Ixazomib with Lenalidomide and Dexamethasone (IRd)

Indication

Ixazomib, with lenalidomide and dexamethasone, is recommended as an option for treating multiple myeloma for patients who have already had 2 or 3 lines of therapy.

(NICE TA870)

ICD-10 codes

Codes with a pre-fix C90

Regimen details

Day	Drug	Dose	Route
1,8 and 15	Ixazomib	4mg	PO
1-21	Lenalidomide	25mg OD	PO
1,8,15 and 22	Dexamethasone	40mg OM	PO

Cycle frequency

28 days

Number of cycles

Until disease progression or unacceptable toxicity. Treatment for longer than 24 cycles should be based on an individual benefit/risk assessment, as the data on the tolerability and toxicity beyond 24 cycles is limited.

Administration

Ixazomib is available as 4mg, 3mg and 2.3mg capsules.

Ixazomib should be taken at approximately the same time on days 1, 8 and 15, at least 1 hour before or 2 hours after food. The capsule should be swallowed whole with water. If a dose is missed, it may be taken if the next scheduled dose is ≥ 72 hours away. A missed dose should not be taken within 72 hours of the next scheduled dose. A double dose should not be taken to make up for a missed dose. If a patient vomits after taking a dose, an additional dose should not be taken. The next dose should be taken at the time of the next scheduled dose.

Lenalidomide is available as 5mg, 10mg, 15mg, 20mg and 25mg capsules.

Lenalidomide should be swallowed whole with water, either with or without food, at the same time each day. The capsules should not be broken, opened or chewed. If a dose is missed it may be taken within 12 hours, however if more than 12 hours has elapsed since the dose was due, the patient should miss the dose and resume with the usual dose the next day.

Lenalidomide patient must be consented and the drug prescribed and dispensed in accordance with the Celgene Pregnancy Prevention Programme.

Dexamethasone is available as 500microgram and 2mg tablets. The dose should be taken in the morning, with or after food.

Pre-medication

Nil

Emetogenicity

This regimen has low emetogenic potential.

Supportive medication

Thromboprophylaxis is required according to standard IMiD-associated VTE risk assessment.
H_2 antagonist or proton pump inhibitor.
Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for the first cycle only.
Bisphosphonates as per local policy.
Antifungal and PCP prophylaxis as per local policy.
Antiviral prophylaxis with aciclovir should be considered to decrease the risk of herpes zoster reactivation.

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Pregnancy test	3 days

Hepatitis B virus status must be established before initiating treatment.
Serum electrophoresis (or alternative biological measure of response if M protein not measurable i.e. sFLC / bone marrow aspirate and trephine)
Glucose
Calcium
Urate

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Weekly for first 8 weeks, then monthly within 72 hours of next cycle
U+Es (including creatinine)	Monthly within 72 hours of next cycle
LFTs	Monthly within 72 hours of next cycle
Pregnancy test	Within 3 days of next cycle

Serum electrophoresis (or alternative biological measure of response if M protein not measurable)
Calcium, albumin
Glucose as clinically indicated
Blood pressure as clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L (see below)
Platelets	≥ 75 x 10^9/L (see below)
Creatinine clearance	≥ 50mL/min
Bilirubin	<ULN
AST/ALT	<ULN

Dose modifications

Dose adjustments for ixazomib are made as per the table below:

Starting dose	4mg
Dose level – 1	3mg
Dose level – 2	2.3mg

If a further dose reduction is required, Ixazomib should be discontinued.

Dose adjustments for lenalidomide are made as per the table below:

Starting dose	25mg
Dose level – 1	15mg
Dose level – 2	10mg
Dose level – 3	5mg

Alternative dose adjustments may include keeping at the same dose and reducing to an alternate day regimen.

- **Haematological toxicity**

Treatment should only be initiated if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 75 x 10^9/L (if bone marrow infiltration may initiate treatment if platelets ≥ 30 x 10^9/L).

Subsequent cycles:

Thrombocytopenia

Platelets (x 10^9/L)	**Action**
< 30 (1st occurrence)	Withhold ixazomib and lenalidomide Once recovered to ≥ 30 x 10^9/L continue with the same dose of ixazomib and one dose level reduction of lenalidomide
< 30 (2nd occurrence)	Withhold ixazomib and lenalidomide Once recovered to ≥ 30 x 10^9/L continue at dose level - 2
< 30 (subsequent occurrence)	Alternate dose reduction of ixazomib and lenalidomide

Neutropenia

Neutrophils (x 10^9/L)	**Action**
< 0.5 (1st occurrence)	Withhold ixazomib and lenalidomide Consider G-CSF. Once recovered to ≥ 0.5 x 10^9/L continue with the same dose of ixazomib and one dose level reduction of lenalidomide
< 0.5 (2nd occurrence)	Withhold ixazomib and lenalidomide Once recovered to ≥ 0.5 x 10^9/L continue with one dose level reduction and the most recent dose of lenalidomide.
< 0.5 (subsequent occurrence)	Alternate dose reduction of ixazomib and lenalidomide

- **Renal impairment**

Ixazomib: No dose adjustment is required for patients with mild or moderate renal impairment (CrCl ≥ 30 mL/min). A dose of 3 mg is recommended in patients with severe renal impairment (CrCl < 30 mL/min) or end-stage renal disease requiring dialysis. Ixazomib can be administered regardless of the timing of dialysis.

Lenalidomide is excreted via the kidney. Close monitoring of renal function is essential.

CrCl (mL/min)	**Lenalidomide dose**
≥ 50	25mg OD
30-49	10mg OD (may escalate to 15mg OD after 2 cycles if patient not responding but is tolerating treatment)
< 30 (not requiring dialysis)	15mg alternate days (may escalate to 10mg OD if patient tolerating treatment)
< 30 (requiring dialysis)	5mg OD (taken after dialysis on dialysis days)

- **Hepatic impairment**

Ixazomib: No dose adjustment of ixazomib is required for patients with mild hepatic impairment (bilirubin ≤ ULN and AST/ALT > ULN or total bilirubin > 1-1.5 x ULN and any AST/ALT).
The reduced dose of 3 mg is recommended in patients with moderate hepatic impairment (bilirubin > 1.5-3 x ULN) or severe hepatic impairment (bilirubin > 3 x ULN).

Lenalidomide has not been studied in hepatic impairment. There are no dose recommendations in hepatic impairment. If patients suffer unexplained deterioration of liver function, consider lenalidomide induced liver injury. In this case liver function should improve on discontinuation of lenalidomide.

- **Other toxicities**

Toxicity	Grade	Action
Rash	Grade 2-3	Withhold lenalidomide until ≤ Grade 1. Resume with one dose level reduction. If reoccurrence withhold ixazomib until ≤ Grade 1. Resume with one dose level reduction and most recent dose of lenalidomide. For subsequent reoccurrence alternate dose reduction of ixazomib and lenalidomide.
	Grade 4	Discontinue treatment
Peripheral Neuropathy	Grade 1 with pain or Grade 2	Withhold ixazomib until ≤ Grade 1 without pain (or baseline). Resume with most recent dose.
	Grade 2 with pain or Grade 3	Withhold ixazomib until ≤ Grade 1 without pain (or baseline). Resume with one dose level reduction.
	Grade 4	Discontinue treatment.

For any other grade 3 or 4 non-haematological toxicity (except alopecia), clinical judgement should determine whether to discontinue treatment or to continue treatment at a reduced dose (following recovery). Refer to dose reduction tables above for dosing guidance. Consultant decision.

Thrombosis:
If a patient experiences a thromboembolic event, treatment with lenalidomide must be discontinued and anticoagulation therapy commenced. Once the patient has been stabilised on anticoagulation treatment and any complications of the thromboembolic event have been managed, lenalidomide may be restarted at the original dose, after a reassessment of risks and benefits of treatment.

Steroid side effects:
For any severe steroid-related side effect, consider alternative steroid dosing.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Teratogenicity
Venous thromboembolism
Psychosis
Viral reactivation in patients previously infected with the varicella zoster or hepatitis B viruses (HBV)
Posterior reversible encephalopathy syndrome

Frequently occurring side effects
Myelosuppression
Diarrhoea
Constipation
Nausea and vomiting
Fatigue

Peripheral neuropathy
Sleep disturbance
Insomnia
High blood sugars
Peripheral oedema, Fluid retention
Dyspepsia
Cutaneous reactions

- **Other side effects**

Reduced appetite
Blurred vision
Altered LFTs

Significant drug interactions – for full details consult product literature/ reference texts

Erythropoetic agents: increased risk of thrombosis – use with caution

Hormone treatments (including combined contraceptive pill, HRT): increased risk of thrombosis – use with caution.

Oral contraceptives: risk of reduced efficacy. Barrier methods of contraception are required in addition to oral contraceptives.

Digoxin: lenalidomide may increase plasma digoxin levels – monitor levels

Strong CYP3A inducers: (e.g. Rifampicin) co-administration with ixazomib is not recommended.

Additional comments

Male and female patients who are able to have children must use effective contraceptive measures during and for 90 days following treatment with ixazomib.
Women of childbearing potential must use effective contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide has been discontinued as per the Celgene pregnancy prevention programme.

References

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