ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MEPACT 4 mg powder for concentrate for dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 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

MEPACT 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.

<u>Posology</u>

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.

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

After reconstitution, filtering using the filter provided and further dilution, MEPACT is administered by intravenous infusion over a period of 1 hour.

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

For further instructions on reconstitution, filtering using the filter provided and dilution prior to 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.

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

No studies of the effects on the ability to drive and use machines have been performed. The very common or common undesirable effects of mifamurtide treatment (such as dizziness, vertigo, fatigue and blurred vision) may have an effect on the ability to drive and use machines.

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, occurring in >50% of patients, were chills, pyrexia, fatigue, nausea, tachychardia 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. This profile is consistent whether summarising all early studies (n=248) or only those studies in osteosarcoma (n=51). It is likely that these adverse reactions also occurred in the large randomised study, but they were not recorded because only serious and life-threatening adverse reactions were collected in that study.

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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions associated with MEPACT in ≥ 1/100 patients

System Organ Class	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
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
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 MEPACT 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 MEPACT 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 MEPACT 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 two patients with pre-existing asthma developed mild to moderate respiratory distress associated with MEPACT 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).

Reporting of suspected adverse reactions
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 national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported within the approved indication. 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 with the additional advantage of a longer half-life in plasma. MEPACT 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 antitumour 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).

Mifamurtide significantly increased the overall survival of patients with newly-diagnosed resectable high-grade osteosarcoma when used in conjunction with combination chemotherapy when compared to chemotherapy alone. 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, resulted in a relative reduction in the risk of death of 28% (p = 0.0313, hazard ratio (HR) = 0.72 [95% confidence interval (CI): 0.53, 0. 97]).

5.2 Pharmacokinetic properties

The pharmacokinetics of mifamurtide have been characterized 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 AUC was 17.0 ± 4.86 h x nM and Cmax 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-normalized 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 4mg 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 ≤ 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 (AUCinf) 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 (AUCinf) of total MTP-PE. Moderate hepatic impairment resulted in a small increase in AUCinf 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% CI: 94.1%-151%). Pharmacokinetic variability was higher in the moderate hepatic impairment group (co-efficient of variation in systemic exposure [AUCinf] 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 AUCinf 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*:* 30 months

Reconstituted suspension*:* Chemical and physical stability has been demonstrated for 6 hours up to 25ºC.

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 are the responsibility of the user and must not be longer than 6 hours at 25ºC. 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 of the reconstituted 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 one vial and one single-use, non-pyrogenic, sterile filter for MEPACT supplied in a PVC-grade blister.

6.6 Special precautions for disposal and other handling

MEPACT must be reconstituted, filtered using the filter provided and further diluted using aseptic technique.

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.

Instructions for preparation of MEPACT for intravenous infusion

Materials provided in each package -
- MEPACT powder for concentrate for dispersion for infusion (vial)
- Filter for MEPACT

Materials required but not provided -
- Sodium chloride 9 mg/ml (0.9%) solution for injection, 100 ml bag
- One single use 60 or 100 ml sterile syringe with luer lock
- Two 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 one minute to ensure thorough hydration of the dry substance.
9. **The vial should then be shaken vigorously for one 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. The liposomal suspension is infused intravenously over about one hour.

Disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda France SAS
Immeuble Pacific
11-13 Cours Valmy
92800 - Puteaux
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/502/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 March 2009
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Takeda Austria GmbH
St. Peter-Straβe 25
A-4020 Linz
Austria

Takeda Italia S.p.A
Via Crosa, 86
28065 Cerano (NO)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP .

An updated RMP should be submitted:
• At the request of the European Medicines Agency;
• Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

MEPACT 4 mg powder for concentrate for dispersion for infusion
Mifamurtide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 4 mg of mifamurtide. After reconstitution, each ml of reconstituted suspension in the vial contains 0.08 mg of mifamurtide.

3. LIST OF EXCIPIENTS

Excipients: Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC),
1,2-Dioleoyl-sn-glycero-3-phospho-L-serine monosodium salt (OOPS)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for dispersion for infusion
Pack of 1 vial of powder, 1 sterile Filter for MEPACT

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous use after reconstitution, filtering using the filter provided and further dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda France SAS
Immeuble Pacific
11-13 Cours Valmy
92800 - Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/502/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

MEPACT 4 mg powder for concentrate for dispersion for infusion
Mifamurtide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 4 mg of mifamurtide. After reconstitution, each ml of reconstituted suspension in the vial contains 0.08 mg of mifamurtide.

3. LIST OF EXCIPIENTS

Excipients: Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC),
1,2-Dioleoyl-sn-glycero-3-phospho-L-serine monosodium salt (OOPS)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for dispersion for infusion
4 mg mifamurtide

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous use after reconstitution, filtering using the filter provided and further dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda France SAS
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/502/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

MEPACT 4 mg powder for concentrate for dispersion for infusion
Mifamurtide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What MEPACT is and what it is used for
2. What you need to know before you use MEPACT
3. How to use MEPACT
4. Possible side effects
5. How to store MEPACT
6. Contents of the pack and other information

1. What MEPACT is and what it is used for

MEPACT contains the active substance mifamurtide, similar to a component of the cell wall of certain bacteria. It stimulates your immune system to help your body kill tumour cells.

MEPACT is used to treat osteosarcoma (bone cancer) in children, adolescents and young adults (between 2 and 30 years). It is used after you have had surgery to remove the tumour and together with chemotherapy to kill remaining cancer cells to reduce the risk of cancer coming back.

2. What you need to know before you use MEPACT

Do not use MEPACT:
- if you are allergic to mifamurtide or any of the other ingredients of this medicine (listed in section 6).
- if you are taking medicines containing ciclosporin or tacrolimus or high doses of non-steroidal-anti-inflammatory drugs (NSAIDs) (see “Using other medicines” below).

Warnings and precautions
Talk to your doctor before using MEPACT:
- if you have or have had problems with your heart or blood vessels, like blood clots (thrombosis), bleeding (haemorrhage) or inflammation of the veins (vasculitis). You should be more closely monitored while receiving MEPACT treatment. If you have long-lasting or worsening symptoms, you should contact your doctor, as MEPACT treatment may need to be delayed or discontinued.
- if you have a history of asthma or other breathing disorders. Before using MEPACT, you should discuss with your doctor whether you should take medicine for your asthma when using MEPACT.
- if you have a history of inflammatory or autoimmune disease or have been treated with corticosteroids or other medicines that may affect your immune system.
- if you have any allergic reactions to any medicines such as rash, breathlessness and high blood pressure. If you have worsening symptoms, you should contact your doctor, as these may have been caused by MEPACT.
- if you have stomach problems such as nausea, vomiting and lack of appetite. If your problems increase, you should contact your doctor, as these may have been caused by MEPACT when used with chemotherapy.

- if you develop chills or shivering, or feel warm. You should take your temperature as you may have a fever. A fever with a low white blood cell count (neutropenia) may be a sign of serious infection.

Detailed information on warnings and precautions relating to side effects that could occur while you are taking the medicine is presented in section 4.

Children and adolescents
It is not recommended to give this medicine to children below the age of 2 years because information on how safe and how well this medicine works is not available for this age group.

Other medicines and MEPACT
Please tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines that may be obtained without a prescription. It is especially important to tell your doctor if you are taking medicines containing any of the following active substances:

- ciclosporin, tacrolimus, used after a transplant to prevent rejection of transplanted organs, or other immunosuppressants used e.g. to treat psoriasis (a skin disease).
- non-steroidal-anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid, ibuprofen, or diclofenac, used for treatment of headaches, fever or pain. You must not use MEPACT with high doses of NSAIDs.
- corticosteroids, used to treat inflammations, allergies or asthma. Regular use of corticosteroids should be avoided when using MEPACT as this may affect the way the medicine works.

It is recommended to separate the times of administration of MEPACT and doxorubicin or other medicines if used in the same chemotherapy treatment regimen.

Pregnancy, breast-feeding and fertility
MEPACT has not been tested in pregnant women. Therefore, MEPACT should not be used during pregnancy and in women not using effective contraception. You should use effective contraception if you are being treated with MEPACT. It is important to tell your doctor if you are pregnant, think you may be pregnant, or are planning to get pregnant.

It is not known whether MEPACT passes to human milk. If you are breast-feeding, you should discuss with your doctor.

Driving and using machines
Some very common and common side effects of MEPACT treatment (such as dizziness, vertigo, fatigue and blurred vision) may affect your ability to drive and use machines.

3. How to use MEPACT

Dose and duration of treatment
MEPACT will be administered only under the supervision of a specialist physician. Always use this medicine exactly as the doctor has told you. Check with the doctor if you are not sure.

The dose of MEPACT is 2 mg mifamurtide/m^2 body surface area. It will be given to you twice a week (at least three days apart) for the first 12 weeks, then once a week for 24 more weeks.

The schedule of your MEPACT treatments can be adjusted to fit with your chemotherapy schedule. It is not necessary to interrupt your schedule of MEPACT if your chemotherapy is delayed; you should complete 36 weeks (9 months) of treatment with MEPACT without an interruption.

How MEPACT is given
The freeze-dried powder has to be reconstituted into a liquid suspension, filtered using the filter provided and further diluted before use. MEPACT is then infused directly into your vein (intravenous) over about one hour. This is done by your doctor or a nurse, who will also monitor you during that time. You do not need to be hospitalised to receive MEPACT. It can also be administered as an outpatient.

If you use more MEPACT than you should
You may experience more severe side effects, including fever, chills, fatigue, nausea, vomiting, headache and hypo- or hypertension. In the event of such an overdose, contact your doctor or nearest hospital.

If you stop using MEPACT
You should not stop treatment with MEPACT before finishing the course of treatment without discussing with your doctor first. If you have any other questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, MEPACT can cause side effects, although not everybody gets them.

The majority of patients experience chills, fever and fatigue especially during the first administration of MEPACT. These are typically mild to moderate and transient and can usually be treated by your doctor, e.g. with paracetamol for fever.
Treatment with MEPACT can often cause stomach problems such as nausea, vomiting and loss of appetite when used with chemotherapy.

Contact your doctor **immediately**:
- if you have continuing fever or chills more than 8 hours after your dose of MEPACT, because this may be a sign of an infection or
- if you experience rash or have any problems breathing (wheezing) or
- if you experience any stomach problems.

<u>Very common side effects (may affect more than 1 in 10 people):</u>
- fever, shaking/shivering, weakness, tiredness or general discomfort
- nausea and/or vomiting, diarrhoea or constipation
- headache or dizziness
- rapid beating of the heart
- high blood pressure or low blood pressure
- no appetite for food
- sweating
- pain, including general pain, pain in your muscles and/or joints and pain in back, chest, abdomen, arm or leg
- cough, trouble breathing or rapid breathing
- low body temperature
- low number of red blood cells

<u>Common side effects (may affect up to 1 in 10 people):</u>
- blue colour of tissues such as the skin or gums caused by too little oxygen
- perceptible increase in frequency or force of heartbeat
- swelling in arms or legs or other swelling
- chest discomfort
- upset stomach, decreased appetite or weight loss
- injection site or catheter site redness, swelling, infection or other local reaction
- rash or redness, inflammation of the skin, itching, dry skin, pale or transient red appearance
- inflammation of skin, tendons, muscles or similar tissues that support body structure

- inflammation of a vein
- upper abdominal or chest wall pain; abdominal bloating or pain
- other pain, including neck, shoulder or throat pain
- muscle spasms or stiffness
- feeling cold
- tired feeling, drowsiness or sleepiness
- burning, pricking/tingling sensation or diminished sensitivity to sensation
- involuntary shaking movement
- dehydration
- mucosal inflammation
- nose, throat, or sinus congestion or inflammation
- infections of the upper respiratory tract (such as a cold) or the urinary tract (such as a bladder infection)
- generalised infection
- *Herpes simplex* (virus) infection
- productive cough, wheezing or exertional or exacerbated shortness of breath
- spitting of blood or nosebleed
- fluid in the lung cavity
- blood in urine, difficulty or pain in urination or frequent urination
- difficulty sleeping, depression, anxiety or confusion
- dizziness
- ears ringing
- blurred vision
- hair loss
- difficult, painful menstruation
- hearing loss
- low number of white blood cells with or without fever, low number of platelets

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store MEPACT

Keep out of the sight and reach of children.

Do not use MEPACT after the expiry date which is stated on the vial label and the carton.

Unopened vial
Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial in outer carton in order to protect from light.

Reconstituted suspension
Once reconstituted in sodium chloride 9 mg/ml (0.9%) solution, store at room temperature (approximately 20ºC - 25ºC) and use within 6 hours.

6. Contents of the pack and other information

What MEPACT contains
- The active substance is mifamurtide. Each vial contains 4 mg of mifurtamide. After reconstitution, each ml of suspension contains 0.08 mg of mifamurtide.
- The other ingredients are 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) and 1,2-Dioleoyl-sn-glycero-3-phospho-L-serine monosodium salt (OOPS).

What MEPACT looks like and contents of the pack
MEPACT is a white to off-white homogeneous cake or powder for concentrate for dispersion for infusion.

MEPACT is supplied in a carton that contains
- One 50 ml vial with a grey butyl stopper, aluminium seal and plastic flip-off cap.
- One latex-free, sterile filter for MEPACT supplied in a blister.

Marketing Authorisation Holder
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Immeuble Pacific
11-13 Cours Valmy
92800 - Puteaux
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Manufacturer
Takeda Austria GmbH
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Austria

Takeda Italia S.p.A
Via Crosa, 86
28065 Cerano (NO)
Italy

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency (EMA) website: http://www.ema.europa.eu/

The following information is intended for medical or healthcare professionals only:

Instructions for preparation of MEPACT for intravenous infusion

Materials provided in each package -
- 1 vial of MEPACT (mifamurtide)
- 1 Filter for MEPACT

Materials required but not provided -
- Sodium chloride 9 mg/ml (0.9%) solution for injection, 100 ml bag
- One single use 60 or 100 ml sterile syringe with luer lock
- Two 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 one minute to ensure thorough hydration of the dry substance.
9. **The vial should then be shaken vigorously for one 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.

Disposal
No special requirements.