure of these concomitant drugs (e.g. rosuvastatin). *Proton Pump Inhibitors:* Increase the dosage of Rezurock to 200mg twice daily when co-administered with proton pump inhibitors.

OATP1B1/BCRP substrates: Consider switching to a drug less sensitive to OATP1B1 and BCRP inhibition when possible. If used together the dose of rosuvastatin should not exceed 5 mg once daily. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 and BCRP.

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: Dose modification is not recommended when administering belumosudil to patients with mild or moderate hepatic impairment (Child-Pugh A and B). Belumosudil is not recommended in patients with severe hepatic impairment. The safety and efficacy of belumosudil in severe (Child-Pugh C) hepatic impairment has not been evaluated. For patients with pre-existing severe hepatic impairment (Child-Pugh C), consider the risks and potential benefits before initiating treatment with belumosudil. 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 ≥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. 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.

Precautions and Warnings: 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. Sodium: This product is essentially sodium free.

Interactions: Effect of CYP3A inhibitors on belumosudil: The co-administration of multiple doses of itraconazole did not alter exposure to belumosudil to any clinically relevant extent. Effect of CYP3A inducers on belumosudil: The co-administration of multiple doses of rifampin decreased belumosudil C_{max} by 59% and AUC by 72%. The co-administration of strong CYP3A4 inducers with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200mg twice daily. The co-administration of moderate CYP3A4 inducers e.g., efavirenz is predicted 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. Increase the dose of belumosudil to 200mg twice daily. Effect of other gastric acid reducing agents on belumosudil: The co-administration 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 co-administration 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 co-administration 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 co-administration 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 co-administration 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*: Belumosudil is a substrate of P-gp. Belumosudil inhibits BCRP, P-gp, and OATP1B1. The co-administration of oral BCRP, P-gp and OATP1B1 substrates with belumosudil may increase the concentrations of the substrate drugs (such as digoxin and docetaxel). The co-administration of belumosudil with drugs transported by OATP1B1 and BCRP can lead to an increase in exposure of these concomitant drugs (e.g. rosuvastatin) which may increase the risk of these substrate-related toxicities. Co-administration of belumosudil increases rosuvastatin C_{max} and AUC by 3.6 and 4.6-fold, respectively. **Pregnancy:** 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. **Breast-feeding:** 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. **Fertility:** There are no human data on the effect of belumosudil on fertility. Based on findings from animal studies, belumosudil may impair male and female fertility at dose levels above the recommended clinical dose. The effects on fertility are reversible.

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 and ALT increased, gamma-glutamyltransferase increased, pruritus, musculoskeletal pain, muscle spasms, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine increased, oedema, pyrexia, weight decreased. *Prescribers should consult the SmPC in relation to other adverse reactions.*

Legal Category: POM

GB List Price and Marketing Authorisation Number: 200mg x 30 tablets (PLGB 04425/0902): £6708.

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

Further information is available from: Medical Information, 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