Ixazomib, lenalidomide and dexamethasone for multiple myeloma

NHS Northern Cancer Alliance

DRUG ADMINISTRATION SCHEDULE

Day	Drug	Dose	Route	Frequency	
1, 8 and 15	Ixazomib	**4mg**	Oral	Once weekly	
1 to 21	Lenalidomide	**25mg**	Oral	Once daily	**21 days only**
1, 8, 15 and 22	Dexamethasone	**40mg***	Oral	Once weekly	

***In elderly patients**, a starting dose of dexamethasone 20mg on days 1, 8, 15 and 22 may be more appropriate.

Pharmaceutical presentation:

- Ixazomib is available as 4mg, 3mg or 2.3mg capsules.
- Lenalidomide is available as 25mg, 20mg, 15mg, 10mg, 7.5mg, 5mg and 2.5mg capsules. Please note the cost is the same for all strengths of lenalidomide, so multiple tablets **should not** be used to make a single dose (e.g. a dose of 20mg will cost 4x as much if made up using 5mg tablets).

CYCLE LENGTH AND NUMBER OF DAYS

28 Day cycle, given until disease progression.

APPROVED INDICATIONS

The treatment of relapsed or refractory multiple myeloma (as a **third or fourth-line** treatment) Patients must be registered via Blueteq and all the appropriate criteria met, including:

1. The patient has a confirmed diagnosis of multiple myeloma.
2. The patient has received 2 or 3 prior lines of treatment and that the numbering of these lines of treatment is in accordance with the International Myeloma Workshop Consensus recommendations for the uniform reporting of clinical trials (http://doi.org/10.1182/blood-2010-10-299487).
   a. A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner (e.g. induction chemotherapy and stem cell transplantation is considered to be 1 line of therapy). A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease. Please indicate the number of prior lines of treatment:
   b. Single agent steroid, e.g. dexamethasone is not considered by NHS England to be a line of treatment
   c. The use of ixazomib will be audited to confirm it is being used in accordance with these treatment criteria (particularly in respect of lines of therapy) and non-compliant use will be monitored and followed-up.
   d. Patients previously treated with 1 or >3 lines of treatment are not eligible for ixazomib.
3. The patient is neither refractory to previous proteasome inhibitor-based nor lenalidomide-based treatment at any line of therapy (in this context, refractory disease is defined as disease progression on treatment or disease progression within 60 days of the last dose of a proteasome inhibitor or lenalidomide).

4. Note: As lenalidomide is only commissioned by NHS England after 2 prior therapies, the only eligible patients who have had prior lenalidomide must have received it in the context of a clinical trial in an earlier line of therapy. Such patients must not be refractory to lenalidomide according to the above definition.
5. The patient has either been refractory to 1 or more lines of therapy or has responded and relapsed after each line of therapy.
6. Please indicated whether the patient has / has not been treated with a previous autologous or allogenic stem cell transplant.
7. The patient must be treatment-naïve to any therapy with ixazomib
8. Ixazomib is only to be used in combination with lenalidomide and dexamethasone* *Note: all 3 drugs in the combination (i.e. ixazomib, lenalidomide and dexamethasone) must be commenced at the same time. Ixazomib cannot be added in as an additional agent in the treatment of patients who have already previously commenced treatment with lenalidomide and dexamethasone.
9. Ixazomib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment, whichever is the sooner
10. Performance status of the patients is 0 or 1 or 2
11. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)

ELIGIBILITY CRITERIA

Absolute Neutrophil Counts (ANC) ≥ 1.0 x 10^9/l, Platelet counts ≥ 75 x 10^9/l (or dependent on bone marrow infiltration by plasma cells platelet counts ≥ 30 x 10^9/l.)

EXCLUSION CRITERIA

Pregnancy / Breast Feeding

Pregnancy prevention programme

Women of childbearing potential

For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:

- She understands the expected teratogenic risk to the unborn child.
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence the treatment as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

Women of non-childbearing potential

Women in the following groups are considered not to have childbearing potential and do not need to undergo pregnancy testing or receive contraceptive advice.

- Age ≥ 50 years and naturally amenorrhoeaic for ≥ 1 year. Please note amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

Men

In view of the expected teratogenic risk of lenalidomide, foetal exposure should be avoided. Pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject.

As a precaution, all male patients taking lenalidomide must meet the following conditions:

- If their partner is pregnant or of childbearing potential and not using effective contraception, male patients should use condoms throughout the duration of treatment, during dose interruption and for 1 week after cessation of treatment, even if the male patient has undergone a vasectomy.
- If pregnancy occurs in a partner of a male patient whilst he is taking lenalidomide or shortly after he has stopped taking lenalidomide, he should inform his treating doctor immediately. The partner should inform her physician immediately. It is recommended that she be referred to a physician specialised in teratology for evaluation and advice.

RECOMMENDED TAKE HOME MEDICATION

- Consider gastroprotection with high dose dexamethasone (e.g. omeprazole 20mg once daily)
- Patients with high tumour burden at the start of treatment may require allopurinol.
- Thrombo-prophylaxis using standard medical prophylaxis dose of Low Molecular Weight Heparin (LMWH) should be prescribed (unless contra-indicated) with all lenalidomide combinations. Duration of LMWH remains uncertain but should be at least for the first 3 months of treatment when the risk of VTE is greatest. LMWH requires dose reduction in renal impairment.
- Aciclovir prophylaxis as per local practice.

INVESTIGATIONS / MONITORING REQUIRED

Prior to first cycle: FBC, U&Es, LFTs, Calcium, Paraprotein
Prior to each cycle: FBC, U&Es, LFTs, Calcium, Paraprotein

Patients should have more regular FBC checks during the first 3 cycles of therapy and treatment interrupted if FBC is outside of the limits listed in DOSE MODIFICATIONS.

ASSESSMENT OF RESPONSE

Serum paraprotein, serum free light chains (SFLC)

REVIEW BY CLINICIAN

Prior to each cycle (unless being seen by a nurse / pharmacist – see below)

NURSE / PHARMACIST LED REVIEW

Nurse or pharmacist led review, within a locally agreed protocol, is acceptable on day 1 for all cycles except the first cycle. If nurse or pharmacist is reviewing the patient they must comply with the necessary precautions of the Pregnancy Prevention Programme

ADMINISTRATION NOTES

- Ixazomib is a substrate for CYP3A4. Strong CYP3A4 inducers such as rifampicin, phenytoin, carbamazepine and St John's Wort should be avoided while receiving ixazomib.
- Revlimid (Lenalidomide) capsules should be taken at about the same time each day. The capsules should not be broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.
- If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day
- Revlimid (Lenalidomide) has the potential to be teratogenic (it is structurally related to thalidomide). **Celgene operates a pregnancy prevention programme to prevent potential harm. Refer to the Celgene documentation prior to prescribing and dispensing.**
- Dispensing pharmacy must be registered to supply.
- A prescription authorisation form (dated the same as the prescription) or electronic PAF must be completed and sent to pharmacy.
- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.
- Patients should not donate blood or semen during therapy or for 1 week following discontinuation of lenalidomide.

TOXICITIES

Common: myelosuppression – neutropenia & thrombocytopenia, fatigue, thrombosis, peripheral neuropathy, peripheral oedema, hepatotoxicity, constipation, muscle cramps, anaemia, diarrhoea, rash, increased rate of infections (bacterial, viral and fungal), Posterior reversible encephalopathy syndrome (PRES)

DOSE MODIFICATION / TREATMENT DELAYS

Thrombocytopenia

Platelets	Recommended Dose Modifications
< 30 x 10^9/l	Withhold ixazomib and lenalidomide until platelet count ≥ 30 x 10^9 /L Following recovery, resume lenalidomide at the next lower dose level and resume ixazomib at its most recent dose. If platelet count falls to < 30 x 10^9/l again withhold ixazomib and lenalidomide until platelet count ≥ 30 x 10^9 /L. Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose.

For additional occurrences, alternate dose modification of lenalidomide and ixazomib.

Neutropenia

Neutrophils:	Recommended Dose Modifications
< 0.5 x 10^9/l	Withhold ixazomib and lenalidomide until ANC is ≥ 0.5 x 10^9/l. Consider adding GCSF as per clinical guidelines Following recovery, resume lenalidomide at the next lower dose level and resume ixazomib at its most recent dose. If ANC count falls to < 0.5 x 10^9/l again withhold ixazomib and lenalidomide until ANC is ≥ 0.5 x 10^9/l. Following count recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose.

For additional occurrences, alternate dose modification of lenalidomide and ixazomib.

Renal Function:

Renal Function (CrCl)	Recommended LENALIDOMIDE Dose Modifications	Recommended IXAZOMIB Dose Modifications
Moderate renal impairment (CrCl 30 - 50ml/min)	10mg once daily (the dose may be escalated to 15mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment)	No dose adjustment necessary in mild to moderate renal impairment.
Severe renal impairment (CrCl <30ml/min) not requiring dialysis	7.5mg daily *or* 15mg every other day	Reduced starting dose of 3mg recommended
End stage renal failure (CrCl < 30ml/min) requiring dialysis	5mg once daily. On dialysis days, the dose should be administered following dialysis	Reduced starting dose of 3mg recommended in end-stage renal disease requiring dialysis, ixazomib is not dialyzable so can be administered without regard to timing of dialysis.

Hepatic Impairment:

Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have been uncommonly reported. Hepatic enzymes should be monitored regularly and the dose should be adjusted for Grade 3 or 4 symptoms.

	Recommended IXAZOMIB Dose Modifications
Mild Hepatic Impairment	No dose adjustment necessary in mild hepatic impairment
Moderate or Severe Hepatic Impairment (total bilirubin > 1.5 x ULN)	Reduced starting dose of 3mg recommended in moderate or severe hepatic impairment.

Rash	
Grade 2 or 3	Withhold lenalidomide until rash recovers to ≤ Grade 1. Following recovery, resume lenalidomide at the next lower dose according to its SmPC. If Grade 2 or 3 rash occurs again, withhold ixazomib and lenalidomide until rash recovers to ≤ Grade 1. Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose.
Grade 4	Discontinue treatment regimen.

Peripheral neuropathy

Grade 1 peripheral neuropathy with pain or Grade 2 peripheral neuropathy	Withhold ixazomib until peripheral neuropathy recovers to ≤ Grade 1 without pain or patient's baseline. Following recovery, resume ixazomib at its most recent dose.
Grade 2 peripheral neuropathy with pain or Grade 3 peripheral neuropathy	Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or ≤ Grade 1 prior to resuming ixazomib. Following recovery, resume ixazomib at the next lower dose.
Grade 4 peripheral neuropathy	Discontinue treatment regimen.
Other non-haematological toxicities	
Other Grade 3 or 4 non-haematological toxicities	Withhold NINLARO. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or at most Grade 1 prior to resuming NINLARO. If attributable to NINLARO, resume NINLARO at the next lower dose following recovery.

TREATMENT LOCATION

Suitable for self-administration in patients own homes, under the supervision of haematology teams from Level 1 – 4 Haematology Services.

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