Mifamurtide Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICID10</th>
<th>Regimen Code</th>
<th>Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td>C41</td>
<td>00100a</td>
<td>ODMS</td>
</tr>
</tbody>
</table>

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/m² body surface area.

It should be administered as adjuvant therapy, in 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.

Please Refer to NCCP regimen 00463 (MAP) Methotrexate (12000mg/m²) DOXOribucin (37.5mg/m²/day) and CISplatin (60mg/m²) Therapy, which is usually used in conjunction with Mifamurtide Therapy.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 4</td>
<td>Mifamurtide</td>
<td>2mg/m²</td>
<td>IV infusion</td>
<td>50ml* 0.9% NaCl over 60 minutes</td>
<td>1-12 inclusive</td>
</tr>
<tr>
<td>1</td>
<td>Mifamurtide</td>
<td>2mg/m²</td>
<td>IV infusion</td>
<td>50ml* 0.9% NaCl over 60 minutes</td>
<td>13-36 inclusive</td>
</tr>
</tbody>
</table>

*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.

Mifamurtide must be reconstituted, filtered using the filter provided in packaging and further diluted using aseptic technique, prior to administration.

Based on the liposomal nature of the product, use of an infusion set with an in-line filter during administration is not recommended.
NCCP Chemotherapy Regimen

ELIGIBILITY:
- 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

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Recommended dose</th>
<th>Hepatic Impairment</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr Cl (ml/min)</td>
<td></td>
<td>Child Pugh Class</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>No dose adjustment necessary</td>
<td>A</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>However, as safety data in patients with moderate hepatic impairment is limited, caution when administering mifamurtide to patients with moderate hepatic impairment is recommended.</td>
</tr>
<tr>
<td>*Severe</td>
<td>No data available</td>
<td>*Severe</td>
<td>No data available</td>
</tr>
<tr>
<td></td>
<td>Exercise caution</td>
<td></td>
<td>Exercise caution</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>1g</td>
<td>PO 60 minutes prior to mifamurtide infusion</td>
</tr>
<tr>
<td>Chlorphenamine</td>
<td>10mg</td>
<td>IV bolus 60 minutes prior to mifamurtide infusion</td>
</tr>
</tbody>
</table>

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.
NCCP Chemotherapy Regimen

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.

REFERENCES:

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>05/03/2013</td>
<td></td>
<td>Dr Michael Capra Dr Deirdre O’Mahony</td>
</tr>
<tr>
<td>2</td>
<td>3/3/2015</td>
<td>Updated Tests section</td>
<td>Dr Maccon Keane</td>
</tr>
<tr>
<td>3</td>
<td>1/3/17</td>
<td>Reviewed- Clarified dosing in renal and hepatic impairment</td>
<td>Dr Michael Capra Prof Maccon Keane</td>
</tr>
<tr>
<td>4</td>
<td>12/02/2019</td>
<td>Updated to new NCCP regimen template</td>
<td>Prof Maccon Keane</td>
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<tr>
<td>5</td>
<td>10/03/2021</td>
<td>Reviewed. Amended treatment table, dose modification in hepatic impairment</td>
<td>Prof Maccon Keane</td>
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</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.