Mifamurtide Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Mifamurtide can be used in combination with post-operative multi-agent chemotherapy for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection, in children, adolescents and young adults. This treatment is an option to be discussed with the patient (or parent of a child).	C41	00100a	ODMS

**If the reimbursement status is not defined [1], the indication has yet to be assessed through the formal HSE reimbursement process.*

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

The recommended dose of mifamurtide for all patients is 2 mg/m^2 body surface area.

It should be administered as adjuvant therapy, combination with post-operative multi-agent chemotherapy, following resection and recovery from surgery (usually +/- 3 weeks post operatively): twice weekly at least 3 days apart for 12 weeks, followed by once-weekly treatments for an additional 24 weeks for a total of 48 infusions in 36 weeks.

Treatment should continue to completion or until unacceptable toxicity occurs.

Day	Drug	Dose	Route	Diluent & Rate	Weeks
1 and 4	Mifamurtide	2mg/m^2	IV infusion	50ml* 0.9% NaCl over 60 minutes	1-12 inclusive
1					13-36 inclusive
*The final volume will be greater than 50 ml as the required dose is added to 50 ml 0.9% NaCl giving a total volume between 50 ml - 100 ml.					

ELIGIBILTY:

- Indications as above
- Patients aged from 2 to 30 years of age.
- Adequate haematological, hepatic and renal function.

EXCLUSIONS:

- Hypersensitivity to mifamurtide or any of the excipients.
- Metastatic disease at presentation.
- Incomplete surgical resection.
- Prior chemotherapy or radiotherapy other than pre-operative multiagent chemotherapy.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Echocardiogram: annually or according to local practice

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Renal and Hepatic Impairment:

Table 1: Dose modification of mifamurtide in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
Cr Cl (ml/min)	**Recommended dose**	**Child Pugh Class**	**Recommended dose**
≥30	No dose adjustment necessary	A	No dose adjustment necessary
		B	
*Severe	No data available Exercise caution	*Severe	No data available Exercise caution
*Continued monitoring of the kidney and liver function is recommended if mifamurtide is used beyond completion of chemotherapy until all therapy is completed.			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (**Refer to local policy).**

PREMEDICATIONS: Paracetamol and chlorphenamine may be utilised as a premedication, to prevent fevers and chills. Corticosteroids, including dexamethasone, should be avoided **(see Drug Interactions).**

Table 2: Suggested Pre-medications prior to mifamurtide infusion

Drugs	Dose	Route
Paracetamol	1g	PO 60minutes prior to mifamurtide infusion
Chlorphenamine	10mg	IV bolus 60minutes prior to mifamurtide infusion

OTHER SUPPORTIVE CARE: No specific recommendations.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Respiratory distress:** In patients with a history of asthma or other chronic obstructive pulmonary disease, consideration should be given to administration of bronchodilators on a prophylactic basis. If a severe respiratory reaction occurs, administration of mifamurtide should be discontinued and appropriate treatment initiated.
- **Neutropenia**: Episodes of neutropenic fever should be monitored and managed appropriately. Mifamurtide may be given during periods of neutropenia, but subsequent fever attributed to the treatment should be monitored closely. Fever or chills persisting for more than 8 hours after mifamurtide administration should be evaluated for sepsis.
- **Inflammatory response**: Mifamurtide should be used with caution in patients with a history of autoimmune, inflammatory or other collagen diseases. During administration, patients should be monitored for unusual signs or symptoms, such as arthritis or synovitis, suggestive of uncontrolled inflammatory reactions.
- **Cardiovascular disorders**: Patients with a history of venous thrombosis, vasculitis or unstable cardiovascular disorders should be closely monitored during administration. If symptoms are persistent and worsening, administration should be delayed or discontinued.
- **Gastrointestinal toxicity**: Nausea, vomiting and loss of appetite are very common adverse reactions to mifamurtide. Gastrointestinal toxicity may be exacerbated when mifamurtide is used in combination with high dose, multi-agent chemotherapy and was associated with an increased use of parenteral nutrition.

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- Mifamurtide is **contraindicated** with concurrent use of:
  - Cyclosporin or other calcineurin inhibitors.
  - High-dose non-steroidal anti-inflammatory drugs (NSAIDs, cyclooxygenase inhibitors).
- The administration of mifamurtide should be separate from the administration times of doxorubicin or other lipophilic medicinal products if used in the same chemotherapy regimen.
- Because mifamurtide acts through stimulation of the immune system, the chronic or routine use of corticosteroids should be avoided during treatment with mifamurtide.

ATC CODE:

Mifamurtide – L03AX15

REFERENCES:

1. Meyers PA, Schwartz CL, Krailo M et al. Osteosarcoma: A Randomized, Prospective Trial of the Addition of Ifosfamide and/or Muramyl Tripeptide to Cisplatin, Doxorubicin and High-Dose Methotrexate. Journal of Clinical Oncology 2005; 23(9): 2004-11.
2. Meyers PA, Schwartz CL, Krailo M et al. Osteosarcoma: The Addition of Muramyl Tripeptide to Chemotherapy Improves Overall Survival – A Report from the Children's Oncology Group. Journal of Clinical Oncology 2008; 26(4): 633-8.
3. Bielack SS. Osteosarcoma: time to move on? Eur J Cancer. 46. England 2010. p. 1942-5.
4. MEPACT ®Summary of Product Characteristics Accessed January 2019 Available at

https://www.medicines.org.uk/emc/product/470/smpc

Version	Date	Amendment	Approved By
1	05/03/2013		Dr Michael Capra Dr Deirdre O'Mahony
2	3/3/2015	Updated Tests section	Dr Maccon Keane
3	1/3/17	Reviewed- Clarified dosing in renal and hepatic impairment	Dr Michael Capra Prof Maccon Keane
4	12/02/2019	Updated to new NCCP regimen template	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/