SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mifamurtide 4 mg powder for concentrate for dispersion for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 4 mg mifamurtide*.

After reconstitution, each mL of suspension in the vial contains 0.08 mg mifamurtide.

*fully synthetic analogue of a component of *Mycobacterium sp.* cell wall.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for dispersion for infusion

White to off-white homogeneous cake or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mifamurtide is indicated in children, adolescents and young adults for the treatment of high grade resectable non metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post operative multi agent chemotherapy. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis (see section 5.1).

4.2 Posology and method of administration

Mifamurtide treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of osteosarcoma.

Posology

The recommended dose of mifamurtide for all patients is 2 mg/m^2 body surface area. It should be administered as adjuvant therapy following resection: 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.

Special populations

Adults > 30 years
None of the patients treated in the osteosarcoma studies were 65 years or older and in the phase III randomised study, only patients up to the age of 30 years were included. Therefore, there are not sufficient data to recommend the use of MIFAMURTIDE in patients > 30 years of age.

Renal or hepatic impairment
There are no clinically meaningful effects of mild to moderate renal (creatinine clearance (CrCL) ≥ 30 mL/min) or hepatic impairment (Child-Pugh class A or B) on the pharmacokinetics of mifamurtide; therefore, dose adjustments are not necessary for these patients. However, as the variability in pharmacokinetics of mifamurtide is greater in subjects with moderate hepatic impairment (see section 5.2), and safety data in patients with moderate hepatic impairment is limited, caution when administering mifamurtide to patients with moderate hepatic impairment is recommended.
As no pharmacokinetic data of mifamurtide is available in patients with severe renal or hepatic impairment, caution when administering mifamurtide to these patients is recommended. Continued monitoring of the kidney and liver function is recommended if mifamurtide is used beyond completion of chemotherapy until all therapy is completed.

Paediatric population < 2 years
The safety and efficacy of mifamurtide in children aged 0 to 2 years have not been established. No data are available.

Method of administration

Mifamurtide is administered by intravenous infusion over a period of 1 hour.

Mifamurtide **must not** be administered as a bolus injection.

For further instructions on reconstitution, filtering using the filter provided and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concurrent use with ciclosporin or other calcineurin inhibitors (see section 4.5).

Concurrent use with high-dose non-steroidal-anti-inflammatory drugs (NSAIDs, cyclooxygenase inhibitors) (see section 4.5).

4.4 Special warnings and precautions for use

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. Two patients with pre-existing asthma developed mild to moderate respiratory distress associated with the treatment (see section 4.8). If a severe respiratory reaction occurs, administration of mifamurtide should be discontinued and appropriate treatment initiated.

Neutropenia

Administration of mifamurtide was commonly associated with transient neutropenia, usually when used in conjunction with chemotherapy. 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 administration of mifamurtide should be evaluated for possible sepsis.

Inflammatory response

Association of mifamurtide with signs of pronounced inflammatory response, including pericarditis and pleuritis, was uncommon. It should be used with caution in patients with a history of autoimmune, inflammatory or other collagen diseases. During mifamurtide 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 mifamurtide administration. If symptoms are persistent and worsening, administration should be delayed or discontinued. Haemorrhage was observed in animals at very high doses. These are not expected at the recommended dose, however monitoring of clotting parameters after the first dose and once again after several doses is recommended.

Allergic reactions

Occasional allergic reactions have been associated with mifamurtide treatment, including rash, shortness of breath and grade 4 hypertension (see section 4.8). It may be difficult to distinguish allergic reactions from exaggerated inflammatory responses, but patients should be monitored for signs of allergic reactions.

Gastrointestinal toxicity

Nausea, vomiting and loss of appetite are very common adverse reactions to mifamurtide (see section 4.8). 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.

Mifamurtide contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit.

4.5 Interaction with other medicinal products and other forms of interaction

Limited studies of the interaction of mifamurtide with chemotherapy have been conducted. Although these studies are not conclusive, there is no evidence of interference of mifamurtide with the anti-tumour effects of chemotherapy and vice versa.

It is recommended to separate the administration times of mifamurtide and doxorubicin or other lipophilic medicinal products if used in the same chemotherapy regimen.

The use of mifamurtide concurrently with ciclosporin or other calcineurin inhibitors is contraindicated due to their hypothesised effect on splenic macrophages and mononuclear phagocytic function (see section 4.3).

Also, it has been demonstrated *in vitro* that high-dose NSAIDs (cyclooxygenase inhibitors) can block the macrophage activating effect of liposomal mifamurtide. Therefore, the use of high-dose NSAIDs is contraindicated (see section 4.3).

Because mifamurtide acts through stimulation of the immune system, the chronic or routine use of corticosteroids should be avoided during treatment with mifamurtide.

In vitro interaction studies showed that liposomal and non-liposomal mifamurtide do not inhibit the metabolic activity of cytochrome P450 in pooled human liver microsomes. Liposomal and non-liposomal mifamurtide do not induce the metabolic activity or the transcription of cytochrome P450 in primary cultures of freshly isolated human hepatocytes. Mifamurtide is, therefore, not expected to interact with the metabolism of substances that are hepatic cytochrome P450 substrates.

In a large controlled randomised study, mifamurtide used at the recommended dose and schedule with other medicinal products that have known renal (cisplatin, ifosfamide) or hepatic (high-dose methotrexate, ifosfamide) toxicities did not exacerbate those toxicities and there was no need to adjust mifamurtide dose.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of mifamurtide in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Mifamurtide is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception.

Breast-feeding

It is unknown whether mifamurtide is excreted in human milk. The excretion of mifamurtide in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of mifamurtide therapy to the woman.

Fertility

No dedicated fertility studies have been conducted with mifamurtide (see section 5.3).

4.7 Effects on ability to drive and use machines

Mifamurtide has a moderate influence on the ability to drive and use machines. Dizziness, vertigo, fatigue and blurred vision have shown as very common or common undesirable effects of mifamurtide treatment.

4.8 Undesirable effects

Summary of the safety profile

Mifamurtide was studied as a single agent in 248 patients with mostly advanced malignancies during the early, single arm phase I and II clinical studies. The most frequent adverse reactions are chills, pyrexia, fatigue, nausea, tachycardia and headache. Many of the very commonly reported adverse reactions as shown in the following summary table are thought to be

related to the mechanism of action of mifamurtide (see table 1). The majority of these events were reported as either mild or moderate.

Tabulated list of adverse reactions

Adverse reactions are classified according to system organ class and frequency. Frequency groupings are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

System organ class	**Frequency category**	**Adverse reaction (preferred term)**
Infections and infestations	Common	Sepsis, Cellulitis, Nasopharyngitis, Catheter site infection, Upper respiratory tract infection, Urinary tract infection, Pharyngitis, *Herpes simplex* infection
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Common	Cancer pain
Blood and lymphatic system disorders	Very Common	Anaemia
	Common	Leukopenia, Thrombocytopenia, Granulocytopenia, Febrile neutropenia
Metabolism and nutrition disorders	Very common	Anorexia
	Common	Dehydration, Hypokalaemia, Decreased appetite
Psychiatric disorders	Common	Confusional state, Depression, Insomnia, Anxiety
Nervous system disorders	Very common	Headache, Dizziness
	Common	Paraesthesia, Hypoaesthesia, Tremor, Somnolence, Lethargy
Eye disorders	Common	Blurred vision
Ear and labyrinth disorders	Common	Vertigo, Tinnitus, Hearing loss
Cardiac disorders	Very common	Tachycardia
	Common	Cyanosis, Palpitations
	Not known	Pericardial effusion

System organ class	Frequency category	Adverse reaction (preferred term)
Vascular disorders	Very common	Hypertension, Hypotension
	Common	Phlebitis, Flushing, Pallor
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea, Tachypnoea, Cough
	Common	Pleural effusion, Exacerbated dyspnoea, Productive cough, Haemoptysis, Wheezing, Epistaxis, Exertional dyspnoea, Sinus congestion, Nasal congestion, Pharyngolaryngeal pain
Gastrointestinal disorders	Very common	Vomiting, Diarrhoea, Constipation, Abdominal pain, Nausea
	Common	Upper abdominal pain, Dyspepsia, Abdominal distension, Lower abdominal pain
Hepatobiliary disorders	Common	Hepatic pain
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis
	Common	Rash, Pruritis, Erythema, Alopecia, Dry skin
Musculoskeletal and connective tissue disorders	Very common	Myalgia, Arthralgia, Back pain, Pain in extremity
	Common	Muscle spasms, Neck pain, Groin pain, Bone pain, Shoulder pain, Chest wall pain, Musculoskeletal stiffness
Renal and urinary disorders	Common	Haematuria, Dysuria, Pollakiuria
Reproductive system and breast disorders	Common	Dysmenorrhoea
General disorders and administration site conditions	Very common	Fever, Chills, Fatigue, Hypothermia, Pain, Malaise, Asthenia, Chest pain
	Common	Peripheral oedema, Oedema, Mucosal inflammation, Infusion site erythema, Infusion site reaction, Catheter site pain, Chest discomfort, Feeling cold
Investigations	Common	Weight decreased

System organ class	Frequency category	Adverse reaction (preferred term)
Surgical and medical procedures	Common	Post-procedural pain

Description of selected adverse reactions

Blood and lymphatic system disorders
Anaemia has very commonly been reported when mifamurtide is used in conjunction with chemotherapeutic agents. In a randomised controlled study, the incidence of myeloid malignancy (acute myeloid leukaemia/myelodysplastic syndrome) was the same in patients receiving Mifamurtide plus chemotherapy as in patients receiving only chemotherapy (2.1%).

Metabolism and nutritional disorders
Anorexia (21%) was very commonly reported in phase I and II studies of mifamurtide

Nervous system disorders
Consistent with other generalised symptoms, the very common nervous system disorders were headache (50%) and dizziness (17%). One patient in the phase III study experienced 2 episodes of grade 4 seizure while on study therapy with chemotherapy and mifamurtide. The second episode involved multiple grand mal seizures over the course of days. Mifamurtide treatment was continued for the remainder of the study without seizure recurrence.

Ear and labyrinth disorders
Although hearing loss may be attributable to ototoxic chemotherapy, like cisplatin, it is unclear whether Mifamurtide in conjunction with multi-agent chemotherapy may increase hearing loss.
A higher percentage of objective and subjective hearing loss was observed overall in patients who received Mifamurtide and chemotherapy (12% and 4%, respectively) in the phase III study (see section 5.1 for a description of the study) compared to those patients that received only chemotherapy (7% and 1%). All patients received a total dose of cisplatin of 480 mg/m^2 as part of their induction (neoadjuvant) and/or maintenance (adjuvant) chemotherapy regimen.

Cardiac and vascular disorders
Mild-moderate tachycardia (50%), hypertension (26%) and hypotension (29%) were very commonly reported in uncontrolled studies of mifamurtide. One serious incident of subacute thrombosis was reported in early studies, but no serious cardiac events were associated with mifamurtide in a large randomised controlled study (see section 4.4).

Respiratory disorders
Respiratory disorders, including dyspnoea (21%), cough (18%) and tachypnoea (13%) were very commonly reported, and 2 patients with pre-existing asthma developed mild to moderate respiratory distress associated with Mifamurtide treatment in a phase II study.

Gastrointestinal disorders
Gastrointestinal disorders were frequently associated with mifamurtide administration, including nausea (57%) and vomiting (44%) in about half of patients, constipation (17%), diarrhoea (13%) and abdominal pain (see section 4.4).

Skin and subcutaneous disorders
Hyperhidrosis (11%) was very common in patients receiving mifamurtide in uncontrolled studies.

Musculoskeletal and connective tissue disorders
Low grade pain was very common in patients receiving mifamurtide, including myalgia (31%), back pain (15%), extremity pain (12%) and arthralgia (10%).

General disorders and administration site conditions
The majority of patients experience chills (89%), fever (85%) and fatigue (53%). These are typically mild to moderate, transient in nature and generally respond to palliative treatment (e.g., paracetamol for fever). Other generalised symptoms that were typically mild to moderate and very common included hypothermia (23%), malaise (13%), pain (15%), asthenia (13%) and chest pain (11%). Oedema, chest discomfort, local infusion or catheter site reactions and 'feeling cold' were less frequently reported in these patients, mostly with late stage malignant disease.

Investigations
An osteosarcoma patient in a phase II study who had high creatinine level at enrolment showed an increase in blood urea and blood creatinine which was associated with mifamurtide use.

Immune system disorders
In a phase I study, there was one report of severe allergic reaction occurring after the first infusion of mifamurtide at 6 mg/m^2 dose level. The patient experienced shaking, chills, fever, nausea, vomiting, uncontrollable coughing, shortness of breath, cyanotic lips, dizziness, weakness, hypotension, tachycardia, hypertension and hypothermia leading to study discontinuation. There was also one report of a grade 4 allergic reaction (hypertension) requiring hospitalization in the phase III study (see section 4.4).

<u>Reporting of suspected adverse reactions</u>
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any

suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The maximum tolerated dose in phase I studies was 4-6 mg/m^2 with a high variability of adverse reactions. Signs and symptoms that were associated with higher doses and/or were dose limiting were not life-threatening, and included fever, chills, fatigue, nausea, vomiting, headache and hypo- or hypertension.

A healthy adult volunteer accidentally received a single dose of 6.96 mg mifamurtide and experienced a reversible treatment-related event of orthostatic hypotension.

In the event of an overdose, it is recommended that appropriate supportive treatment be initiated. Supportive measures should be based on institutional guidelines and the clinical symptoms observed. Examples include paracetamol for fever, chills and headache and anti-emetics (other than steroids) for nausea and vomiting.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Other immunostimulants, ATC code: L03AX15

Mechanism of action

Mifamurtide (muramyl tripeptide phosphatidyl ethanolamine, MTP-PE) is a fully synthetic derivative of muramyl dipeptide (MDP), the smallest naturally-occurring immune stimulatory component of cell walls from *Mycobacterium sp*. It has similar immunostimulatory effects as natural MDP. Mifamurtide is a liposomal formulation specifically designed for *in vivo* targeting to macrophages by intravenous infusion.

MTP-PE is a specific ligand of NOD2, a receptor found primarily on monocytes, dendritic cells and macrophages. MTP-PE is a potent activator of monocytes and macrophages. Activation of human macrophages by mifamurtide is associated with production of cytokines, including tumour necrosis factor (TNF-α), interleukin-1 (IL-1β), IL-6, IL-8, and IL-12 and adhesion molecules, including lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1). *In vitro*-treated human monocytes killed allogeneic and autologous tumour cells (including melanoma, ovarian, colon, and renal carcinoma), but had no toxicity towards normal cells.

In vivo administration of mifamurtide resulted in the inhibition of tumour growth in mouse and rat models of lung metastasis, skin and liver cancer, and fibrosarcoma. Significant enhancement of disease-free survival was

also demonstrated in the treatment of dog osteosarcoma and hemangiosarcoma with mifamurtide as adjuvant therapy. The exact mechanism by which mifamurtide activation of monocytes and macrophages leads to anti-tumour activity in animals and humans is not yet known.

Clinical safety and efficacy

The safety of liposomal mifamurtide has been assessed in more than 700 patients with various kinds and stages of cancer and in 21 healthy adult subjects (see section 4.8).

In a randomised phase III study of 678 patients (age range from 1.4 to 30.6 years) with newly-diagnosed resectable high-grade osteosarcoma, the addition of adjuvant mifamurtide to chemotherapy (either doxorubicin cisplatin and methotrexate with or without ifosfamide), significantly increased the 6-year overall survival and resulted in a relative reduction in the risk of death by 28% ($p = 0.0313$, hazard ratio (HR) = 0.72 [95% confidence interval (CI): 0.53, 0. 97]).

Paediatric population

Based on the prevalence of the disease, children and young adults were studied in the pivotal trial. However, no specific subset analyses for efficacy are available in patients < 18 years of age and ≥ 18 years of age.

5.2 Pharmacokinetic properties

The pharmacokinetics of mifamurtide have been characterised in healthy adult subjects following a 4 mg intravenous infusion and in paediatric and adult patients with osteosarcoma following a 2 mg/m^2 intravenous infusion.

In 21 healthy adult subjects mifamurtide was cleared rapidly from serum (minutes) with a half-life of 2.05 ± 0.40 hours, resulting in a very low serum concentration of total (liposomal and free) mifamurtide. The mean area under the curve (AUC) was 17.0 ± 4.86 h x nM and C_{max} (maximum concentration) was 15.7 ± 3.72 nM.

In 28 osteosarcoma patients aged 6 to 39 years serum total (liposomal and free) mifamurtide concentrations declined rapidly with a mean half-life of 2.04 ± 0.456 hours. BSA-normalised clearance and half-life were similar across the age range and consistent with that determined in healthy adult subjects, supporting the recommended dose of 2 mg/m^2.

In a separate study in 14 patients, mean serum concentration-time curves of total and free mifamurtide that were assessed after the first infusion of mifamurtide and after a last infusion 11 or 12 weeks later, were almost superimposable and the mean AUC values of the free mifamurtide after the first and last infusion were similar. These data

indicate that neither total nor free mifamurtide accumulated during the treatment period.

At 6 hours after injection of radiolabelled liposomes containing 1 mg mifamurtide, radioactivity was found in liver, spleen, nasopharynx, thyroid, and, to a lesser extent, in lung. The liposomes were phagocytosed by cells of the reticuloendothelial system. In 2 of 4 patients with lung metastases, radioactivity was associated with lung metastases.

Metabolism of liposomal MTP-PE has not been studied in humans.

After injection of radiolabelled liposomes containing mifamurtide, mean half-life of radiolabelled material was biphasic with an α-phase of about 15 minutes and a terminal half-life of approximately 18 hours.

Special populations

Renal impairment

The pharmacokinetics of a single 4 mg dose of mifamurtide following a 1 hour intravenous infusion were evaluated in adult volunteers with mild (n = 9) or moderate (n = 8) renal impairment and in age-, sex-, and weight-matched healthy adults with normal renal function (n = 16). There was no effect of mild (50 mL/min ≤ creatinine clearance [CLcr] ≤ 80 mL/min) or moderate (30 mL/min ≤ CLcr < 50 mL/min) renal insufficiency on the clearance of total MTP-PE, when compared with that observed in healthy adult subjects with normal renal function (CLcr > 80 mL/min). Additionally, the systemic exposures AUC from zero to infinity (AUC_{inf} of free (non-liposome associated) MTP-PE in mild or moderate renal insufficiency were similar to those observed in healthy adult subjects with normal renal function.

Hepatic impairment

The pharmacokinetics of a single 4 mg dose of mifamurtide following a 1 hour intravenous infusion were evaluated in adult volunteers with mild (Child-Pugh class A; n = 9) or moderate (Child-Pugh class B; n = 8) hepatic impairment and in age, sex-, and weight-matched healthy adults with normal hepatic function (n = 19). There was no effect of mild hepatic impairment on the systemic exposure (AUC_{inf}) of total MTP-PE. Moderate hepatic impairment resulted in a small increase in AUC_{inf} of total MTP-PE, with the geometric least square mean ratio (expressed as %) for moderate hepatic impairment in reference to the matched normal hepatic function group being 119% (90% confidence interval [CI]: 94.1%-151%). Pharmacokinetic variability was higher in the moderate hepatic impairment group (co-efficient of variation in systemic exposure [AUC_{inf}] was 50% versus < 30% in the other hepatic function groups).

Mean half-lives of total and free MTP-PE in mild hepatic impairment were 2.02 hours and 1.99 hours, respectively, and were comparable to those in subjects with normal hepatic function (2.15 hours and 2.26 hours, respectively). Mean half-lives of total and free MTP-PE in moderate hepatic impairment were 3.21 hours and 3.15 hours, respectively. Additionally, the geometric mean plasma AUC_{inf} of free (non-liposome

associated) MTP-PE in mild and moderate hepatic impairment were 47% higher than the corresponding values in the matched normal hepatic function groups. These changes were not considered to be clinically meaningful as the maximum tolerated dose (4-6 mg/m^2) of mifamurtide is 2-3 times the recommended dose (2 mg/m^2).

5.3 Preclinical safety data

In sensitive species (rabbit and dog) the highest daily dose of liposomal mifamurtide that did not cause adverse effects was 0.1 mg/kg, corresponding to 1.2 and 2 mg/m^2, respectively. The no-adverse-effect level for mifamurtide in animals corresponds roughly to the 2 mg/m^2 recommend dose for humans.

Data from a six-month dog study of daily intravenous injections of up to 0.5 mg/kg (10 mg/m^2) mifamurtide provide an 8- to 19-fold cumulative exposure safety margin for overt toxicity for the intended clinical dose in humans. Major toxic effects associated with these high daily and cumulative doses of mifamurtide were mainly exaggerated pharmacological effects: pyrexia, signs of pronounced inflammatory response manifested as synovitis, bronchopneumonia, pericarditis and inflammatory necrosis of the liver and bone marrow. The following events were also observed: haemorrhage and prolongation of coagulation times, infarcts, morphological changes in the wall of small arteries, oedema and congestion of the central nervous system, minor cardiac effects, and slight hyponatraemia. Mifamurtide was not mutagenic and did not cause teratogenic effects in rats and rabbits. Embryotoxic effects were observed only at maternal toxic levels.

There were no results from general toxicity studies that suggested harmful effects on male or female reproductive organs. Specific studies addressing reproductive function, perinatal toxicity and carcinogenic potential have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC)

1,2-Dioleoyl-sn-glycero-3-phospho-L-serine monosodium salt (OOPS)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial of powder

3 years

Reconstituted suspension

Chemical and physical stability has been demonstrated for 6 hours up to 25 ºC.

From a microbiological point of view, immediate use is recommended.

If not used immediately, the reconstituted, filtered and diluted solution in-use storage times and conditions prior to use of the reconstituted product must not be longer than 6 hours at 25 ºC.

Do not refrigerate or freeze the solution.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C). Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 mL type I glass vial with a grey butyl rubber stopper, aluminium seal and plastic flip-off cap, containing 4 mg of mifamurtide.

Each carton contains 1 vial and 1 single-use, non-pyrogenic, sterile filter for Mifamurtide supplied in a PVC-grade blister.

6.6 Special precautions for disposal

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

Each vial should be reconstituted with 50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. After reconstitution, each mL suspension in the vial contains 0.08 mg mifamurtide. The volume of reconstituted suspension corresponding to the calculated dose is extracted through the filter provided and further diluted with additional 50 mL sodium chloride 9 mg/mL (0.9%) solution for injection according to the detailed instructions shown below.

The reconstituted, filtered and diluted suspension for infusion is a homogenous, white to off-white, opaque liposomal suspension, free of visible particles and free of foam and lipid lumps.

Instructions for preparation of Mifamurtide for intravenous infusion

Materials provided in each package:

- Mifamurtide powder for concentrate for dispersion for infusion (vial)
- Filter for Mifamurtide

Materials required but not provided:

- Sodium chloride 9 mg/mL (0.9%) solution for injection, 100 mL bag
- 1 single use 60 or 100 mL sterile syringe with luer lock
- 2 medium (18) gauge sterile injection needles

It is recommended that the reconstitution of the liposomal suspension should be performed in a laminar flow cabinet utilising sterile gloves using aseptic technique.

The lyophilised powder should be allowed to reach a temperature between approximately 20 °C-25 °C prior to reconstitution, filtering using the filter provided and dilution. This should take approximately 30 minutes.

1. The cap of the vial should be removed and the stopper cleaned using an alcohol pad.
2. The filter should be removed from the blister pack, and the cap removed from the filter spike. The spike should then be inserted into the vial septum firmly until seated. The filter luer connector cap should not be removed at this time.
3. The 100 mL sodium chloride 9 mg/mL (0.9%) solution for injection bag, needle and syringe should be unpacked (not provided in the pack).
4. The site of the sodium chloride 9 mg/mL (0.9%) solution for injection bag where the needle is going to be inserted should be swabbed with an alcohol pad.
5. Using the needle and syringe, 50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection should be withdrawn from the bag.
6. After removing the needle from the syringe, the syringe should be attached to the filter by opening the filter luer connector cap (figure 1).

Figure 1

7. The sodium chloride 9 mg/mL (0.9%) solution for injection is added to the vial by slow, firm depression of the syringe plunger. **The filter and syringe must not be removed from the vial**.
8. The vial should be allowed to stand undisturbed for 1 minute to ensure thorough hydration of the dry substance.
9. **The vial should then be shaken vigorously for 1 minute while keeping the filter and syringe attached**. During this time the liposomes are formed spontaneously (figure 2).

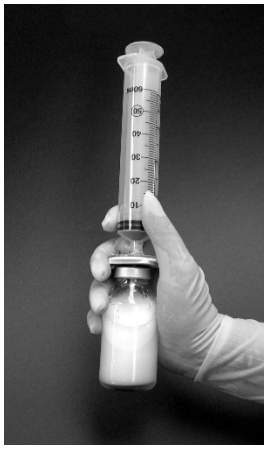

Figure 2

10. The desired dose may be withdrawn from the vial by inverting the vial and slowly pulling back on the syringe plunger (figure 3). Each mL reconstituted suspension contains 0.08 mg mifamurtide. The volume of suspension to be withdrawn for dose quantities is calculated as follows:

    Volume to withdraw = [12.5 x calculated dose (mg)] mL

    For convenience, the following table of concordance is provided:

Dose	**Volume**

1.0 mg	12.5 mL
2.0 mg	25 mL
3.0 mg	37.5 mL
4.0 mg	50 mL

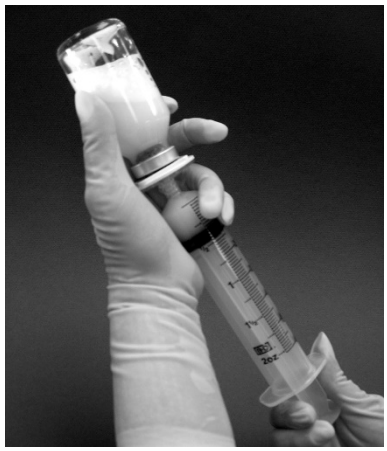

Figure 3

11. The syringe should then be removed from the filter and a new needle placed on the suspension-filled syringe. The bag injection site should be wiped with an alcohol pad and the suspension in the syringe should be injected into the original bag containing the remaining 50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection (figure 4).

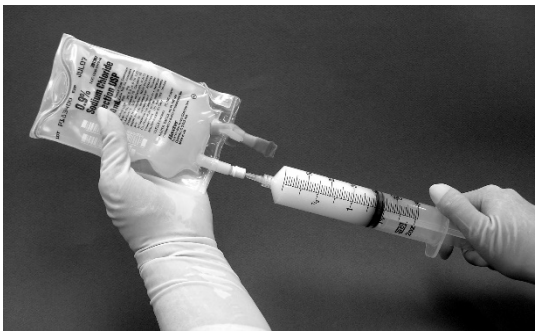

Figure 4

12. The bag should be gently swirled to mix the solution.
13. Patient identification, time and date should be added to the label on the bag containing the reconstituted, filtered and diluted liposomal suspension.
14. Chemical and physical in-use stability has been demonstrated for 6 hours at room temperature (between approximately 20 °C-25 °C).
15. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at room temperature.

16. Based on the liposomal nature of the product, use of an infusion set with an in-line filter during administration is not recommended.
17. The liposomal suspension is infused intravenously over about 1 hour.

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Takeda France SAS

Immeuble Pacific

11-13 Cours Valmy

92800 - Puteaux

France

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 44272/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

26/07/2024