ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pepaxti 20 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 20 mg melphalan flufenamide (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).
Lyophilised white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy.
For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation (see section 4.4).

4.2 Posology and method of administration

Treatment with Pepaxti must be initiated and supervised by physicians experienced in the treatment of multiple myeloma.

Posology

The recommended starting dose of Pepaxti is 40 mg on Day 1 of each 28-day treatment cycle. For patients with a body weight of 60 kg or less the recommended starting dose is 30 mg on Day 1 of each 28-day cycle. It is recommended that treatment should be continued until disease progression or unacceptable toxicity (see section 5.1).

The recommended dose of dexamethasone is 40 mg orally on Days 1, 8, 15 and 22 of each 28-day treatment cycle. For patients 75 years of age and older the recommended dose of dexamethasone is 20 mg. For additional information regarding administration of dexamethasone, see section 5.1 and the corresponding Summary of Product Characteristics.

Dose modification for adverse reactions
Pepaxti must be withheld if the neutrophil count is less than 1×10^9/L or the platelet count is less than 50×10^9/L.

The recommended dose reduction and dosage modifications for adverse reactions of Pepaxti are presented in Table 1 and Table 2, respectively.

Table 1: Recommended dose reduction for adverse reactions of Pepaxti

Dose reduction	Dose* in patients with body weight greater than 60 kg	Dose* in patients with body weight of 60 kg or less
	40 mg	30 mg
First	30 mg	20 mg
Second	20 mg	15 mg
Third	15 mg	Permanently discontinue Pepaxti in patients who are unable to tolerate 15 mg
Subsequent	Permanently discontinue Pepaxti in patients who are unable to tolerate 15 mg	-

*Administered intravenously on Day 1 of each 28-day cycle. For dose modifications, see Table 2

Table 2: Recommended dose modifications for adverse reactions of Pepaxti (Grading of adverse reaction according to CTCAE v 5.0)

Adverse reaction	Severity	Dose modification
Haematologic adverse reaction *(see section 4.4)*	Platelet count less than 50×10^9/L on an intended Pepaxti dosing day	• Withhold Pepaxti and monitor platelet count weekly until platelet count is 50×10^9/L or greater. • Resume Pepaxti at 1 dose level lower.
	Absolute neutrophil count less than 1×10^9/L on an intended Pepaxti dosing day	• Withhold Pepaxti and monitor neutrophil count weekly until neutrophil count is 1×10^9/L or greater. • Resume Pepaxti at 1 dose level lower.
Non-haematologic adverse reaction *(see section 4.8)*	Grade 2	• Consider withholding Pepaxti until resolved to at least Grade 1 or baseline. • Consider resuming Pepaxti at 1 dose level lower.
	Grade 3 or 4	• Withhold Pepaxti until resolved to at least Grade 1 or baseline. • Consider resuming Pepaxti at 1 dose level lower.

Recommended concomitant medicinal products
Consideration should be taken if prophylactic concomitant treatment with antimicrobials should be administered to reduce the risk of infections (see section 4.8).
Anti-emetic agents should be administered prior to and during the treatment with Pepaxti at the discretion of the physician and in accordance with local practice (see section 4.4).

Special populations

Elderly
No dose adjustment is recommended for elderly patients.

Renal impairment
No dose adjustment of Pepaxti is required in patients with estimated glomerular filtration rate (eGFR) above 45 mL/min/1.73 m^2. A dose of 30 mg is recommended in patients with eGFR 30-45 mL/min/1.73 m^2. There are insufficient data in patients with eGFR below 30 mL/min/1.73 m^2 to support a dose recommendation (see section 4.4 and 5.2).

Hepatic impairment
No dose adjustment of Pepaxti is required for patients with mild hepatic impairment (see section 5.2). There are insufficient data in patients with moderate or severe hepatic impairment to support a dose recommendation.

Paediatric population
The safety and efficacy of Pepaxti in children below 18 years of age have not been established. No data are available.

Method of administration

Pepaxti is for intravenous use.
Pepaxti should be administered as a 30-minute infusion via a peripheral venous route or a central venous access device, such as a peripherally inserted central catheter (PICC) or a tunnelled central venous catheter. If administered peripherally, it is recommended to alternate veins for infusion. In case of extravasation, the administration should be interrupted immediately and a central venous line should be used.

Pepaxti must be reconstituted and diluted by a healthcare professional prior to administration. Infusion of the diluted solution must begin within 60 minutes of start of initial reconstitution or be placed in a refrigerator within 30 minutes from start of initial reconstitution.
For instructions on reconstitution 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.
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Melphalan flufenamide can cause local tissue damage. Should extravasation occur, it should not be administered by direct infusion into a peripheral vein (see section 4.2).

Thrombocytopenia

Pepaxti may cause thrombocytopenia. Thrombocytopenia (including platelet count decreased) was frequently reported in clinical studies (see section 4.8). As thrombocytopenia may increase the risk for serious bleeding events, patients should be advised to contact a physician if signs or symptoms of bleeding and bruising occur.

Platelet counts should be monitored at baseline, during treatment, and as clinically indicated. Patients should be monitored more frequently during the first two months of treatment. Pepaxti should not be administered if the platelet count is less than 50×10^9/L. Treatment should be withheld until platelet count is 50×10^9/L or greater (without recent transfusions) and resume treatment at one dose level lower. The dose and/or dose schedule should be adjusted based on signs and symptoms of bleeding (see section 4.2). Treating thrombocytopenia with transfusions and/or other treatments should be considered as clinically indicated.

Neutropenia

Pepaxti may cause neutropenia. Neutropenia (including neutrophil count decreased) was frequently reported in clinical studies (see section 4.8). As neutropenia may increase the risk for infections, patients should be advised to contact a physician if signs or symptoms of infection occur.

Neutrophil count should be monitored at baseline, during treatment, and as clinically indicated. Patients should be monitored more frequently during the first two months of treatment. Pepaxti should not be administered if absolute neutrophil count is less than 1×10^9/L. Treatment should be withheld until absolute neutrophil count is 1×10^9/L or greater and resume treatment at one dose level lower. The dose and/or dose schedule should be adjusted based on signs and symptoms of infection (see section 4.2). Treating neutropenic patients with haematopoietic growth factors and/or prophylactic antimicrobials should be considered as clinically indicated (see section 4.2).

Anaemia

Anaemia was frequently reported in clinical studies (see section 4.8). Red blood cell counts should be monitored at baseline, during treatment, and as clinically indicated. Patients should be monitored more frequently during the first two months of treatment. Treating anaemia with transfusions and/or erythropoietin should be considered as clinically indicated.

Infections

Pepaxti may cause infections, including Grade ≥ 3 infections such as pneumonia and upper respiratory tract infection (see section 4.8). Patients should be closely monitored for signs of infection. Treating infections with antimicrobials should be considered as clinically indicated.

Gastrointestinal events

Nausea and diarrhoea are very common and vomiting is common during treatment with Pepaxti (see section 4.8). Prophylaxis with anti-emetic agents should be considered prior to and during infusion with melphalan flufenamide (see section 4.2).

Thromboembolic events

Venous thromboembolic events have been observed in patients receiving Pepaxti in combination with dexamethasone (see section 4.8). Patients with known risk factors for thromboembolism, including prior thrombosis, should be closely monitored. A decision to take prophylactic measures should be made after a careful assessment of the individual patient's underlying risk factors, including the occurrence of thrombocytopenia. In high-risk patients, anti-thrombotic prophylaxis can be considered.

Mutagenicity

Melphalan, a metabolite of melphalan flufenamide, is mutagenic in animals and chromosome aberrations have been observed in patients being treated with melphalan.

Carcinogenicity

Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)
AML and MDS have occurred in patients with multiple myeloma who have received Pepaxti (see section 4.8). The leukaemogenic risk must be balanced against the potential therapeutic benefit when considering the use of melphalan flufenamide. Patients should be monitored closely before and during treatment for occurrence of AML and MDS.

Second primary malignancies (SPM)
The use of alkylating agents has been linked to the development of a SPM and SPMs have been reported also after use of Pepaxti, see section 4.8. When the melphalan flufenamide metabolite melphalan is used in combination with lenalidomide and prednisone, and to a lesser extent in combination with thalidomide and prednisone, it has been linked to an increased risk of solid SPMs for elderly patients with newly diagnosed multiple myeloma. Melphalan flufenamide is not indicated in combination with lenalidomide or thalidomide. Patients should be monitored closely before and during treatment for occurrence of SPM.

Prior autologous stem cell transplant
Pepaxti is not recommended in patients who have progressed within 36 months after an ASCT (see section 4.1). This is based on results from study OP-103 (OCEAN), a randomised phase 3 trial in patients with relapsed or refratory multiple myeloma following 2 to 4 lines of prior therapy and refractory to lenalidomide and the last line of therapy. Post-hoc analyses showed that patients on melphalan flufenamide/dexamethasone who had progressed less than 36 months after an ASCT had a lower survival compared to the pomalidomide/dexamethasone comparator arm, with a median OS of

15.7 months (95% CI: 11.9, 20.5, n=101) compared to 28.7 months (95% CI: 20.2, 34.1; n=101), respectively. For patients who had no prior ASCT or progressed more than 36 months after an ASCT, median OS was 23.6 months (95% CI: 18.9, 28.0; n=145) on melphalan flufenamide/dexamethasone vs. 19.8 months (95% CI: 12.6, 26.5; n=148) in the pomalidomide/dexamethasone arm.

Myeloablative conditioning treatment

The efficacy and safety of Pepaxti at doses required for myeloablation have not been studied in humans. Pepaxti should not be used for conditioning treatment prior to stem cell transplantation.

Renal impairment

Since patients with renal impairment may have marked bone marrow suppression, these patients should be closely monitored. There are insufficient data in patients with eGFR below 30 mL/min/1.73 m^2 to support a dose recommendation (see section 4.2).

Attenuated live vaccines

A risk of severe illness that may lead to fatal outcome has been described with the metabolite melphalan in patients receiving attenuated live vaccines. This risk is increased in patients who are already immunosuppressed by their underlying disease. An inactivated or mRNA based vaccine should be used when such a vaccine exists.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with melphalan flufenamide. Based on available *in vitro* and clinical data, there is a low risk of pharmacokinetic or pharmacodynamic drug interactions for melphalan flufenamide (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
As with all cytotoxic treatments, male and female patients who use melphalan flufenamide should use effective and reliable contraceptive methods until six months after cessation of treatment.

Pregnancy
There are no data from the use of melphalan flufenamide in pregnant women. Studies in animals with the melphalan flufenamide metabolite melphalan have shown reproductive toxicity (see section 5.3). Due to the genotoxic properties and structural similarity of melphalan flufenamide with known teratogenic compounds, it is possible that melphalan flufenamide can induce congenital malformations in offspring of treated patients. Melphalan flufenamide should not be used during pregnancy unless the clinical condition of the woman requires treatment with melphalan flufenamide.

Breast-feeding
It is unknown whether melphalan flufenamide or its metabolites are excreted in human milk. Due to its genotoxic properties, melphalan flufenamide is contraindicated during breast-feeding (see section 4.3).

Fertility
Melphalan flufenamide, as other agents with alkylating properties, is expected to suppress ovary function in premenopausal women, resulting in amenorrhea in a large number of patients.
Studies in animals have shown melphalan flufenamide can have adverse effects on spermatogenesis (see section 5.3). Therefore it is possible that melphalan flufenamide may cause temporary or permanent adverse effects on male fertility.Cryopreservation of semen before treatment is advised.

4.7 Effects on ability to drive and use machines

Pepaxti has moderate influence on the ability to drive and use machines. It is possible that certain adverse reactions of melphalan flufenamide, such as dizziness and nausea, may affect this ability.

4.8 Undesirable effects

Summary of the safety profile

The safety of Pepaxti in combination with dexamethasone has been evaluated in 491 patients with multiple myeloma, including 147 patients with triple-class refractory disease who have received at least three prior lines of therapies. The most frequent adverse reactions are thrombocytopenia (83%), neutropenia (72%), anaemia (66%), nausea (21%), diarrhoea (19%) and pyrexia (19%). The most frequent serious adverse reactions are pneumonia (11%), thrombocytopenia (5%) and respiratory tract infection (4%).

Tabulated list of adverse reactions

Table 3 summarises adverse reactions that were reported in patients receiving Pepaxti. The data reflect exposure of Pepaxti in 13 patients as single agent and in 478 patients in combination with dexamethasone.

Adverse reactions are described using MedDRA terms.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions reported in patients with multiple myeloma treated with Pepaxti in clinical studies

System OrganClass	Adverse reactions	Frequency overall	Frequency Grade 3/4
Infections and infestations	Septic shock	Uncommon	Uncommon
	Sepsis[1]	Common	Common
	Pneumonia[2]	Very common	Common
	Respiratory tract Infection[3]	Very common	Common
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Myelodysplastic syndrome (MDS)	Uncommon	Uncommon
	Acute myeloid leukaemia (AML)	Uncommon	Uncommon
Blood and lymphatic systemdisorders	Febrile neutropenia	Common	Common
	Thrombocytopenia[4]	Very common	Very common
	Neutropenia[5]	Very common	Very common
	Anaemia	Very common	Very common
	Leukopenia	Common	Common
	Lymphopenia	Common	Common
Metabolism and nutrition disorders	Decreased appetite	Common	Uncommon
	Hypokalaemia	Common	Common
	Hyperuricaemia	Common	Uncommon
Nervous system disorders	Headache	Common	Uncommon
	Dizziness	Common	Uncommon
Vascular disorders	Deep vein thrombosis	Common	Uncommon
	Haematoma	Common	-

System OrganClass	Adverse reactions	Frequency overall	Frequency Grade 3/4
Respiratory,thoracic and mediastinal disorders	Pulmonary embolism	Uncommon	Uncommon
	Dyspnoea	Very common	Uncommon
	Dyspnoea exertional	Common	-
	Cough	Very common	Uncommon
	Epistaxis	Common	Uncommon
Gastrointestinal disorders	Diarrhoea	Very common	Common
	Nausea	Very common	Uncommon
	Vomiting	Common	Uncommon
General disorders and administration site conditions	Pyrexia	Very common	Common
	Fatigue	Very common	Common
	Asthenia	Very common	Common

[1] Sepsis includes the events sepsis, escherichia sepsis, bacterial sepsis, and urosepsis
[2] Pneumonia includes the events pneumonia, pneumocystis jirovecii pneumonia, COVID-19 pneumonia, Pneumonia influenzal, and pneumonia viral
[3] Respiratory tract infection includes the events respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection, bronchitis, bronchitis viral, and lower respiratory tract infection
[4] Thrombocytopenia includes the events thrombocytopenia and platelet count decreased
[5] Neutropenia includes the events neutropenia and neutrophil count decreased

Description of selected adverse reactions

Thrombocytopenia
Thrombocytopenia was reported in 83% of patients, Grade 3/4 thrombocytopenia was reported in 74% of patients treated with Pepaxti. 33% of patients experienced Grade 3/4 thrombocytopenia during the first treatment cycle. Median time to onset of Grade 3 or 4 thrombocytopenia was 43 days from first dose. Grade 3/4 thrombocytopenia resulted in dose delay, dose reduction and dose discontinuation of Pepaxti in 41%, 23% and 12%, respectively.

Bleeding
Any Grade bleeding was reported in 21% of patients. Grade 3 bleeding was reported in 2% and Grade 4 bleeding was reported in <1% of patients. The most commonly reported bleedings were epistaxis, affecting 6% of patients, and unspecified haematoma, affecting 2% of patients. Bleedings starting in cycle concomitant with Grade 3/4 thrombocytopenia were reported in 14% of patients.

Neutropenia
Neutropenia was reported in 72% of patients, Grade 3/4 neutropenia was reported in 66% of patients treated with Pepaxti. 38% of patients experienced Grade 3/4 neutropenia during the first treatment cycle. Median time to onset of Grade 3 or 4 neutropenia was 22 days from first dose.

Grade 3/4 neutropenia resulted in dose delay, dose reduction and dose discontinuation of Pepaxti in 26%, 9% and 4%, respectively.

Infections occurred in cycle concomitant with Grade 3/4 neutropenia in 21% of patients. Clinically significant infections (Grade 3 or higher) were reported in 8% of patients with concomitant Grade 3-4 neutropenia. Febrile neutropenia was reported in 4% of patients.

Infections
All patients in the target population are at risk of infections due to their immunodeficient status. Myelosuppression and immunosuppressive effects induced by melphalan flufenamide may facilitate the development of infections which may have fatal outcome in the most severe manifestations. Adoption of prophylactic measures such as the administration of antimicrobials can be useful (see section 4.2).
In patients receiving Pepaxti, 52% of patients experienced any type of infection. Pneumonia and other respiratory tract infection are the most common types of infections.

Anaemia
Anaemia was reported in 66% of patients, and Grade 3 anaemia was reported in 41% of patients and Grade 4 anaemia was reported in 1% of patients treated with Pepaxti.

Second primary malignancies
Alkylating agents have been associated with development of MDS, AML and other second primary malignancies. Development of MDS and AML in patients receiving Pepaxti in clinical studies was uncommon. Also a low number of other second primary malignancies have been reported, the most common being basal cell carcinoma and squamous cell carcinoma.

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

In the event of overdose, gastrointestinal events like nausea and vomiting, and haematological events due to bone marrow suppression are likely to occur. The patient should be monitored for any signs or symptoms of adverse reactions, including complete blood counts weekly for at least 4 weeks, and appropriate supportive treatment, such as blood transfusion, antimicrobials and/or haematopoietic growth factors should be instituted if needed. There is no known specific antidote to melphalan flufenamide.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, nitrogen mustard analogues, ATC code: L01AA10

Mechanism of action
Melphalan flufenamide is a peptide conjugated alkylating drug. The drug is composed of a di-peptide and an alkylating moiety of the nitrogen mustard analogues group. The lipophilic intact peptide conjugate is rapidly distributed via passive transport into cells where it is bound to and catalysed by esterases and peptidases to the metabolite melphalan. Similar to other nitrogen mustard drugs, cross-linking of DNA is involved in the antitumor activity of melphalan flufenamide. In cellular assays, melphalan flufenamide inhibited proliferation and induced apoptosis of haematopoietic tumour cells. Retained cytotoxic activity was demonstrated in multiple myeloma cells with absent or impaired p53 functionality. Melphalan flufenamide showed synergistic cytotoxicity with dexamethasone in melphalan resistant and non-resistant multiple myeloma cell lines.

Pharmacodynamic effects
Cardiac electrophysiology
At the approved dose, melphalan flufenamide does not affect the ECG parameters PR interval, QRS interval, or QTc interval to any clinically relevant extent.

Clinical efficacy and safety

The efficacy and safety of melphalan flufenamide in combination with dexamethasone were evaluated in HORIZON, a multicentre, single-arm study in 157 patients with relapsed-refractory multiple myeloma (RRMM). A total of 157 patients received melphalan flufenamide 40 mg on Day 1 and dexamethasone 40 mg (20 mg for patients ≥ 75 years of age) on Day 1, 8, 15 and 22 of each 28 day cycle. Patients were treated until disease progression or unacceptable toxicity. 110 of the patients had multiple myeloma that was refractory to at least one proteasome inhibitor, at least one immunomodulatory agent and an anti-CD38 monoclonal antibody, i.e. were triple-class refractory (TCR) and had received at least 3 prior lines of therapies. Primary refractory patients were excluded from the study.

The median duration of melphalan flufenamide treatment in the TCR patient population (n=110) was 3.0 months (range 1.0 to 28.0 months).

Out of the 110 ≥3rd line TCR patients in the HORIZON study, 52 patients had no ASCT or progressed more than 36 months after an ASCT and 58 patients had progressed within 36 months from an ASCT. The disease characteristics and efficacy results in TCR patients who have received at least 3 prior lines of therapies and who had no ASCT or progressed more than 36 months after an ASCT are summarised in Table 4 and Table 5.

The major efficacy outcome measure was overall response rate (ORR) assessed according to the IMWG criteria by investigators.

Table 4: Disease characteristics in triple-class refractory patients who have received at least 3 prior lines of therapies and who had no ASCT or progressed more than 36 months after an ASCT in HORIZON study

Parameter	**HORIZON study (n=52)**
Median years from diagnosis to start of study treatment (range)	7.4 (0.7 - 24.6)
Prior treatment regimens, median (range)	5 (3 - 10)
Age, median (range) Patients <65 years of age, n (%) Patients 65-74 years of age, n (%) Patients ≥75 years of age, n (%)	70 (42 - 86) 18 (35%) 18 (35%) 16 (31%)
Documented refractory status, n (%) Lenalidomide Pomalidomide Bortezomib Carfilzomib Daratumumab	 47 (90%) 49 (94%) 37 (71%) 26 (50%) 49 (94%)
Alkylator refractory Melphalan exposed Melphalan refractory	32 (62%) 30 (58%) 11 (21%)
Previous stem cell transplant, n (%)	19 (37%)
ECOG at baseline, n (%) 0/1 2/3	 9 (17%)/34 (65%) 8 (15%)/1 (2%)
International Staging System at Baseline, n (%) I II III Missing/Unknown	 15 (29%) 15 (29%) 19 (37%) 3 (6%)
High-risk cytogenetics[a], n (%)	21 (40%)
Extramedullary disease (EMD), n (%)	22 (42%)

[a] del(17p), t(4;14), t(14;16), gain (1q) and t(14;20)

Table 5: Efficacy results for triple-class refractory patients who have received at least 3 prior lines of therapies and who had no ASCT or progressed more than 36 months after an ASCT in HORIZON study

	HORIZON study, n=52
Response	**Assessed by investigator**
Overall response rate (ORR)[a], 95% CI (%)	28.8% (17.1%, 43.1%)
Stringent complete response (sCR)	0
Complete response (CR)	0
Very good partial response (VGPR)	5 (9.6%)
Partial response (PR)	10 (19.2%)
Duration of response (DOR)	
Median, 95% CI (months)	7.6 (3.0-12.3)
Time to response, median range (months)	2.3 (1.0-10.5)

[a] Includes sCR + CR + VGPR + PR.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Pepaxti in all subsets of the paediatric population in the treatment of multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following Pepaxti 40 mg, melphalan flufenamide peak plasma concentrations of an average 159 ng/mL (CV% 39) were reached during the 30-minute infusion. Peak plasma concentrations of the active metabolite melphalan were reached 4 to 15 minutes after the end of infusion of Pepaxti 40 mg. Following Pepaxti 40 mg, the mean (CV%) C_{max} was 432 ng/mL (30%) and AUC0-INF was 873 ng/mL·hr (28%) for the metabolite melphalan after a single dose. The mean (CV%) C_{max} was 419 ng/mL (33%) and AUC0-INF was 815 ng/mL·hr (29%) for the metabolite melphalan at steady-state. Comparison of PK parameters of the metabolite melphalan showed that the 90% CI for the adjusted geometric mean ratio for peripheral and central intravenous infusion was within 0.8 and 1.25 for C_{max}, AUC(0-t), and AUC(0-∞), which concludes bioequivalence for peripheral and central venous infusion of melphalan flufenamide.

Melphalan flufenamide and the metabolite melphalan AUC increases in an approximately dose proportional manner over the dose range 25 to 130 mg.

Distribution
In vivo the disappearance of melphalan flufenamide from plasma is rapid and is attributed to distribution to peripheral tissues.

The mean (CV%) volume of distribution was 35 L (71%) for melphalan flufenamide and the mean apparent volume of distribution is 76 L (32%) for the metabolite melphalan after a single dose of melphalan flufenamide.

Biotransformation
Melphalan flufenamide is metabolised in tissues into the metabolite desethyl-melphalan flufenamide and into the metabolite melphalan. There is no appreciable metabolism of melphalan flufenamide to the metabolite melphalan in plasma. Melphalan is metabolised primarily by spontaneous hydrolysis to monohydroxy-melphalan and dihydroxy-melphalan.

Elimination
After the end of infusion of Pepaxti 40 mg, the mean (CV%) elimination half-life of melphalan flufenamide is 2.1 minutes (34%). The mean (CV%) elimination half-life of the metabolite melphalan is 70 minutes (21%). The mean (CV%) clearance of melphalan flufenamide and the metabolite

melphalan is 692 L/hr (49%) and 23 L/hr (23%), respectively, at the recommended dose of Pepaxti 40 mg.

Renal and hepatic excretion of unchanged melphalan flufenamide is assessed to be negligible as total plasma clearance of melphalan flufenamide greatly exceeds renal glomerular filtration rate (GFR) and hepatic blood flow.

Specific populations
Elderly patients (> 65 years old)
Based on population PK analysis, no differences in the pharmacokinetics of the metabolite melphalan were observed based on age or gender.

Renal impairment
The melphalan flufenamide metabolite melphalan is partially cleared through renal excretion. In melphalan flufenamide treated patients in study OP-103 72 patients had normal renal function, 112 patients had mild renal impairment and 43 patients had moderate renal impairment.

Based on population PK analysis melphalan AUC was on average 6% higher in mild impairment, 18% higher in patients with moderate renal impairment with eGFR 45-60 mL/min/1.73 m^2 and 32% higher in patients with moderate renal impairment with eGFR 30-45 mL/min/1.73 m^2 compared to patients with normal renal function. A larger effect of Pepaxti on thrombocyte levels was observed in patients with a lower eGFR. A Pepaxti dose of 30 mg is recommended in patients with eGFR 30-45 mL/min/1.73 m^2. There are insufficient data in patients with eGFR below 30 mL/min/1.73 m^2 to support a dose recommendation.

Hepatic impairment
No differences in the PK of the metabolite melphalan were observed in patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 × ULN and any AST). The effect of moderate to severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST) on PK is not known.

Body weight
Higher exposures of the metabolite melphalan were observed in patients with lower body weight. At a body weight of 60 kg C_{max} was on average 36% higher and AUC on average 31% higher compared to a body weight of 95 kg. Higher incidence of thrombocytopenia and neutropenia was observed in patients with lower body weight. A Pepaxti dose of 30 mg is recommended in patients with a body weight of 60 kg or less.

5.3 Preclinical safety data

Carcinogenicity and mutagenicity
Pepaxti is genotoxic. Mechanistic *in vitro* studies showed that melphalan flufenamide caused irreversible DNA damage.
No carcinogenicity or mutagenicity studies have been conducted with melphalan flufenamide.

Reproductive toxicology
In repeated dose toxicology studies, melphalan flufenamide was administered intravenously to rats at 20, 40, or 55 mg/m^2, and to dogs at 0.45 or 0.90 mg/kg (9 or 18 mg/m^2) every 21 days for two or three doses. Decreased testes weights and depletion of germ cells were observed in both species, and epididymal oligospermia was observed in dogs. Adverse effects on male reproductive organs were observed in dogs at exposures below the recommended clinical dose of 40 mg. The reversibility of adverse effects on male reproductive organs was not assessed.

Reproduction toxicity studies have not been conducted with melphalan flufenamide. The melphalan flufenamide metabolite melphalan was teratogenic in rats after single dose exposure. In repeated dose reproductive toxicity studies, melphalan exposure resulted in maternal toxicity and induced congenital

malformations. In a study in mice, a reduction in number of pups per litter was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

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
4 years

Diluted solution
From a microbiological point of view the product should be used immediately. If not used immediately, the diluted solution can be stored in a refrigerator (2 °C – 8 °C) prior to administration for up to 6 hours. Do not freeze. If refrigerated, allow the diluted solution to equilibrate to room temperature (20 °C – 25 °C) for maximum 30 minutes prior to administration.

The diluted solution for infusion may be kept at room temperature for up to 1.5 hours (including infusion time).

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 mL Type 1 glass vial sealed with chlorobutyl rubber stopper and aluminium overseal with a plastic removable cap containing 20 mg powder. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Pepaxti should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution.

Additional solvents required for preparation
5% glucose solution for injection/infusion (room temperature).
250 mL bag of cold (2 °C – 8 °C) sodium chloride 9 mg/mL (0.9%) solution for injection (refrigerate for at least 4 hours).

Table 6 Dilution volumes per Pepaxti dose

Volume description	**Pepaxti dose**			
	40 mg (2 vials)	30 mg (1.5 vials)	20 mg (1 vial)	15 mg (0.75 vial)
Volume of reconstituted Pepaxti solution needed for final product	80 mL	60 mL	40 mL	30 mL
Final total volume of infusion bag after dilution	250 mL	230 mL	210 mL	200 mL

Volume description	**Pepaxti dose**			
	40 mg (2 vials)	30 mg (1.5 vials)	20 mg (1 vial)	15 mg (0.75 vial)
Pepaxti concentration after dilution	0.16 mg/mL	0.13 mg/mL	0.10 mg/mL	0.08 mg/mL

Preparation steps
Read the complete instructions prior to starting preparation.
Steps 3 to 5 must be completed within 30 minutes.

Reconstitution and dilution steps

Step 1
Determine the number of vials needed for the dose as per Table 6 "Dilution volumes per Pepaxti dose". Place vial(s) at room temperature for at least 30 minutes.

Step 2
Shake the vial(s) vigorously or vortex to disintegrate the lyophilised powder cake into a loose powder.

Steps 3 to 5 must be completed within 30 minutes.

Step 3

For a Pepaxti dose of 40 mg	For a Pepaxti dose of 30 mg	For a Pepaxti dose of 20 mg	For a Pepaxti dose of 15 mg
Aseptically reconstitute each of the 2 vials with 40 mL of 5% glucose solution for infusion to obtain a final concentration of 0.5 mg/mL.	Aseptically reconstitute each of the 2 vials with 40 mL of 5% glucose solution for infusion to obtain a final concentration of 0.5 mg/mL.	Aseptically reconstitute 1 vial with 40 mL of 5% glucose solution for infusion to obtain a final concentration of 0.5 mg/mL.	Aseptically reconstitute 1 vial with 40 mL of 5% glucose solution for infusion to obtain a final concentration of 0.5 mg/mL.

Ensure the 5% glucose solution for infusion is at room temperature (20 °C – 25 °C). Shake the vial(s) vigorously until solution is clear.
Let the vial(s) stand to allow air bubbles to dissipate to confirm a clear solution.

Step 4
Withdraw 80 mL from a refrigerated (2 °C – 8 °C) 250 mL bag of sodium chloride 9 mg/mL (0.9%) solution for injection. Discard the withdrawn 80 mL.

Step 5

For a Pepaxti dose of 40 mg	For a Pepaxti dose of 30 mg	For a Pepaxti dose of 20 mg	For a Pepaxti dose of 15 mg
Withdraw 80 mL of reconstituted solution from the Pepaxti vials and transfer into an intravenous (IV) solution for injection containing sodium chloride 9 mg/mL (0.9%) to obtain a final concentration of 0.16 mg/mL.	Withdraw 60 mL of reconstituted solution from the Pepaxti vials and transfer into an intravenous (IV) solution for injection containing sodium chloride 9 mg/mL (0.9%) to obtain a final concentration of 0.13 mg/mL.	Withdraw 40 mL of reconstituted solution from the Pepaxti vial and transfer into an intravenous (IV) solution for injection containing sodium chloride 9 mg/mL (0.9%) to obtain a final concentration of 0.10 mg/mL.	Withdraw 30 mL of reconstituted solution from the Pepaxti vial and transfer into an intravenous (IV) solution for injection containing sodium chloride 9 mg/mL (0.9%) to obtain a final concentration of 0.08 mg/mL.

Discard any unused portion left in the vial(s).
Gently invert the bag to mix the solution. Do not shake. Check that the solution is clear and colourless to pale yellow. Do not use if solution discolouration or particles are observed.

Storage timelines
Pepaxti degrades in solution, especially at room temperature, and the storage timelines for diluted solution should not be exceeded.

For immediate administration
Infusion of the diluted solution must begin **within 60 minutes** of start of reconstitution (step 3).

For delayed administration
If not used for immediate administration, the diluted solution should be placed in a refrigerator (2 °C – 8 °C) within 30 minutes after initial reconstitution (step 3) and can be stored for **up to 6 hours.**

Administration
Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Do not use if visibly opaque particles, discolouration or foreign particles are observed.

Administration steps

Step 6
Administer Pepaxti as a 30-minute intravenous infusion via peripheral venous route or a central venous access device, for example PICC or tunnelled central venous catheter. If the infusion bag has been stored in a refrigerator, allow to reach to room temperature (20 °C – 25 °C). Start infusion within 30 minutes of removing the diluted solution from the refrigerator.

Step 7
Upon completion of Pepaxti infusion, flush the catheter with sodium chloride 9 mg/mL (0.9%) solution for injection.

Disposal
Pepaxti is a cytotoxic medicinal product for single use only. The procedure for the safe handling and disposal of nitrogen mustard analogues must be followed by healthcare professionals or medical personnel and should comply with the current recommendations for cytotoxic medicinal products. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Oncopeptides AB (publ)
Luntmakargatan 46
111 37 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER

EU/1/22/1669/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 August 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER 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. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Eumedica NV
Chemin de Nauwelette 1
7170 Manage
Belgium

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Pepaxti 20 mg powder for concentrate for solution for infusion
melphalan flufenamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 20 mg melphalan flufenamide (as hydrochloride)

3. LIST OF EXCIPIENTS

and sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Intravenous use after reconstitution and 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

Cytotoxic: handle with caution.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package 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

Oncopeptides AB (publ)
111 37 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1669/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pepaxti 20 mg powder for concentrate
melphalan flufenamide

2. METHOD OF ADMINISTRATION

IV use after reconstitution and dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mg/mL after reconstitution.

6. OTHER

Cytotoxic: handle with caution.
Read the package leaflet before use.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Pepaxti 20 mg powder for concentrate for solution for infusion
melphalan flufenamide

Read all of this leaflet carefully before you are given 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 or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pepaxti is and what it is used for

Pepaxti belongs to a group of cancer medicines called alkylating agents. It works by attaching to DNA (the genetic instruction needed for cells to survive and multiply) and damaging it, thereby helping to stop the cancer cells from growing.

Pepaxti is given with the steroid dexamethasone, to treat adults with the blood cancer multiple myeloma. It is used when the disease does not respond to at least three types of cancer medicines. If you have been treated with a blood stem cell transplant (a procedure where the cells that make your blood are cleared out and replaced), the time to when the multiple myeloma came back after transplantation should be at least 3 years.

2. What you need to know before you are given Pepaxti

Do not use Pepaxti
- if you are allergic to melphalan flufenamide or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding.

Warnings and precautions
Talk to your doctor or nurse before you are given Pepaxti.

Abnormal bleeding and bruising and low number of platelets (blood cells)
Pepaxti can lower the number of blood cells called platelets that help to clot your blood. Tell your doctor or nurse immediately if you start bleeding e.g. a nosebleed or get bruises on your skin.

Fever and low number of white blood cells
Pepaxti can lower the number of white blood cells that are important for fighting infections. Tell your doctor or nurse immediately if you have symptoms of infection such as fever, chills or cough.

Low number of red blood cells
Pepaxti can lower the number of red blood cells, which transport oxygen to the cells in your body. Your doctor will regularly take blood samples to monitor your blood cells. Tell your doctor or nurse immediately if you feel weak or tired, if you look pale or if you feel short of breath.

Infections
Infections such as lung infection (pneumonia) and upper respiratory tract infection (causing cold-like symptoms) are very common with Pepaxti. Tell your doctor or nurse immediately if you develop fever or other signs of infection. Your doctor might recommend preventive antibiotics to lower the risk of developing infections.

Risk of diarrhoea, nausea or vomiting
You should tell your doctor if you get diarrhoea, nausea, or vomiting.

Risk of development of blood clots
The use of Pepaxti in combination with dexamethasone may increase the risk of developing blood clots. Tell your doctor or nurse if you have ever had a blood clot in a vein (thrombosis). Tell your doctor or nurse immediately if you develop a swelling of a leg or an arm, if you find it harder to breathe, or experience chest pain.

Risk of additional cancer
It is important to note that patients with multiple myeloma treated with Pepaxti may develop additional types of cancer, therefore your doctor should carefully evaluate the benefit and risk for you when you are prescribed this medicine.

Kidney disease
If you have lowered kidney function, the side effects of Pepaxti on your blood cells may be worse. There is too little information available on use of the medicine in patients with severely lowered kidney function to be able to recommend a safe and effective dose.

Vaccinations
Vaccines that contain live but weakened organisms, known as live attenuated vaccines (like measles, mumps, and rubella vaccines) should not be used while you are being treated with Pepaxti, as they may lead to an infection. Some other types of vaccines known as inactivated vaccines or mRNA based vaccines can, however, be used. Tell your healthcare provider you are being treated with Pepaxti before you get vaccinated.

Children and adolescents
Pepaxti is not intended for use in children or adolescents below 18 years of age.

Other medicines and Pepaxti
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

Pregnancy
This medicine is not recommended for use during pregnancy unless clearly necessary. Avoid becoming pregnant while being treated with this medicine as it may harm your unborn baby. Your doctor will discuss with you the potential risks of using Pepaxti during pregnancy.

If you are a woman who could become pregnant:
- Your doctor will ask you to take a pregnancy test before you start treatment with Pepaxti.
- You must use effective contraception during treatment and for 6 months after your last dose of Pepaxti. Talk to your doctor about effective contraception methods that may be right for you.

If you are a man who could father a child:
- You must use effective contraception during treatment and for 6 months after your last dose of Pepaxti.

Breast-feeding
You should not breast-feed during treatment with Pepaxti since it may be harmful for your baby.

Fertility
Pepaxti can affect ovaries or sperm, which may cause infertility (inability to have a baby). In women, menstruation can stop. In men, inability to father a child (sterility) due to lack of sperm can be permanent. Ask your doctor for advice on sperm preservation before treatment.

Driving and using machines
Pepaxti can cause nausea and dizziness, which may reduce your ability to drive or use machines.

3. How Pepaxti is given

Pepaxti is made up into a solution and given by your doctor or nurse as a drip into a vein (intravenous infusion) over 30 minutes. Your doctor will decide on the correct dose of Pepaxti. The recommended starting dose is 40 mg once every 4 weeks. If you have a body weight of 60 kg or less, the recommended starting dose is 30 mg once every 4 weeks. Treatment will carry on as long as you are benefitting from it and do not have unacceptable side effects. As part of your treatment, you will also take another medicine, dexamethasone, by mouth.

If you are given more Pepaxti than you should
This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose) your doctor will check you, including taking blood samples to monitor your blood cells.

If a dose of Pepaxti is missed
It is very important to go to all your appointments, to make sure your treatment works. If you miss an appointment, contact your doctor or hospital as soon as possible.

4. Possible side effects

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

Contact a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:
- Fever, chills, sore throat, cough, or any other signs of infection (due to lack of white blood cells called neutrophils, which fight infections).
- Rapid breathing, rapid pulse, fever and chills, passing very little to no urine, nausea and vomiting, confusion, unconsciousness (due to serious bacterial infection of the blood called sepsis or septic shock).
- Bleeding or bruising without a cause, including nosebleeds (due to low number of blood platelets [thrombocytopenia]).
- Shortness of breath (from serious chest infection, inflammation of the lungs, or blood clot in the lungs).
- Leg or arm pain and swelling, especially in your lower leg or calves (caused by blood clots).

Other side effects that can occur

Very common (may affect more than 1 in 10 people):
- Lower number of blood platelets (thrombocytopenia)
- Lower number of a type of white blood cells called neutrophils (neutropenia)

- Lower number of red blood cells which carry oxygen in the blood (anaemia), causing weakness and fatigue
- Infection of the lungs (pneumonia)
- Infection of the airways presenting with e.g. fever, cough, and cold-like symptoms
- Diarrhoea
- Nausea
- Fever
- Cough
- Shortness of breath
- Extreme tiredness (fatigue)
- Weakness

Common (may affect up to 1 in 10 people):
- Serious bacterial infection of the blood (sepsis)
- Fever together with reduced number of some white blood cells (neutropenia)
- Lower number of a type of white blood cells called lymphocytes (lymphopenia), which also help fight infections
- Overall lower number of white blood cells
- Decreased appetite
- Low potassium level (may cause muscle weakness and irregular heartbeat)
- High uric acid level in the blood (may cause gout and kidney problems)
- Headache
- Dizziness
- Shortness of breath when active
- Nosebleed
- Vomiting
- Deep vein thrombosis (blood clot in a vein)
- Bruises

Uncommon (may affect up to 1 in 100 people):
- Serious bacterial infection of the blood with dangerously low blood pressure (septic shock) which can be life threatening or even fatal
- Blood clot in the lungs
- A type of blood cancer called myelodysplastic syndrome (MDS)
- A type of blood cancer called acute myeloid leukaemia (AML)

Your doctor or nurse may give you additional medicines to treat your symptoms and/or prevent side effects.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. 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 Pepaxti

Pepaxti will be stored at the hospital or clinic so these instructions are for the healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after “EXP”. The expiry date refers to the last day of that month.
Store in a refrigerator (2 ºC – 8 ºC). Do not freeze.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. These measures will help protect the environment.

6. Contents of the pack and other information

What Pepaxti contains
- The active substance is melphalan flufenamide. One vial contains 20 mg of melphalan flufenamide (as hydrochloride).
- The other ingredient is sucrose (sugar).

What Pepaxti looks like and contents of the pack
Pepaxti is a white to off-white powder in a glass vial.

Each carton contains one vial.

Marketing Authorisation Holder
Oncopeptides AB (publ)
Luntmakargatan 46
111 37 Stockholm
Sweden

Manufacturer
Eumedica NV
Chemin de Nauwelette 1
7170 Manage
Belgium

For any information about this medicine, please contact the Marketing Authorisation Holder:

Oncopeptides AB (publ)
e-mail: medinfo@oncopeptides.com

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Step-by-step instructions for use and handling, reconstitution and administration

Pepaxti should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution.

Additional solvents required for preparation
5% glucose solution for injection/infusion (room temperature).

250 mL bag of cold (2 °C – 8 °C) sodium chloride 9 mg/mL (0.9%) solution for injection (refrigerate for at least 4 hours).

Table 1 Dilution volumes per Pepaxti dose

Volume description	**Pepaxti dose**			
	40 mg (2 vials)	30 mg (1.5 vials)	20 mg (1 vial)	15 mg (0.75 vial)
Volume of reconstituted Pepaxti solution needed for final product	80 mL	60 mL	40 mL	30 mL
Final total volume of infusion bag after dilution	250 mL	230 mL	210 mL	200 mL
Pepaxti concentration after dilution	0.16 mg/mL	0.13 mg/mL	0.10 mg/mL	0.08 mg/mL

Preparation steps
Read the complete instructions prior to starting preparation.
Steps 3 to 5 must be completed within 30 minutes.

Reconstitution and dilution steps

Step 1
Determine the number of vials needed for the dose as per Table 1 "Dilution volumes per Pepaxti dose". Place vial(s) at room temperature for at least 30 minutes.

Step 2
Shake the vial(s) vigorously or vortex to disintegrate the lyophilised powder cake into a loose powder.

Steps 3 to 5 must be completed within 30 minutes.

Step 3

For a Pepaxti dose of 40 mg	For a Pepaxti dose of 30 mg	For a Pepaxti dose of 20 mg	For a Pepaxti dose of 15 mg
Aseptically reconstitute each of the 2 vials with 40 mL of 5% glucose solution for infusion to obtain a final concentration of 0.5 mg/mL.	Aseptically reconstitute each of the 2 vials with 40 mL of 5% glucose solution for infusion to obtain a final concentration of 0.5 mg/mL.	Aseptically reconstitute 1 vial with 40 mL of 5% glucose solution for infusion to obtain a final concentration of 0.5 mg/mL.	Aseptically reconstitute 1 vial with 40 mL of 5% glucose solution for infusion to obtain a final concentration of 0.5 mg/mL.

Ensure the 5% glucose solution for infusion is at room temperature (20 °C – 25 °C). Shake the vial(s) vigorously until solution is clear.
Let the vial(s) stand to allow air bubbles to dissipate to confirm a clear solution.

Step 4
Withdraw 80 mL from a refrigerated (2 °C – 8 °C) 250 mL bag sodium chloride 9 mg/mL (0.9%) solution for injection. Discard the withdrawn 80 mL.

Step 5

For a Pepaxti dose of 40 mg	For a Pepaxti dose of 30 mg	For a Pepaxti dose of 20 mg	For a Pepaxti dose of 15 mg
Withdraw 80 mL of reconstituted solution from the Pepaxti vials and transfer into an intravenous (IV) solution for injection containing sodium chloride 9 mg/mL (0.9%) to obtain a final concentration of 0.16 mg/mL.	Withdraw 60 mL of reconstituted solution from the Pepaxti vials and transfer into an intravenous (IV) solution for injection containing sodium chloride 9 mg/mL (0.9%) to obtain a final concentration of 0.13 mg/mL.	Withdraw 40 mL of reconstituted solution from the Pepaxti vial and transfer into an intravenous (IV) solution for injection containing sodium chloride 9 mg/mL (0.9%) to obtain a final concentration of 0.10 mg/mL.	Withdraw 30 mL of reconstituted solution from the Pepaxti vial and transfer into an intravenous (IV) solution for injection containing sodium chloride 9 mg/mL (0.9%) to obtain a final concentration of 0.08 mg/mL.

Discard any unused portion left in the vial(s).
Gently invert the bag to mix the solution. Do not shake. Check that the solution is clear and colourless to pale yellow. Do not use if solution discolouration or particles are observed.

Storage timelines
Pepaxti degrades in solution, especially at room temperature, and the storage timelines for diluted solution should not be exceeded.

For immediate administration
Infusion of the diluted solution must begin **within 60 minutes** of start of reconstitution (step 3).
For delayed administration
If not used for immediate administration, the diluted solution should be placed in a refrigerator (2 °C – 8 °C) within 30 minutes after initial reconstitution (step 3) and store for **up to 6 hours.**

Administration
Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Do not use if visibly opaque particles, discolouration or foreign particles are observed.

Administration steps
Step 6 Administer Pepaxti as a 30-minute intravenous infusion via peripheral venous route or a central venous access device, for example PICC or tunnelled central venous catheter. If the infusion bag has been stored in a refrigerator, allow to reach to room temperature (20 °C – 25 °C). Start infusion within 30 minutes of removing the diluted solution from the refrigerator.
Step 7 Upon completion of Pepaxti infusion, flush the catheter with sodium chloride 9 mg/mL (0.9%) solution for injection.

Disposal
Pepaxti is a cytotoxic medicinal product for single use only. The procedure for the safe handling and disposal of nitrogen mustard analogues must be followed by healthcare professionals or medical personnel and should comply with the current recommendations for cytotoxic medicinal products. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.