Regimen Monograph

A - Regimen Name

DEXAPOMA+ISAT Regimen

Dexamethasone-Pomalidomide-Isatuximab

Disease Site

Hematologic
Multiple Myeloma

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of relapsed or refractory multiple myeloma (MM) in patients with good performance status, who have received at least 2 previous lines of treatment (including lenalidomide and a proteasome inhibitor).

(Refer to NDFP form for details)

Supplementary Public Funding

dexamethasone
ODB - General Benefit (dexamethasone)

isatuximab
New Drug Funding Program (Isatuximab - In Combination with Pomalidomide and Dexamethasone for Relapsed or Refractory Multiple Myeloma) (NDFP Website)

pomalidomide
Exceptional Access Program (pomalidomide - In combination with isatuximab and dexamethasone for relapsed or refractory multiple myeloma, according to specific criteria) (EAP Website)

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B - Drug Regimen

Cycle 1:

dexamethasone†	40* mg	IV / PO	Days 1, 8, 15, and 22
isatuximab	10 mg /kg	IV	Days 1, 8, 15, and 22
pomalidomide^	4 mg	PO daily	Days 1 to 21

Cycle 2 and onwards:

dexamethasone†	40* mg	IV / PO	Days 1, 8, 15, and 22
isatuximab	10 mg /kg	IV	Days 1 and 15
pomalidomide^	4 mg	PO daily	Days 1 to 21

†Give before isatuximab on isatuximab infusion days (also refer to premedication section).

*Decrease dexamethasone dose to 20 mg in patients ≥ 75 years old.

^Pomalidomide may only be prescribed and dispensed by physicians and pharmacists registered with a controlled distribution program. Patients must also be registered and meet all conditions of the program.

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low
No routine prophylaxis for pomalidomide

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Other Supportive Care:

- Isatuximab can interfere with cross-matching for blood transfusions; type and screen and RBC genotyping tests should be done before starting this drug.
- Consider antiviral prophylaxis for herpes zoster reactivation.
- Prophylactic antithrombotics, such as low dose aspirin, low molecular weight heparins or warfarin, are recommended.
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Pre-medications (prophylaxis for infusion reaction):

To be given 15-60 minutes prior to infusion:

- Dexamethasone 40 mg IV/PO*
- Acetaminophen 650-1000 mg PO (or equivalent)
- Diphenhydramine 25-50 mg IV/PO (or equivalent)†
- H2 antagonist

*Dexamethasone is part of combination therapy; the treatment dose will serve as pre-medication on infusion days. Additional corticosteroids are not required as pre-medication on infusion days when dexamethasone is given. Decrease dexamethasone dose to 20 mg in patients ≥ 75 years old.

†IV preferred for at least the first 4 infusions.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Pomalidomide may only be prescribed and dispensed by physicians and pharmacists registered with a controlled distribution program. Patients must also be registered and meet all conditions of the program.

People of child bearing potential must have two negative pregnancy tests before initiating treatment.

Start treatment only if ANC ≥ 1 x 10^9/L and platelets ≥ 50 x 10^9/L.

Dosage with toxicity

Dose Levels:

Dose Level	Pomalidomide Dose (mg/day)	Dexamethasone Dose (mg/day)	
0	4	40	20*
-1	3	20	12
-2	2	12	8
-3	1	8	4
-4	Discontinue	4	Discontinue
-5	N/A	Discontinue	N/A

*Starting dose for patients ≥ 75 years old.

Dose Modifications:

Dose reductions are not recommended for **isatuximab**. Doses may be delayed or discontinued in case of neutropenia or IRs.

Dexamethasone doses may be held or reduced for dexamethasone-related adverse events (i.e. hypertension, hyperglycemia, fluid retention) to improve tolerability.

Hematological toxicity

Toxicity	Action	
	Pomalidomide	**Isatuximab**
Grade 3 Neutropenia (ANC 0.5 to < 1 x 10^9/L)	• Continue same dose or consider dose reduction. • Consider G-CSF.	• Hold.* • Consider G-CSF. • Restart after recovery at same dose.
Grade 4 neutropenia (ANC < 0.5 x 10^9/L) OR Febrile neutropenia (fever ≥ 38.5^{0}C and ANC < 1 x 10^9/L)	• Hold*; monitor CBC weekly. • Consider G-CSF. • Restart after recovery with 1 dose level ↓.	• Hold.* • Consider G-CSF. • Restart after recovery at same dose.
Grade 4 thrombocytopenia (platelets < 25 x 10^9/L)	• Hold*; monitor CBC weekly. • Consider transfusion support as needed. • Restart after recovery with 1 dose level ↓.	• Continue same dose.

*Do not re-start until ANC returns to ≥ 1 x 10^9/L and platelets ≥ 50 x 10^9/L, and non-hematological toxicities resolve to ≤ grade 2.

Non-hematological toxicity

Toxicity	Dose of Pomalidomide*
Grade 2 or 3 skin rash	Hold or discontinue. Resume if benefit outweighs potential risk.
Grade 4 rash or rash with exfoliation, bullae or purpura, angioedema, anaphylaxis, or suspected SJS/TEN/DRESS	Discontinue.
Grade 3 or 4 non-hematologic/organ toxicities	Hold until recovery* then ↓ 1 dose level. Consider discontinuing if grade 4.
Acute onset or worsening of pulmonary symptoms	Hold and investigate for pneumonitis. Resume only after an evaluation of the benefits and risks.
PML	Hold and investigate. Discontinue if confirmed.

*Do not re-start until ANC returns to ≥ 1 x 10^9/L and platelets ≥ 50 x 10^9/L, and non-hematological toxicities resolve to ≤ grade 2.

Management of Isatuximab Infusion-related Reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1	• Continue or stop the infusion. • Monitor the symptoms closely.	• No specific recommendations available.
2	• Stop the infusion. • Manage the symptoms.* **Restart:** • Do not restart if symptoms do not resolve rapidly or do not improve to ≤ Grade 1. • After symptom resolution (≤ Grade 1), restart at 50% of the initial infusion rate ± pre-medications. • If no reaction occurs after 30 minutes, may escalate to initial rate, then incrementally. Refer to Administration section for infusion rates table.	• Discontinue permanently (do not rechallenge) if previously interrupted dose was not restarted
3 or 4	• Stop treatment. • Aggressively manage symptoms.*	• Discontinue permanently (do not re-challenge).

*Give diphenhydramine 25 mg IV (or equivalent) and/or methylprednisolone 100 mg IV (or equivalent) and/or epinephrine (for Gr. 3-4) as needed to manage symptoms.

Hepatic Impairment

Pomalidomide is primarily metabolized in the liver. Hepatic impairment results in a 51-72% increase in drug exposure. The starting dose of pomalidomide should be adjusted as follows:

Hepatic Impairment	Pomalidomide Dose* (mg/day)	Isatuximab Dose**
Mild	3	No dose adjustment necessary
Moderate	3	No data
Severe	2	

*Use should be avoided in patients with serum bilirubin > 1.5 x ULN and AST/ALT > 3 x ULN.
**The effect of moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and any AST) on isatuximab pharmacokinetics is unknown.

Renal Impairment

No dose adjustment for isatuximab is recommended in patients with renal impairment.

Pomalidomide and its metabolites are renally excreted. Pomalidomide is dialysable. The starting dose of pomalidomide should be adjusted for severe impairment requiring dialysis, as follows:

Creatinine Clearance (mL/min)	Pomalidomide Starting Dose (mg/day)
< 30 requiring dialysis	3 (taken after dialysis)

Dosage in the Elderly

The starting dose of dexamethasone should be reduced to 20 mg in patients ≥ 75 years. No dose adjustments for pomalidomide or isatuximab are recommended based on age.

When pomalidomide was given in combination with dexamethasone, patients > 65 years were observed to have higher incidences of infection and pneumonia than younger patients.

No overall safety or efficacy differences were observed between younger and older patients given isatuximab.

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F - Adverse Effects

Refer to isatuximab, pomalidomide drug monograph(s) for additional details of adverse effects.

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression ± infection (including atypical, viral reactivation), bleeding (may be severe) • Infusion related reaction (may be severe) • Fatigue • Diarrhea	• Constipation • Nausea, vomiting • Musculoskeletal pain • Cough, dyspnea • Edema - limbs • Arrhythmia • Peripheral neuropathy • Anorexia, weight loss • Headache	• Cardiotoxicity • Atrial fibrillation • Venous thromboembolism • Hypersensitivity • SJS/TEN • DRESS • Renal failure • Tumor lysis syndrome • Secondary malignancy • Increased LFTs • Pneumonitis • PML

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G - Interactions

Refer to isatuximab, pomalidomide drug monograph(s) for additional details.

- Avoid strong inhibitors of CYP1A2 if possible. If not possible to avoid, reduce the pomalidomide dose by 50%.
- Avoid CYP1A2 inducers if possible; cigarette smoking may reduce the efficacy of pomalidomide.
- Pomalidomide increases thromboembolic risk and would have an additive effect if co-administered with other thromboembolic agents. Hormonal contraceptives are not recommended due to the increased risk of thromboembolism.
- Isatuximab interferes with the indirect antiglobulin (Coombs) test by binding to CD38 on RBCs. Patient's blood should be typed and screened, and RBC genotyped prior to initiating treatment. Notify blood transfusion centres of this in the event of a planned transfusion and educate patients.
- Isatuximab may interfere with the serum protein electrophoreses (SPE) and immunofixation (IFE) assays used to monitor M-protein. This can impact the monitoring of response and disease progression in some patients with IgG kappa myeloma protein.

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H - Drug Administration and Special Precautions

Refer to isatuximab, pomalidomide drug monograph(s) for additional details.

Administration: Pomalidomide

Pomalidomide may only be prescribed and dispensed by physicians and pharmacists registered with a controlled distribution program. Patients must also be registered and meet all conditions of the program.

- Capsule should be swallowed whole with a glass of water. Do not crush or open the capsule.
- Doses may be administered with or without food.
- Missed dose: If less than 12 hours has passed since the missed dose, the dose may be taken. If more than 12 hours has passed since the missed dose, skip this dose and take the next one at its usual time the next day. Do not give a double dose to make up for a missed one.
- On dialysis days, administer pomalidomide after the completion of hemodialysis due to possible significant decrease in drug exposure.
- People who could become pregnant or who plan to become pregnant can handle pomalidomide capsules if they are using latex gloves.
- Store at room temperature (15-30°C) in original package in order to protect from light.

Administration: Isatuximab

- Refer to Infusion Rate table below.
- Dilute with 250 mL of NS or D5W.
- The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di (2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
- Mix by gently inverting the bag. Do not shake.
- Administer by IV infusion using an IV tubing infusion set (in polyethylene [PE], polyvinyl chloride [PVC] with or without di (2-ethylhexyl) phthalate [DEHP], polybutadiene [PBD] or polyurethane [PU]) with an in-line filter (polyethersulfone [PES], polysulfone or nylon).
- Do not infuse concomitantly in the same IV line with other agents.
- Store unopened vials between 2 to 8°C (36°F to 46°F). Protect from light.

Infusion Rate

Isatuximab should be administered at the initial infusion rate with incremental escalation as described below. Infusion rate escalations should only be considered in the absence of infusion-related reactions (IRs).

	Dilution Volume	Initial Rate	Absence of IRs	Rate Escalation	Maximum Rate
1st Infusion	250 mL	25 mL/hr	For 60 min	25 mL/hr q30 min	150 mL/hr
2nd Infusion	250 mL	50 mL/hr	For 30 min	50 mL/hr for 30 min, then ↑ by 100 mL/hr	200 mL/hr
Subsequent Infusions	250 mL	200 mL/hr	-	-	200 mL/hr

Contraindications

- Patients who have a hypersensitivity to isatuximab, dexamethasone, pomalidomide, or any of their components, or to thalidomide or lenalidomide.
- Patients who are pregnant, at risk of becoming pregnant, or are breastfeeding (Refer to Pregnancy and Lactation section)
- People unable to comply with required contraceptive measures

Warnings/Precautions

- Patients with primary refractory disease or who progressed or were refractory to anti-CD38 treatment were excluded from isatuximab clinical trials.
- Avoid use of pomalidomide in patients with active / history of hepatitis A, B, or C.
- Avoid use of pomalidomide in patients taking other immunosuppressive treatments, to reduce the risk of developing serious infections.
- Patients should not donate blood or semen while taking pomalidomide, during treatment interruptions, and for 4 weeks after treatment cessation.
- Use with caution and consider prophylaxis when pomalidomide is used in combination with corticosteroids or thrombogenic agents, such as hormones and erythropoietin or in patients with risk factors for arterial or venous thromboembolism (e.g. hypertension, hyperlipidemia, previous history of thromboembolism, or taking other agents that increase thromboembolic risk).
- Use pomalidomide with caution in patients with pre-existing ≥ grade 2 neuropathy.
- Use with caution when operating machinery, or when driving, as confusion, fatigue, depressed level of consciousness and dizziness may occur with treatment.
- Use with caution in patients with significant cardiac dysfunction (i.e. CHF NYHA Class III or IV, MI within 12 months, unstable or poorly controlled angina) as pomalidomide use has not been studied in these patients. Atrial fibrillation has occurred, especially in patients with pre-existing cardiac disease or cardiac risk factors.

Pregnancy/Lactation

- This regimen is **contraindicated for use in pregnancy and in people who do not comply with the contraception conditions of pomalidomide's controlled distribution program.** Refer to the controlled distribution program for full details.
- Adequate contraception should be used by patients and their partners while on therapy and after treatment is completed. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is contraindicated during this treatment. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects:
  - Pomalidomide: Probable
  - Isatuximab: Unknown

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; Baseline, weekly for the first 8 weeks then before each cycle
- Blood type and screen, and RBC genotype; Before starting isatuximab. In the event of a planned transfusion, notify blood transfusion centres.
- Liver function tests; Baseline and before each cycle
- Electrolytes, renal function tests; Baseline and before each cycle
- Controlled distribution program requirements regarding pregnancy tests for women of child-bearing potential; Before starting, during treatment and for at least 4 weeks after discontinuation
- Clinical toxicity assessment for infusion-related reactions, infection (including viral reactivation), bleeding, hypersensitivity, thromboembolism, secondary malignancies, pneumonitis, hepatitis, TLS, neurological, GI, cardiac, and skin effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

DEXAPOMA: Outpatient prescription for home administration

Approximate Patient Visit	2 to 3 hours
Pharmacy Workload (average time per visit)	21.025 minutes
Nursing Workload (average time per visit)	49.833 minutes

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K - References

Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019 Dec 7;394(10214):2096-2107.

CADTH Reimbursement Recommendation: Isatuximab (Sarclisa). Canadian Journal of Health Technologies. February 2022.

DEXAPOMA regimen monograph, Ontario Health (Cancer Care Ontario).

Isatuximab drug monograph. Ontario Health (Cancer Care Ontario).

Pomalidomide drug monograph. Ontario Health (Cancer Care Ontario).

San Miguel J et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM- 003): a randomized, open-label, phase 3 trial. Lancet Oncol 2013;14:1055-66.

PEBC Advice Documents or Guidelines

- Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

February 2024 Expanded to full regimen monograph

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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