Chemotherapy Protocol

Myeloma

DRD Daratumumab-Lenalidomide-Dexamethasone

Regimen

- Myeloma – DRD Daratumumab-Lenalidomide-Dexamethasone

Indication

- Daratumumab in combination with lenalidomide and dexamethasone is recommended for use within the Cancer Drugs Fund as an option for treating untreated multiple myeloma patients who are ineligible for an autologous stem cell transplant.
- This regimen was based on MAIA trial and has been slightly modified to simplify the schedule (i.e. SC instead of IV Daratumumab and two divided doses of dexamethasone instead of once weekly dosing).
- Cancer Drug Fund approval – BLUETEQ is required prior to treatment.
- The Cancer Drug Fund stipulates that the patient is contraindicated for thalidomide containing chemotherapy or intolerant to thalidomide.

Toxicity

Drug	Adverse Effect
Daratumumab	Infusion related reactions, hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, respiratory tract infections (including pneumonia), neutropenia, thrombocytopenia, anaemia, lymphopenia, peripheral neuropathy, diarrhoea, muscle spasms, fatigue, pyrexia and peripheral oedema, blood transfusion related events
Dexamethasone	Weight gain, gastrointestinal disturbances, hyperglycaemia, CNS disturbances, Cushingoid changes, glucose intolerance.
Lenalidomide	Peripheral neuropathy, bone marrow suppression, pneumonia, infection, venous thrombotic events, respiratory dysfunction, rashes, hypokalaemia, hypomagnesaemia, hypocalcaemia, teratogenic risk, GI disturbances, flu-like symptoms.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Bloods

- FBC, U&Es, Ca^{2+} and LFTs prior to day one of each cycle of treatment.

- Paraprotein and / or light chains prior to each cycle.

- All patients should be tested for hepatitis B virus (HBV) before initiating treatment with daratumumab. Those patients who test positive for HBV infection should be discussed with a consultant specialising in HBV prior to initiating treatment with daratumumab to plan monitoring requirements whilst on treatment. Patients may also be tested for hepatitis C, CMV and HIV at the same time if clinically appropriate.

- Send a blood sample to transfusion and inform patient and transfusion laboratory that patient is due to commence daratumumab. Patient will require red cell phenotyping as cross match fails due to binding of daratumumab to red cells.

- Regular monitoring of blood glucose is considered good practice due to dexamethasone use.

- Pregnancy testing in women of childbearing potential. A negative pregnancy test must be obtained within 3 days of starting lenalidomide the test must be repeated every 4 weeks (every 2 weeks in women with irregular menstrual cycles) with the final test 4 weeks after the last dose of lenalidomide.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

No dose reductions of daratumumab are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity. Always refer to the responsible consultant, as any dose delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or where the haemoglobin is less than 8g/dL (80g/L).

Consider growth factor support as an alternative to the options below, particularly where there is evidence of bone marrow suppression.

To initiate a new cycle of daratumumab, the neutrophil count should be $1x10^9$/L or greater and the platelet count should be $50x10^9$/L or greater, unless the low counts are due to bone marrow infiltration with myeloma. In this situation the daratumumab may be administered at the discretion of the treating consultant haematologist with the appropriate blood product and growth factor support.

Dose Reduction Steps

	Lenalidomide
Starting Dose	25 mg
Dose Level -1	20 mg
Dose Level -2	15 mg
Dose Level -3	10 mg
Dose Level -4	5 mg
Dose Level -5	2.5 mg

Neutrophils (x10^9/L)	**Dose Modifications (Lenalidomide)**
First Occurrence	
Fall to less than 1.0	Interrupt lenalidomide treatment and monitor FBC weekly. Consider G-CSF treatment.
Return to 1.0 with no other observed toxicity	Resume at 25 mg daily
Return to 1.0 or greater and dose-dependent haematological toxicities other than neutropenia are observed	Resume at the next lower dose
Subsequent Occurrence	
Fall to less than 1.0	Interrupt lenalidomide treatment and monitor FBC weekly. Consider G-CSF treatment.
Return to 1.0 or greater	Resume at the next lower dose
Platelets (x10^9/L)	**Dose Modifications**
First Occurrence	
Fall to less than 30	Interrupt lenalidomide treatment and monitor FBC weekly. Consider transfusion.
Returns to 30 or greater	Resume at the next lower dose

Subsequent Occurrence	
Fall to less than 30	Interrupt lenalidomide treatment and monitor FBC weekly. Consider transfusion.
Returns to 30 or greater	Resume at the next lower dose

Hepatic Impairment

Drug	Bilirubin µmol/L	AST/ALT units/L	Dose (% of original dose)
Lenalidomide	N/A	N/A	No formal studies conducted. No specific dose recommendations.
Daratumumab	No formal studies of daratumumab in patients with hepatic impairment have been conducted. Based on population pharmacokinetic analysis no dosage adjustments are necessary for patients with hepatic impairment		

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Lenalidomide	30 and 50	10 mg daily The dose may be escalated to 15 mg after 2 cycles if patient is not responding to treatment and tolerates the dose
	Less than 30	7.5 mg daily or 15 mg every other day
	Less than 30 with Dialysis	5 mg daily Administer after dialysis
Daratumumab	No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic analysis no dosage adjustments are necessary for patients with renal impairment	

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Lenalidomide

In general, lenalidomide treatment should be stopped when the patient develops NCI-CTC grade 3 or 4 toxicities. Restart at next lower dose level when toxicity has resolved to grade 2 or lower depending on the physician's discretion.

Allergic or hypersensitivity reactions that occur at NCI-CTC grade 2, withhold treatment until the symptoms have resolved to NCI-CTC grade 1 or below. Treatment may be cautiously

restarted at a daily dose of 15mg. For NCI-CTC grade 3 or above reactions discontinue the lenalidomide.

Thromboembolism

The combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism. Appropriate thromboprophylaxis is recommended, especially in patients with additional thrombotic risk factors.

Patients and their carers should be made aware of the symptoms of thromboembolism and advised to seek a medical advice if they develop shortness of breath, chest pain or swelling of a limb.

If the patient develops thromboembolic events, treatment must be discontinued.
Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment.

Skin Rash

Lenalidomide should be interrupted or discontinued for NCI-CTC grade 2 or 3 skin rash.

Allergic or Hypersensitivity Reactions

Cases of allergic reactions including angioedema, anaphylactic reaction and severe cutaneous reactions including SJS, TEN and DRESS have been reported in patients treated with lenalidomide (see section 4.8).

Patients should be advised of the signs and symptoms of allergic and hypersensitivity reactions and should be instructed to seek medical attention immediately if they develop these symptoms.

Lenalidomide must be discontinued for angioedema, anaphylactic reaction, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected and should not be resumed following discontinuation for these reactions.

Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity.

Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with lenalidomide. Patients should be monitored for new or worsening neurological symptoms, cognitive or behavioural signs and symptoms.
If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, lenalidomide must be permanently discontinued.

Teratogenicity

Lenalidomide is highly teratogenic.

All prescribers, patients and pharmacy staff must comply with the manufacturer's Pregnancy Prevention Programme.

Women of child-bearing potential taking thalidomide must use one agreed effective method of contraception for at least 4 weeks before starting thalidomide, while on Lenalidomide and for one month after. They must have a negative pregnancy test within 3 days prior to starting treatment. Pregnancy testing should be repeated monthly thereafter until one month after stopping Lenalidomide (or every 2 weeks in women with irregular menstrual cycles). If a woman taking Lenalidomide thinks she may be pregnant she must stop the drug immediately and seek medical advice.

Men taking Lenalidomide must use a barrier method of contraception throughout treatment and for one week after stopping, if their partner is capable of bearing children.

Other

Dexamethasone

For patients who are elderly or unable to tolerate the standard dose of dexamethasone the dose given the day after bortezomib alone may be reduced. Please note the doses before and the day after each daratumumab are to reduce the risk of infusion related reactions and as a steroid component of the triple combination.

Infusion related reactions (IRR)

Daratumumab solution for subcutaneous injection can cause severe and/or serious IRRs, including anaphylactic reactions. In clinical studies, approximately 11% (52/490) of patients experienced an IRR. Most IRRs occurred following the first injection and were Grade 1-2. IRRs occurring with subsequent injections were seen in less than 1% of patients.

The median time to onset of IRRs following daratumumab injection was 3.7 hours (range 0.15-83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in less than 1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritus, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia.

Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs, especially during and following the first and second injections. If an anaphylactic reaction or life-threatening (Grade 4) reactions occur, appropriate emergency care should be initiated immediately. Daratumumab therapy should be discontinued immediately and permanently.

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following Daratumumab injection. Patients with a history of chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g. short- and long-

acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease.

Interference with Serological Testing

Daratumumab binds to CD38 in red blood cells and results in a positive indirect antiglobulin test (Coombs test). Daratumumab mediated positive indirect antiglobulin test may persist for up to six months after the last daratumumab infusion. Daratumumab bound red blood cells masks detection of antibodies to minor antigens in the patient serum. The determination of a patient ABO and Rh blood type are not impacted.

Blood transfusion must be informed that a patient is receiving daratumumab. Patients must be typed and screened prior to daratumumab. All patients must be given an identification card that should be carried for six months after stopping therapy and agree to inform all healthcare professionals who treat them that they have received daratumumab.

Daratumumab is a human IgG kappa monoclonal antibody detectable on both the serum electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in all patients with IgG kappa myeloma.

Reactivation of Hepatitis B Virus

Hepatitis B virus reactivation has been reported in patients treated with daratumumab and lenalidomide. All patients must be screened for hepatitis B before initiation of treatment. This includes all patients with unknown serology who are on treatment already.

Monitoring is required for patients with positive serology for clinical and laboratory signs of hepatitis B reactivation during treatment and for at least six months after completion of daratumumab. Those with positive serology must seek medical help immediately if they experience symptoms of hepatitis B. Daratumumab and lenalidomide must be stopped if hepatitis B reactivation occurs during treatment.

Regimen

Cycles 1 to 2

Drug	Dose	Days	Administration
Daratumumab	1800mg	Days 1, 8, 15 and 22	Subcutaneous
Dexamethasone	20mg PO (this includes dexamethasone pre-meds) i.e. on daratumumab days, the pre-med dose of dexamethasone is sufficient. On non-daratumumab days, 20mg is	Days 1, 2, 8, 9, 15, 16, 22 and 23	20mg Oral 10mg oral (or iv dose equivalent) for over 75yrs and less than BMI 18.5

	to be administered.		
Lenalidomide	25mg PO	Days 1 to 21 (NOCTE)	Oral

Cycles 3 to 6

Drug	Dose	Days	Administration
Daratumumab	1800mg	Days 1, and 15	Subcutaneous
Dexamethasone	20mg PO (this includes dexamethasone pre-meds) i.e. on daratumumab days, the pre-med dose of dexamethasone is sufficient. On non-daratumumab days, 20mg is to be administered.	Days 1, 2, 15 and 16	20mg Oral 10mg oral (or iv dose equivalent) for over 75yrs and less than BMI 18.5
Lenalidomide	25mg PO	Days 1 to 21 (NOCTE)	Oral

Cycles 7 and further cycles

Drug	Dose	Days	Administration
Daratumumab	1800mg	Day 1	Subcutaneous
Dexamethasone	20mg PO (this includes dexamethasone pre-meds) i.e. on daratumumab days, the pre-med dose of dexamethasone is sufficient. On non-daratumumab days, 20mg is to be administered.	Days 1 and 2	20mg Oral 10mg oral (or iv dose equivalent) for over 75yrs and less than BMI 18.5
Lenalidomide	25mg PO	Days 1 to 21 (NOCTE)	Oral

Cycle Frequency

28-day cycle until disease progression or intolerance

Dose Information

- Dexamethasone is available as 2mg and 500microgram tablets and 3.3mg in 1ml injection (equivalent to 4mg orally)
- Lenalidomide is available as 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg, and 25mg capsules

Administration Information

- The first dose of daratumumab should be administered in an environment where resuscitation facilities are available.
- For first dose a cannula should be inserted to allow emergency treatment of anaphylaxis
- Pre-medications (oral or intravenous) should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every administration of Daratumumab.
- For patients with a history of chronic obstructive pulmonary disease, the use of post-injection medicinal products including short and long-acting bronchodilators, and inhaled corticosteroids should be considered.
- Inject 15 mL daratumumab solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the umbilicus over approximately 3-5 minutes. Do not inject daratumumab solution for subcutaneous injection at other sites of the body as no data are available.
- First dose daratumumab that the patient should be observed with hourly observations for 4 hours following subcutaneous administration. If no infusion-related reactions following the first dose then neither cannulation nor additional post injection observations are needed with subsequent doses. If IRR with first dose then continue to observe for 4 hours following subsequent doses until IRRs subside.

Following the first four injections, if the patient experiences no major IRRs, inhaled post-injection medicinal products may be discontinued at the discretion of the physician.

- If the patient experiences no major IRRs after the first three injections, post-injection corticosteroids (excluding any background regimen corticosteroids) may be discontinued.
- No modification to rate or dose of daratumumab administration was required to manage IRRs in clinical studies.
- Injection sites should be rotated for successive injections.
- Daratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.
- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

- During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as Daratumumab.

- Lenalidomide should be taken at night to avoid daytime drowsiness

- Lenalidomide prescriptions must be accompanied by a completed Prescription Authorisation Form

Additional therapy

- Consider allopurinol 300mg once a day for seven days for the first cycle only oral

- Anti-emetics

  - Metoclopramide 10mg three times a day when required oral (this is not included in the regimen on ARIA but can be added from favourites if required)

- Premedication required 1 to 3 hours before every daratumumab infusion:

  - Dexamethasone – see regimen for dose details
  - Chlorphenamine 4mg oral
  - Paracetamol 1000mg oral
  - Montelukast 10mg oral for the first four doses only

- Thromboprophylaxis according to local formulary choice. For example;
  - Dalteparin 5000units once a day subcutaneous injection
  - Enoxaparin 40mg once a day subcutaneous injection
  - Heparin 5000units twice a day subcutaneous injection
  - Apixaban 2.5mg twice a day oral (unlicensed use)
  - Aspirin 75mg once daily (patients with no or one risk factor)

- Bisphosphonates in accordance with local policies.

- Mouthwashes according to local or national policy on the treatment of mucositis.

- Laxatives as required for Lenalidomide-induced constipation.

- Gastric protection with a proton pump inhibitor or an H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

- As required for the treatment of infusion related reactions for patients at high risk of respiratory complications:

  - Salbutamol 2.5mg nebulised
  - Hydrocortisone sodium succinate 100mg intravenous
  - Chlorphenamine 10mg intravenous
  - Paracetamol 1000mg oral
  - Oxygen as required

Additional Information

- All instances of infusion related reaction must be recorded on ARIA.
- Daratumumab interferes with indirect antiglobulin tests as it binds to CD38 on red blood corpuscles (RBCs) and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered.
- Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.
- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.
- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.
- For all patients taking lenalidomide; the patient, prescriber and supplying pharmacy must comply with an appropriate pregnancy prevention programme.

Reference

1. eMC (2023). Apixaban 2.5mg film-coated tablets. Available at: https://www.medicines.org.uk/emc/product/14534. Accessed [15/10/2023].
2. eMC (2023). Darzalex 1800mg solution for injection. Available at: https://www.medicines.org.uk/emc/search?q=daratumumab. Accessed [15/10/2023].
3. eMC (2023). Revlimid 25mg Hard Capsules. Available at: https://www.medicines.org.uk/emc/product/10047/smpc Accessed [15/10/2023].
4. Facon, T., Kumar, S. et al (2019). Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. Available at: https://www.nejm.org/doi/full/10.1056/nejmoa1817249. Accessed [15/10/2023].
5. IMWG Guidelines (2023). IMWG Guidelines for the Prevention of Thalidomide and Lenalidomide-Associated Thrombosis in Myeloma. Available at: https://www.myeloma.org/resource-library/imwg-guidelines-prevention-thalidomide-lenalidomide-associated-thrombosis-myeloma. Accessed [15/10/2023].
6. Moik, F., et al (2020). Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: Updated systematic review and meta-analysis of randomized controlled trials. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7292654/ [Accessed 15/10/2023]

REGIMEN SUMMARY

Myeloma – DRD Daratumumab-Lenalidomide-Dexamethasone

Cycle 1 Day 1

1.Warning – Inform blood transfusion

Administration Instructions
Daratumumab interferes with indirect antiglobulin tests as it binds to CD38 on red blood corpuscles (RBCs) and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered.

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response

Please inform blood transfusion when a patient is prescribed daratumumab

2.Antihistamine oral

Administration Instructions
Oral antihistamine according to local formulary choices. To be taken 1 -3 hours prior to daratumumab infusion
For example;
Chlorphenamine 4mg Oral
Loratadine 10mg Oral
Cetirizine 10mg Oral
Fexofenadine 120mg Oral
Acrivastine 8mg Oral

3.Dexamethasone 20mg oral

Administration Instructions
To be taken 1 -3 hours prior to daratumumab infusion. Can be administered as 20mg intravenous. Reduce dose to 10mg intravenous equivalent or 10mg orally in patients over 75 years old.

4.Paracetamol 1000mg oral

Administration Instructions
To be taken 1 -3 hours prior to daratumumab infusion Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

5.Montelukast 10mg oral

Administration Instructions
To be taken 1-3 hours prior to daratumumab

6.Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes

Administration Instructions
Inject the daratumumab solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject daratumumab solution for subcutaneous injection at other sites of the body as no data are available.

Injection sites should be rotated for successive injections

Daratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.

Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as daratumumab.

7.Chlorphenamine 10mg intravenous when required for the relief of infusion related reactions

8.Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

9.Paracetamol 1000mg oral when required for the relief of infusion related reactions
Administration Instructions
Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

10.Salbutamol 2.5mg nebulised when required for the relief of infusion related reactions

Cycle 1 Days 8, 15, 22

11.Warning – Check if Antihistamine Taken
Administration Instructions
Ensure the patient has taken the antihistamine premedication. If not please administer one of the following according to local formulary choice; To be taken 1 -3 hours prior to daratumumab infusion
Chlorphenamine 4mg Oral
Loratadine 10mg Oral
Cetirizine 10mg Oral
Fexofenadine 120mg Oral
Acrivastine 8mg Oral

12.Warning – Check if the Dexamethasone Taken
Administration Instructions
Ensure the patient has taken the dexamethasone premedication. If not please administer dexamethasone 20mg oral or intravenous if the patient is unable to tolerate the oral dose. Reduce dose to 10mg intravenous equivalent or 10mg orally in patients over 75 years old.

13.Warning – Check if the Paracetamol Taken
Administration Instructions
Please check if the patient has taken paracetamol. If not please administer paracetamol 1000mg. The maximum dose is 4000mg/24 hours

14.Montelukast 10mg oral
Administration Instructions
To be taken 1-3 hours prior to daratumumab

15.Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes
Administration Instructions
Inject the daratumumab solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject daratumumab solution for subcutaneous injection at other sites of the body as no data are available.

Injection sites should be rotated for successive injections

Daratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.

Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as daratumumab.

16.Chlorphenamine 10mg intravenous when required for the relief of infusion related reactions

17.Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

18.Paracetamol 1000mg oral when required for the relief of infusion related reactions
Administration Instructions

Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

19. Salbutamol 2.5mg nebulised when required for the relief of infusion related reactions

Cycle 1 Take home medicines (day 1 only)

20. Warning – Pregnancy Prevention Programme
    Administration Instructions
    Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients

21. Dexamethasone 20mg on days 2, 8, 9, 15, 16, 22 and 23 oral
    Administration Information
    Reduce dose to 10mg in patients over 75 years old
    Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

22. Dexamethasone 20mg on day 1 of the next cycle
    Take in the morning prior to daratumumab injection
    Note to pharmacy; dispense for day 1 of the next cycle

23. Lenalidomide 25mg once a day for 21 days from Day 1 to 21 of cycle oral
    Administration Instructions
    Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.
    Oral chemotherapy. Take at night to avoid daytime drowsiness. To start at 25mg and adjust the dose according to toxicity and patient's tolerance

24. Allopurinol 300mg once a day for 7 days oral
    Administration information
    Take in the morning with food and plenty of water. This should be supplied for the first cycle only.

25. Aciclovir 400mg twice a day for 28 days oral
    Administration Instructions
    Please supply 28 days or an original pack if appropriate.

26. Levofloxacin 500mg once a day for 84 days oral
    Administration Instructions
    Please supply 12 weeks on cycle 1 only

27. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral
    Administration Instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
    This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice

28. Fluconazole 100mg once a day oral
    Administration information
    Prescribe if recurrent oral candidiasis.

29. Gastric Protection
    Administration Instructions
    The choice of gastric protection is dependent on local formulary choice and may include;

    - Esomeprazole 20mg once a day oral
    - Omeprazole 20mg once a day oral
    - Lansoprazole 15mg once a day oral
    - Pantoprazole 20mg once a day oral
    - Rabeprazole 20mg once a day oral
    - Cimetidine 400mg twice a day oral
    - Famotidine 20mg once a day oral
    - Nizatidine 150mg twice a day oral

    Please supply 28 days or the nearest original pack size.

30. Anthistamine on the days of daratumumab administration
    Administration Instructions

Take on the day of daratumumab administration. To be taken 1 -3 hours prior to daratumumab infusion Please supply 1 x OP. This is to cover all cycles. To be supplied as per local formulary choice
- Chlorphenamine 4mg Oral
- Loratadine 10mg Oral
- Cetirizine 10mg Oral
- Fexofenadine 120mg Oral
- Acrivastine 8mg Oral

31.Paracetamol 1000mg oral on the days of daratumumab administration

Administration Instructions
Take 1000mg prior to daratumumab administration. To be taken 1 -3 hours prior to daratumumab infusion Please supply 1 x 100 x 500mg. This is to cover all cycles

32.Thromboprophylaxis according to local formulary choice;

Administration Instructions
The choice of thromboprophylaxis is dependent on local formulary choice and may include;
- Dalteparin 5000units once a day subcutaneous injection
- Enoxaparin 40mg once a day subcutaneous injection
- Heparin 5000units twice a day subcutaneous injection
- Apixaban 2.5mg twice a day oral (unlicensed use)
- Aspirin 75mg once daily (patients with no or one risk factor)

Please supply 28 days or nearest original pack size.

Cycles 2 days 1, 8, 15, 22

33.Warning – Check if Antihistamine Taken

Administration Instructions
Ensure the patient has taken the antihistamine premedication. If not please administer one of the following according to local formulary choice;
- Chlorphenamine 4mg Oral
- Loratadine 10mg Oral
- Cetirizine 10mg Oral
- Fexofenadine 120mg Oral
- Acrivastine 8mg Oral

34.Warning – Check if the Dexamethasone Taken

Administration Instructions
Ensure the patient has taken the dexamethasone premedication. If not please administer dexamethasone 20mg oral or intravenous if the patient is unable to tolerate the oral dose. Reduce dose to 10mg intravenous equivalent or 10mg orally in patients over 75 years old.

35.Warning – Check if the Paracetamol Taken

Administration Instructions
Please check if the patient has taken paracetamol. If not please administer paracetamol 1000mg. The maximum dose is 4000mg/24 hours

36.Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes

Administration Instructions
Inject the daratumumab solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject daratumumab solution for subcutaneous injection at other sites of the body as no data are available.

Injection sites should be rotated for successive injections

Daratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.

Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as daratumumab.

37.Chlorphenamine 10mg intravenous when required for the relief of infusion related reactions

38. Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

39. Paracetamol 1000mg oral when required for the relief of infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

40. Salbutamol 2.5mg nebulised when required for the relief of infusion related reactions.

Cycles 2 Take home medicines (day 1 only)

41. Warning – Pregnancy Prevention Programme
    Administration Instructions Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

42. Dexamethasone 20mg on days 2, 8, 9, 15, 16, 22 and 23 oral
    Administration Information
    Reduce dose to 10mg in patients over 75 years old.
    Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

43. Dexamethasone 20mg on day 1 of the next cycle
    Take in the morning prior to daratumumab injection. Reduce dose to 10mg in patients over 75 years old.
    Note to pharmacy; dispense for day 1 of the next cycle.

44. Lenalidomide 25mg once a day for 21 days from Day 1 to 21 of cycle oral
    Administration Instructions Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. Take at night to avoid daytime drowsiness. To start at 25mg and adjust the dose according to toxicity and patient's tolerance.

45. Aciclovir 400mg twice a day for 28 days oral
    Administration Instructions
    Please supply 28 days or an original pack if appropriate.

46. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral
    Administration Instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
    This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

47. Fluconazole 100mg once a day for 28 days oral
    Administration Instructions

48. Gastric Protection
    Administration Instructions
    The choice of gastric protection is dependent on local formulary choice and may include;

    - Esomeprazole 20mg once a day oral
    - Omeprazole 20mg once a day oral
    - Lansoprazole 15mg once a day oral
    - Pantoprazole 20mg once a day oral
    - Rabeprazole 20mg once a day oral
    - Cimetidine 400mg twice a day oral
    - Famotidine 20mg once a day oral
    - Nizatidine 150mg twice a day oral

    Please supply 28 days or the nearest original pack size.

49. Thromboprophylaxis according to local formulary choice;
    Administration Instructions
    The choice of thromboprophylaxis is dependent on local formulary choice and may include;
    - Dalteparin 5000units once a day subcutaneous injection
    - Enoxaparin 40mg once a day subcutaneous injection

- Heparin 5000units twice a day subcutaneous injection
- Apixaban 2.5mg twice a day oral (unlicensed use)
- Aspirin 75mg once daily (patients with no or one risk factor)

Please supply 28 days or nearest original pack size.

Cycles 3 to 6 day 1 and 15

50.Warning – Check if Antihistamine Taken

Administration Instructions
Ensure the patient has taken the antihistamine premedication. If not please administer one of the following according to local formulary choice;
Chlorphenamine 4mg Oral
Loratadine 10mg Oral
Cetirizine 10mg Oral
Fexofenadine 120mg Oral
Acrivastine 8mg Oral

51.Warning – Check if the Dexamethasone Taken

Administration Instructions
Ensure the patient has taken the dexamethasone premedication. If not please administer dexamethasone 20mg oral or intravenous if the patient is unable to tolerate the oral dose. Reduce dose to 10mg intravenous equivalent or 10mg orally in patients over 75 years old.

52.Warning – Check if the Paracetamol Taken

Administration Instructions
Please check if the patient has taken paracetamol. If not please administer paracetamol 1000mg. The maximum dose is 4000mg/24 hours

53.Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes

Administration Instructions
Inject the daratumumab solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject daratumumab solution for subcutaneous injection at other sites of the body as no data are available.

Injection sites should be rotated for successive injections.

Daratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.

Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as daratumumab.

54.Chlorphenamine 10mg intravenous when required for the relief of infusion related reactions

55.Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

56.Paracetamol 1000mg oral when required for the relief of infusion related reactions

Administration Instructions
Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

57.Salbutamol 2.5mg nebulised when required for the relief of infusion related reactions

Cycles 3,4,5 Take home medicines (day 1 only)

58.Warning – Pregnancy Prevention Programme

Administration Instructions Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients

59. Dexamethasone 20mg on days 2, 15 and 16 oral
    Administration Information
    Reduce dose to 10mg in patients over 75 years old
    Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

60. Dexamethasone 20mg on day 1 of the next cycle
    Take in the morning prior to daratumumab injection. Reduce dose to 10mg in patients over 75 years old.
    Note to pharmacy; dispense for day 1 of the next cycle

61. Lenalidomide 25mg once a day for 21 days from Day 1 to 21 of cycle oral
    Administration Instructions Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. Take at night to avoid daytime drowsiness. To start at 25mg and adjust the dose according to toxicity and patient's tolerance.

62. Aciclovir 400mg twice a day for 28 days oral
    Administration Instructions
    Please supply 28 days or an original pack if appropriate.

63. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral
    Administration Instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
    This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

64. Fluconazole 100mg once a day for 28 days oral
    Administration Instructions

65. Gastric Protection
    Administration Instructions
    The choice of gastric protection is dependent on local formulary choice and may include;

    - esomeprazole 20mg once a day oral
    - omeprazole 20mg once a day oral
    - lansoprazole 15mg once a day oral
    - pantoprazole 20mg once a day oral
    - rabeprazole 20mg once a day oral
    - cimetidine 400mg twice a day oral
    - famotidine 20mg once a day oral
    - nizatidine 150mg twice a day oral

    Please supply 28 days or the nearest original pack size.

66. Thromboprophylaxis according to local formulary choice;
    Administration Instructions
    The choice of thromboprophylaxis is dependent on local formulary choice and may include;
    - dalteparin 5000units once a day subcutaneous injection
    - enoxaparin 40mg once a day subcutaneous injection
    - heparin 5000units twice a day subcutaneous injection
    - Apixaban 2.5mg twice a day oral (unlicensed use)
    - Aspirin 75mg once daily (patients with no or one risk factor)

    Please supply 28 days or nearest original pack size.

Cycle 6 Take home medicines (day 1 only)

67. Warning – Pregnancy Prevention Programme
    Administration Instructions Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients

68. Dexamethasone 20mg on days 2, 15 and 16 oral
    Administration Information
    Reduce dose to 10mg in patients over 75 years old

Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

69.Dexamethasone 20mg on day 1 of the next cycle

Administration Information
Reduce dose to 10mg in patients over 75 years old
Take in the morning with or after food. Please dispense on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

70.Lenalidomide 25mg once a day for 21 days from Day 1 to 21 of cycle oral

Administration Instructions Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. Take at night to avoid daytime drowsiness. To start at 25mg and adjust the dose according to toxicity and patient's tolerance.

71.Aciclovir 400mg twice a day for 28 days oral

Administration Instructions
Please supply 28 days or an original pack if appropriate.

72.Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral

Administration Instructions
Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

73.Fluconazole 100mg once a day for 28 days oral

Administration Instructions

74.Gastric Protection

Administration Instructions
The choice of gastric protection is dependent on local formulary choice and may include;

- esomeprazole 20mg once a day oral
- omeprazole 20mg once a day oral
- lansoprazole 15mg once a day oral
- pantoprazole 20mg once a day oral
- rabeprazole 20mg once a day oral
- cimetidine 400mg twice a day oral
- famotidine 20mg once a day oral
- nizatidine 150mg twice a day oral

Please supply 28 days or the nearest original pack size.

75.Thromboprophylaxis according to local formulary choice;

Administration Instructions
The choice of thromboprophylaxis is dependent on local formulary choice and may include;
- dalteparin 5000units once a day subcutaneous injection
- enoxaparin 40mg once a day subcutaneous injection
- heparin 5000units twice a day subcutaneous injection
- Apixaban 2.5mg twice a day oral (unlicensed use)
- Aspirin 75mg once daily (patients with no or one risk factor)

Please supply 28 days or nearest original pack size.

Cycles 7 and further cycles day 1

76.Warning – Check if Antihistamine Taken

Administration Instructions
Ensure the patient has taken the antihistamine premedication. If not please administer one of the following according to local formulary choice;
Chlorphenamine 4mg Oral
Loratadine 10mg Oral
Cetirizine 10mg Oral
Fexofenadine 120mg Oral

Acrivastine 8mg Oral

77. Warning – Check if the Dexamethasone Taken
Administration Instructions
Ensure the patient has taken the dexamethasone premedication. If not please administer dexamethasone 20mg oral or intravenous if the patient is unable to tolerate the oral dose. Reduce dose to 10mg intravenous equivalent or 10mg orally in patients over 75 years old.

78. Warning – Check if the Paracetamol Taken
Administration Instructions
Please check if the patient has taken paracetamol. If not please administer paracetamol 1000mg. The maximum dose is 4000mg/24 hours

79. Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes
Administration Instructions
Inject the daratumumab solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject daratumumab solution for subcutaneous injection at other sites of the body as no data are available.

Injection sites should be rotated for successive injections.

Daratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.

Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as daratumumab.

80. Chlorphenamine 10mg intravenous when required for the relief of infusion related reactions

81. Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

82. Paracetamol 1000mg oral when required for the relief of infusion related reactions
Administration Instructions
Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

83. Salbutamol 2.5mg nebulised when required for the relief of infusion related reactions

Cycle 7 and further cycles Take home medicines (day 1 only)

84. Warning – Pregnancy Prevention Programme
Administration Instructions Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

85. Dexamethasone 20mg on day 2 oral
Administration Information
Reduce dose to 10mg in patients over 75 years old.
Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

86. Dexamethasone 20mg on day 1 of the next cycle
Administration Information
Reduce dose to 10mg in patients over 75 years old.
Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

87. Lenalidomide 25mg once a day for 21 days from Day 1 to 21 of cycle oral
Administration Instructions Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

Oral chemotherapy. Take at night to avoid daytime drowsiness. To start at 25mg and adjust the dose according to toxicity and patient's tolerance.

88.Aciclovir 400mg twice a day for 28 days oral

Administration Instructions
Please supply 28 days or an original pack if appropriate.

89.Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral

Administration Instructions
Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

90.Fluconazole 100mg once a day for 28 days oral

Administration Instructions

91.Gastric Protection

Administration Instructions
The choice of gastric protection is dependent on local formulary choice and may include;

- esomeprazole 20mg once a day oral
- omeprazole 20mg once a day oral
- lansoprazole 15mg once a day oral
- pantoprazole 20mg once a day oral
- rabeprazole 20mg once a day oral
- cimetidine 400mg twice a day oral
- famotidine 20mg once a day oral
- nizatidine 150mg twice a day oral

Please supply 28 days or the nearest original pack size.

92.Thromboprophylaxis according to local formulary choice;

Administration Instructions
The choice of thromboprophylaxis is dependent on local formulary choice and may include;
- Dalteparin 5000units once a day subcutaneous injection
- Enoxaparin 40mg once a day subcutaneous injection
- Heparin 5000units twice a day subcutaneous injection
- Apixaban 2.5mg twice a day oral (unlicensed use)
- Aspirin 75mg once daily (patients with no or one risk factor)

Please supply 28 days or nearest original pack size.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Oct 2023	None	Noriko Kendall Pharmacist	Dr Mathew Jenner Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.