Regimen Monograph

A - Regimen Name

CARFDEXA+ISAT Regimen

Carfilzomib-Dexamethasone-Isatuximab

CARFDEXA(W)+ISAT Regimen

Carfilzomib (weekly)-Dexamethasone-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 patients with relapsed or refractory multiple myeloma and good performance status, who have received at least 1 prior line of therapy. (Refer to NDFP form for details)

Supplementary Public Funding	**dexamethasone** ODB - General Benefit (dexamethasone) (ODB Formulary)
	carfilzomib New Drug Funding Program (Isatuximab and Carfilzomib - In Combination with Dexamethasone for Relapsed or Refractory Multiple Myeloma) (NDFP Website)
	isatuximab New Drug Funding Program (Isatuximab and Carfilzomib - In Combination with Dexamethasone for Relapsed or Refractory Multiple Myeloma) (NDFP Website)

back to top

B - Drug Regimen

Once weekly carfilzomib dosing:

Cycle 1:

dexamethasone^,#	40 mg /day	IV / PO	Days 1, 8, 15, 22
isatuximab	10 mg /kg	IV	Days 1, 8, 15, 22
carfilzomib§	20 mg /m²	IV	Day 1
carfilzomib§	70 mg /m²	IV	Days 8, 15

Cycle 2 and onwards:

dexamethasone^,#	40 mg /day	IV / PO	Days 1, 8, 15, 22*
isatuximab	10 mg /kg	IV	Days 1 and 15
carfilzomib§	70 mg /m²	IV	Days 1, 8, 15

Twice weekly carfilzomib dosing:

Cycle 1:

dexamethasone^,#	20 mg /day	IV / PO	Days 1, 2, 8, 9, 15, 16, 22, 23
isatuximab	10 mg /kg	IV	Days 1, 8, 15, and 22
carfilzomib§	20 mg /m²	IV	Days 1, 2
carfilzomib§	56 mg /m²	IV	Days 8, 9, 15, 16

Cycle 2 and onwards:

dexamethasone^,#	20 mg /day	IV / PO	Days 1, 2, 8, 9, 15, 16, 22, 23
isatuximab	10 mg /kg	IV	Days 1 and 15
carfilzomib§	56 mg /m²	IV	Days 1, 2, 8, 9, 15, 16

^The dexamethasone dose should be reduced in elderly patients ≥ 75 years of age.

#In the clinical trial, dexamethasone was administered first, followed by isatuximab, and then carfilzomib.

§For patients with BSA > 2.2 m^2, carfilzomib should be dosed based on a maximum BSA of 2.2 m^2.

*In the Arrow study, dexamethasone was given on Days 1, 8, and 15 for Cycle 10 onwards.

back to top

C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Low

- Also refer to CCO Antiemetic Summary

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

Pre-medications (prophylaxis for infusion reaction (IR)):

To be given 15-60 minutes prior to **isatuximab** infusion:

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

In the IKEMA study, pre-medications for isatuximab were re-considered if no reactions occurred after 4 consecutive doses.

*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 in patients ≥ 75 years old.

^Give dexamethasone IV on the days of isatuximab and/or carfilzomib administration and PO on the other days (based on isatuximab product monograph).

†IV preferred for at least the first 4 infusions.

On **carfilzomib** treatment days, dexamethasone should be given at least 30 minutes, but no more than 4 hours before carfilzomib.

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.
- Consider thromboprophylaxis in patients being treated with carfilzomib. The choice of agent should be based on patient risk factors and clinical status.
- Patients at risk of tumour lysis syndrome (i.e. high tumour burden) should have appropriate prophylaxis and be monitored closely.
- Adequate hydration is required prior to carfilzomib dosing in cycle 1, especially in patients at high risk for tumour lysis syndrome or renal toxicity (IKEMA study).
- The total fluid volume may be adjusted as clinically indicated in patients with baseline or at high risk of cardiac failure.
- On the days where both isatuximab and carfilzomib are given, the **volume of isatuximab infusion should be considered** in the total pre-hydration volume for carfilzomib.
    - Cycle 1
        - Oral fluids (30 mL/kg/day for 48 hours before start of cycle), and
        - IV fluids (week 1): 250-500 mL before each dose, and if needed after each dose.
    - Subsequent doses/cycles:
        - Continue oral and/or IV hydration as needed

back to top

E - Dose Modifications

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

Hypertension should be well-controlled prior to initiation of treatment with carfilzomib.

Carfilzomib doses do not need to be re-calculated for weight changes ≤ 20%.

Dosage with toxicity

Dose Levels for Carfilzomib:

Dose Level	Carfilzomib Dose (mg/m^2) Once Weekly Dosing	Carfilzomib Dose (mg/m^2) Twice Weekly Dosing
0	70	56
-1	56	45
-2	45	36
-3	36	27
-4	Discontinue	Discontinue

Dose Modifications:

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

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

Suggested Dose Modifications for Hematological Toxicity

Toxicity	Action	
	Carfilzomib	**Isatuximab**
Grade 3 Neutropenia (ANC 0.5 to < 1 x10^9/L)	• Continue same dose. • Consider G-CSF according to local guidelines.	• Hold.* • Consider G-CSF according to local guidelines. • Restart after recovery at same dose
Grade 4 neutropenia (ANC < 0.5 x10^9/L)	• 1st instance: hold* until recovery, and then restart at the same dose level. • Consider G-CSF according to local guidelines. • Subsequent instances: hold* until recovery; consider restarting at 1 dose level ↓.	• Hold.* • Consider G-CSF according to local guidelines. • Restart after recovery at same dose
Febrile neutropenia (fever ≥ 38.5°C and ANC < 1)	• 1st instance: hold* until recovery (and fever resolves), and then restart at the same dose level. • Consider G-CSF according to local guidelines. • Subsequent instances: hold* until recovery (and fever resolves); consider restarting at 1 dose level ↓.	• Hold.* • Consider G-CSF according to local guidelines. • Restart after recovery at same dose.
Platelets < 25 x10^9/L; thrombocytopenic bleeding	• 1st instance: hold* until recovery (and bleeding is controlled), and then restart at the same dose level. • Consider transfusion support as needed. • Subsequent instances: hold* until recovery (and bleeding is controlled); consider restarting at 1 dose level ↓.	• Continue same dose.

*Do not restart until ANC ≥ 1 x 10^9/L (or baseline values for febrile neutropenia) and platelets ≥ 25 x 10^9/L with resolution of fever and bleeding.

Suggested Dose Modifications for Non-Hematological Toxicity

Toxicity	Carfilzomib Dose
Serum creatinine ≥ 2 x baseline, or CrCl < 15 mL/min (or CrCl decreases to ≤ 50% of baseline) or need for dialysis	Hold: • If attributable to carfilzomib, resume at 1 dose level ↓ when renal function has recovered to within 25% of baseline. • If not attributable to carfilzomib, may resume at physician's discretion. If tolerated, the reduced dose may be increased to the previous dose.
Grade 3 or 4 cardiac events	Hold until resolved. Consider risk vs. benefit of restarting; resume at 1 dose level ↓.
Hypertensive crisis/emergency	Hold until resolved or under control. Consider the risk vs. benefit of restarting; consider restarting at 1 dose level ↓.
Tumour lysis syndrome	Hold until resolved. Manage promptly.
ARDS, ILD, pneumonitis, pulmonary hypertension, Grade 3 or 4 dyspnea	Hold until resolved. Consider the risk vs. benefit of restarting.
Thrombotic microangiopathy (including TTP/HUS)	Hold and evaluate. Discontinue if confirmed.
PRES	Hold and evaluate. Discontinue if confirmed.
PML	Hold and evaluate. Discontinue if confirmed.
Other drug related Grade 3 or 4 non-hematological toxicities	Hold until resolved or at baseline. Then, if appropriate to reinitiate, consider restarting at 1 dose level ↓ If tolerated, the reduced dose may be increased to the previous dose.

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

In a pharmacokinetic study, carfilzomib AUC increased by 50% in patients with baseline mild or moderate hepatic impairment compared to those with normal hepatic function. The incidence of serious adverse events was higher in patients with hepatic impairment as well.

Hepatic Impairment	Carfilzomib Starting Dose	Dexamethasone Starting Dose	Isatuximab Dose
Mild (bilirubin >1 - 1.5 x ULN or AST > ULN)	Reduce dose by 25%	No dosage adjustment necessary	No dosage adjustment necessary
Moderate (bilirubin >1.5 - 3 x ULN)			No data
Severe (bilirubin > 3 x ULN)	No data		

Renal Impairment

No dosage adjustment required for dexamethasone or isatuximab.

No starting dose adjustment is required for carfilzomib in patients with baseline renal impairment. For patients on dialysis receiving carfilzomib, administer dose after dialysis.

Dosage in the Elderly

The dexamethasone dose should be reduced in elderly patients.

There was a higher incidence of certain adverse effects (including cardiac failure) observed in patients ≥ 65 years of age, especially in those ≥ 75 years of age treated with carfilzomib.

back to top

F - Adverse Effects

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

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression ± infection (including viral reactivation), bleeding (may be severe)	• Infusion related reaction (may be severe) • Fatigue • Hypertension (may be severe) • Diarrhea • Cough, dyspnea	• Musculoskeletal pain • Headache • Constipation • Peripheral neuropathy • Nausea, vomiting • Venous thromboembolism • Creatinine increased (may be severe) • Steroid effects	• Cardiotoxicity • Arterial thromboembolism • QT interval prolonged • Pericarditis • Adult respiratory distress syndrome (ARDS) • Pneumonitis • Pulmonary hypertension • Cataract • Tumour lysis syndrome • GI perforation • GI obstruction • Pancreatitis • Hepatic failure • Thrombotic microangiopathy (including TTP, HUS) • RPLS / PRES • PML • Secondary malignancy

back to top

G - Interactions

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

- Caution with P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron) and monitor digoxin levels when given with carfilzomib.
- Caution and consider non-hormonal method(s) of contraception as use of oral contraceptives or other hormonal methods of contraception may have reduced efficacy and may increase the risk of blood clots.
- 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.

back to top

H - Drug Administration and Special Precautions

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

Administration: dexamethasone

- Oral self-administration or may be given by IV route on carfilzomib clinic days.
- Dexamethasone IV/PO should be given at least 30 minutes, but no more than 4 hours before carfilzomib.
- Give tablets with food, preferably in the morning.

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 for Isatuximab

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

Administration: carfilzomib

- Reconstitute vials with Sterile Water for Injection. Volume for reconstitution depends on vial size; refer to product monograph for instructions.
- After reconstitution, gently swirl and/or invert the vial slowly for 1 minute. Do not shake.
- If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear, colourless and free of visible particulates.
- May further dilute dose in 50-100 mL D5W. Do not dilute in NS for IV administration.
- DO NOT administer as an IV bolus. May be administered directly by IV infusion or in an IV bag.
- Do not mix with or administer as an infusion with other medications.
- Infuse over 30 minutes for regimens with a usual dose of 56 mg/m^2 and 70 mg/m^2. Keep infusion time consistent during treatment regardless of any dose modifications.
- Flush line with NS or D5W before and after carfilzomib administration .
- If a dose is missed, a minimum of 5 days between doses is required for once weekly dosing.
- Store unopened vials refrigerated at 2–8°C in original package and protected from light. Reconstituted or diluted drug do not require protection from light during administration.

Contraindications

- Patients who have a hypersensitivity to these drug or any of their components

Warnings/Precautions

- Use carfilzomib with caution in patients on a controlled sodium diet. Each mL of the reconstituted carfilzomib solution contains 0.3 mmols (7 mg) of sodium.
- The risk of heart failure is increased in elderly patients (≥ 75 years). Patients with NYHA Class III/IV heart failure, recent MI, conduction abnormalities, angina or arrhythmias uncontrolled by medications were not eligible for carfilzomib-based clinical trials. These patients may be at greater risk of cardiac complications and should have their medical management optimized, including hypertension, prior to starting treatment with carfilzomib and monitored closely throughout.
- Patients with primary refractory disease or who progressed or were refractory to anti-CD38 treatment were excluded from isatuximab clinical trials.
- Patients should use caution when driving or using machinery as fatigue, dizziness and a drop in blood pressure may occur with carfilzomib treatment.

Pregnancy/Lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Consider non-hormonal method(s) of contraception as use of oral contraceptives or other hormonal methods of contraception may have reduced efficacy and may increase the risk of blood clots.
- Breastfeeding is not recommended during this treatment. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Unknown

back to top

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 with differential; Baseline and before each cycle; more frequently as clinically indicated
- 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
- Renal function tests; Baseline and before each cycle
- Electrolytes, including potassium; Baseline and before each cycle
- Blood pressure; Baseline and before each treatment
- Blood glucose levels; Baseline and as clinically indicated
- Clinical toxicity assessment for infusion reactions, hypersensitivity, bleeding, infection, TLS, thromboembolism, secondary malignancies, GI, skin, respiratory, ophthalmic, cardiovascular and neurological effects; At each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- LVEF assessment (especially in patients ≥ 75 years, or those at greater risk for cardiac complications); Baseline and as clinically indicated
- ECG; Baseline and as clinically indicate

back to top

J - Administrative Information

Dexamethasone PO - Outpatient prescription for home administration

Approximate Patient Visit	
CARFDEXA+ISAT	1.5 to 5 hours
CARFDEXA(W)+ISAT	1.5 to 5 hours
Pharmacy Workload **(average time per visit)**	
CARFDEXA+ISAT	27.856 minutes
CARFDEXA(W)+ISAT	32.949 minutes
Nursing Workload **(average time per visit)**	
CARFDEXA+ISAT	49.00 minutes
CARFDEXA(W)+ISAT	57.361 minutes

back to top

K - References

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

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

Carfilzomib drug monograph, Ontario Health (Cancer Care Ontario).

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

Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet 2021; 397: 2361–71.

Moreau P, Mateos MV, Berenson JR, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. Lancet Oncol. 2018 Jul;19(7):953-964.

PEBC Advice Documents or Guidelines

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

February 2024 Expanded to full regimen monograph

back to top

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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, 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.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top