Regimen Monograph

A - Regimen Name

PMDR Regimen

Pamidronate

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
Prevention of skeletal events (pathologic fractures, bony pain, and radiation requirement) in patients with active myeloma, especially those with lytic lesions / osteoporosis/ osteopenia

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B - Drug Regimen

pamidronate	90 mg	IV	Day 1

Administer concurrently with first-line or salvage cytotoxic chemotherapy

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C - Cycle Frequency

REPEAT EVERY 28 DAYS
In the absence of unacceptable toxicity

In the management of multiple myeloma, to reduce risk of osteonecrosis of the jaw after two years of treatment, consideration is given to either:

Discontinuing treatment in patients who have responded and who have stable bone metastases
OR
Decreasing frequency to every three months if the patient still needs active treatment

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D - Premedication and Supportive Measures

Antiemetic Regimen: Not applicable

Other Supportive Care:

- All patients, especially those with hypercalcemia, should be adequately hydrated.
- Calcium and vitamin D supplements should be given to patients at risk of low serum calcium and who have no history of hypercalcemia.

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E - Dose Modifications

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

Dosage with toxicity

Dosage in myelosuppression: No dosage adjustment required.

Toxicity	Action
Osteonecrosis of jaw	Refer patient to dentist or dental surgeon; consider hold or discontinue.
Atypical fractures of the femur	Consider discontinuing
Severe musculoskeletal pain	Discontinue

Ocular symptoms other than uncomplicated conjunctivitis	Refer to ophthalmologist; consider discontinuing.
Nephrotoxicity	Hold until recovered to within 10% of baseline

Hepatic Impairment

AUC is increased in mild to moderate hepatic impairment but not considered clinically relevant; no dosage adjustment is required. No data available in patients with severe hepatic dysfunction and so should be used with caution.

Renal Impairment

Patients with severe renal impairment (< 30mL/min) have 3 times higher pamidronate exposure than those with normal renal function.

Baseline		**During Treatment**	
Level	**Action**	**Level/change**	**Action**
Clcr > 90 mL/min	No adjustment needed	Creatinine ↑ of 44 µmol/L if normal baseline	Hold until returns to within 10% of baseline
Clcr 30-90 mL/min	Do not exceed infusion rate of 22.5 mg/h	Creatinine ↑ of 88 µmol/L if abnormal baseline	
Clcr < 30 mL/min or Creatinine > 440 µmol/L (tumour induced hypercalcemia - TIH) or > 180 µmol/L (myeloma)	Only use for life-threatening hypercalcemia where the benefit exceeds risk	Clcr < 30 mL/min or Creatinine > 440 µmol/L (TIH) or > 180 µmol/L (myeloma)	Only use for life-threatening hypercalcemia where the benefit exceeds risk

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F - Adverse Effects

Refer to pamidronate 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
• Flu-like symptoms	• Headache • Musculoskeletal pain (may be severe) • Cough, dyspnea • Anorexia • Abnormal electrolytes • Abdominal pain • Dyspepsia	• Arrhythmia, atrial fibrillation • Cardiotoxicity (due to fluid overload) • Hypersensitivity • Myelosuppression • Atypical fractures • Osteonecrosis (jaw, external ear canal) • Nephrotoxicity • Increased LFTs • Pneumonitis • Ocular (conjunctivitis, uveitis) • Viral reactivation • Seizure

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G - Interactions

Refer to pamidronate drug monograph(s) for additional details.

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H - Drug Administration and Special Precautions

Refer to pamidronate drug monograph(s) for additional details.

Administration:

- Pamidronate must **not** be mixed with calcium-containing solutions (e.g., Ringer's solution).
- Pamidronate is generally mixed in 250-500mL solution (D5W or NS) and infused over 2-4 hours.
- According to the product monograph, it is recommended not to exceed 90 mg in 500 mL over 4 hours (i.e. 22.5 mg/h infusion rate) in multiple myeloma and tumour-induced hypercalcemia.
- Pamidronate must never be given as a bolus injection because of the risk of thrombophlebitis, severe local reactions and renal failure; it should always be diluted and administered as a slow IV infusion.
- All patients, especially those who are dehydrated or hypercalcemic, must be adequately rehydrated prior to treatment with pamidronate.
- Store unopened vials at room temperature (15-25°C). Protect vials from heat.

Contraindications:

- Patients with known or suspected hypersensitivity to pamidronate, or any of its components, or to other bisphosphonates
- Pregnant and/or breastfeeding women

Warnings/Precautions:

- Pamidronate should not be given together with other bisphosphonates to treat hypercalcemia, since the combined effects of these agents are unknown.
- Patients must be adequately hydrated throughout treatment, but special care should be taken in the elderly and patients with cardiac disease, to prevent fluid overload and cardiac failure.
- Avoid in patients with severe renal impairment, except in life-threatening cases of hypercalcemia.
- Use with caution in patients with risk factors for ONJ (see adverse effects description section).
- Patients should not drive, operate machinery or perform tasks that require alertness if they experience somnolence and/or dizziness after infusion.

Pregnancy/Lactation:

- Pamidronate is **contraindicated** in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose (general recommendation).
- Breastfeeding is **contraindicated**.
- Fertility effects: Probable

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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

Recommended Clinical Monitoring

- Dental examination with appropriate preventative dentistry should be considered prior to treatment. Regular dental check- ups. Avoid invasive dental surgeries while on treatment.
- Renal function tests; Baseline and at each visit
- Electrolytes, including corrected serum calcium, phosphates, magnesium, and serum albumin; Baseline and as clinically indicated
- Fluid balance (e.g. urine output, daily weights), especially in patients with pre-existing renal disease or risk of renal impairment; As clinically indicated
- Clinical toxicity assessment (including flu-like syndrome, hypersensitivity, hydration status, pain, dental, otic and ocular effects); At each visit

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

Suggested Clinical Monitoring

- CBC, in patients with anemia, leukopenia, or thrombocytopenia; Baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	Intermate Infusor: 0.5 hour; IV infusion: 2.5-4 hours

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K - References

Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. N Engl J Med 1996;334:488-93.

Corso A, Varettoni M, Zappasodi P, et al. A different schedule of zoledronic acid can reduce the risk of the osteonecrosis of the jaw in patients with multiple myeloma. Leukemia 2007;21(7):1545-8.

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

Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. Annals of Oncology 2006;17:897–907.

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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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