BELUMOSUDIL mesilate for chronic GvHD

[NICE TA949 – Licensed indication]

Belumosudil mesilate is an oral selective inhibitor of ROCK2 recommended for treating chronic graft-versus-host disease (GvHD) in people 12 years and over, after 2 or more systemic treatments

Blueteq completion required
Prescribe treatment on EPR (non-cancer indication).

PRE-ASSESSMENT

1. Investigations to include FBC, blood film and manual differential, coagulation screen, urea, creatinine, electrolytes, liver function tests, calcium, lipid profile, glucose, amylase.
2. Ensure diagnosis of cGvHD is confirmed and patient has had 2 prior lines of therapy.
3. Pregnancy Test - for all women of childbearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.
4. Pregnancy & lactation – Pregnancy should be avoided during treatment. Women of childbearing potential (WOCBP) and male partners of WOCBP must use a highly effective method of contraception and continue for at least for one week after the last dose. There are no data on safety in breast-feeding mothers. Patients must not breastfeed for 30 days after the last dose due to the potential for adverse reactions.
5. Record performance status (WHO/ECOG).
6. Record height and weight.
7. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
8. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see fertility guidelines). Effects on fertility from belumosudil alone are potentially reversable on treatment withdrawal. Consider sperm storage/ cryopreservation in appropriate patients.
9. Counsel patient regarding potential increase in infections including shingles, and consider prophylactic aciclovir, especially in those patients with a prior history of shingles.
10. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

Drug	Dose	Frequency	Route	Administration details
BELUMOSUDIL	**200mg**	**ONCE DAILY**	PO	Take with a meal at approximately the same time each day.

Further dosing information is available on page overleaf.

Where patients are taking strong CYP3A inducers*/proton pump inhibitors:

Drug	Dose	Frequency	Route	Administration details
BELUMOSUDIL	**200mg**	**TWICE DAILY**	PO	Take with a meal at approximately the same time each day.

Ideally co-administration with strong CYP3A inducers should be avoided. Where patients are taking proton pump inhibitors, consider switching to famotidine instead.

FREQUENCY

Continuous daily tablet.

DURATION & MONITORING OF DISEASE RESPONSE:

Treatment can be continued as long as the benefit-risk remains positive.

Symptoms should be monitored at baseline, 3 and 6 months using standardised chronic graft versus host disease staging assessment (NSSG B.2.7b).

Median time to response in the ROCKSTAR study was 5 weeks, and >90% of responses occurred within 6 months. Treatment should be discontinued after 6 months if there has been no improvement in symptoms since starting therapy.

CONTRAINDICATIONS

Women who are or are planning to become pregnant or who are currently breastfeeding.

Hypersensitivity to belumosudil or it's excipients.

DOSING AND DOSE MODIFICATIONS

Belumosudil is only available in 200mg tablet strength, dose reductions can be initiated at the clinician's discretion.

Non-haematologic toxicities

Hepatotoxicity (unless other apparent causes)	**Dose modification**
Grade 3 AST or ALT (5 - 20 x ULN*) or Grade 2 bilirubin (1.5 – 3 x ULN)	Hold belumosudil until recovery of bilirubin, AST or ALT to Grade 0–1, then resume treatment at the same dose. Consider a dose reduction trial if a second treatment interruption is required.
Grade 4 AST or ALT (more than 20 x ULN) or Grade ≥3 bilirubin (more than 3 x ULN)	Discontinue belumosudil permanently.

Other non-haematologic	Dose modification
Grade 3	Hold belumosudil until recovery to Grade 0 – 1, then resume treatment at the same dose. Consider a dose reduction trial if a second treatment interruption is required.
Grade 4	Discontinue belumosudil permanently.

*ULN= upper limit of normal; grading in accordance with CTCAE v5.0 guidelines.

Renal impairment

No dose adjustment is required for patients with mild to moderate renal impairment (>=30mL/min). No data are available for patients with severe renal impairment (creatinine clearance < 30ml/min) or patients with end stage renal disease on dialysis. Use with caution.

Hepatic impairment

No dosage adjustment is recommended when administering belumosudil to patients with mild to moderate hepatic impairment (Child-Pugh A and B).

Belumosudil in patients with severe hepatic impairment (Child-Pugh C) without liver GvHD needs a careful risk vs. benefit assessment before initiation and close monitoring for toxicity. The safety and efficacy of belumosudil in severe hepatic impairment has not been evaluated.

INVESTIGATIONS

- Monitoring for toxicity: Monthly bilirubin, ALT, and AST
- cGvHD response should be assessed at baseline, 3 and 6 months.

TAPERING THERAPY

In patients who respond, aim to taper corticosteroids first, followed by a taper of calcineurin inhibitor (CNI) if applicable. Re-escalate therapy if there is a flare of GvHD.

Corticosteroid:
- In the belumosudil trials, corticosteroid therapy could be tapered at investigator's discretion after 4 weeks of belumosudil therapy.
- Aim for 10% dose reduction every 5 days, aiming to taper over 8 weeks.

Calcineurin Inhibitor:
- Aim for a 25% dose reduction every month once no active GvHD.
- Taper only once off systemic corticosteroids.

CONCURRENT MEDICATION

Consider prophylactic aciclovir in patients with a prior history of shingles.

EMETIC RISK

Low

DRUG INTERACTIONS

Strong CYP3A inducers

Co-administration of strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, phenobarbital or St John's Wort) with belumosudil may decrease belumosudil exposure potentially increasing risk of treatment failure.

These interactions should be avoided, if co-administration is necessary, then increase the dosage of belumosudil to 200 mg twice daily.

Strong CYP3A inhibitors

No dose adjustments are necessary – exposure to itraconazole, a strong CYP3A inhibitor did not alter drug exposure to a clinically relevant degree.

CYP3A substrates

No dose adjustment is recommended for co-administration of other CYP3A4 substrates such as ciclosporin, tacrolimus or midazolam.

Proton pump inhibitors (PPIs):

Increase the dosage of belumosudil to 200 mg **twice daily** when coadministered with proton pump inhibitors - or consider switch to a H_2-receptor antagonist such as famotidine.

Antacids

Co-administration with agents that reduce gastric acid (e.g. Gaviscon®, Peptac®, Maalox®) should be avoided as this may decrease belumosudil exposure.

Antacid doses should be taken 12-hours apart from time of belumosudil dosing where possible.

Transporters

Belumosudil is a substrate of P-gp. Belumosudil inhibits BCRP, P-gp, and OATP1B1.

Co-administration of oral BCRP, P-gp and OATP1B1 substrates with belumosudil may increase the concentrations of the substrate drugs (such as digoxin or dabigatran). Co-administration should be avoided where 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.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Adverse reactions leading to dose interruption occurred in 29% of patients in the ROCKSTAR study. Those occurring in more than 2% of patients are documented below.

- Hepatic: Raised ALT, AST or GGT (occurred in 5-8% of patients)

- Haematological: Anaemia, leucopenia, thrombocytopenia (occurred in 3-5% of patients)
- Infections: Sinusis, gastroenteritis, respiratory tract infections
- General: Fatigue, oedema, fever, dizziness
- Vascular disorders: Bleeding, hypertension
- Gastrointestinal disorders: Nausea, diarrhoea, abdominal pain
- Respiratory: Dyspnoea, cough, congestion
- Musculoskeletal: Muscle pain, arthralgia
- Nervous system: Headache, neuropathy
- Metabolism: Decreased appetite, hyperglycaemia
- Skin: Rash

There is a report of skin malignancy while on belumosudil treatment: patients should be informed to perform skin checks and take appropriate precautions with sun exposure (coverage and SPF).

Most events should resolve without need for discontinuation, interruption, or dose reductions. Events generally occur early during belumosudil treatment with the incidence decreasing thereafter.

TREATMENT RELATED MORTALITY

Treatment related mortality is extremely rare (<1%).

REFERENCES

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DOCUMENT CONTROL

Author(s): Dr Charlotte Brierley, Specialist Haematology Registrar; Dr Kirsty Sharplin, Consultant Haematologist; Donna Constantine, Advanced Cancer Pharmacist.

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Review

Name	Revision	Date	Vers	Review date
New protocol	New protocol	March 2024	1.0	March 2026
Donna Constantine, Advanced Cancer Pharmacist	Minor amendments to interactions in line with SPC update. Prescribing location added.	April 2025	1.1	March 2026