# EU risk management plan for Pepaxti® (melphalan flufenamide)

**RMP version to be assessed as part of this application:**

| | |
|---|---|
| RMP version number | 1.3 |
| Data lock point for this RMP | 10 November 2023 |
| Date of final sign-off | 27 November 2023 |

**Rationale for submitting an updated RMP:**

There is one reason for updating the RMP:

- Removal of the extended indication in the melflufen Product Information (due to company decision).

**Summary of significant changes in this RMP:**

This RMP has been updated to revert back to the originally approved indication for melflufen; in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 3 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.

**Other RMP versions under evaluation:** Not applicable

**Details of the currently approved RMP:**

Version number: 1.2

Approved with procedure: Type II variation, EMEA/H/C/005681/II/0002

Date of approval (opinion date): 14 September 2023

**QPPV name**: Martynas Juzenas

**QPPV oversight declaration:** The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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# List of abbreviations and definition of terms

| | |
|---|---|
| ADE | Adverse drug experience |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AML | Acute myeloid leukaemia |
| CAR | Chimeric antigen receptor |
| CSR | Clinical study report |
| eGFR | Estimated glomerular filtration rate |
| ECG | Electrocardiogram |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EPAR | European public assessment report |
| FDA | Food and Drug Administration |
| $IC_{50}$ | Half maximal inhibitory concentration |
| ImiD | Immunomodulatory agent |
| IMWG | International Myeloma Working Group |
| INN | International nonproprietary name |
| ISS | Integrated summary of safety |
| $LD_{50}$ | Lethal dose in half of the animals |
| MDS | Myelodysplastic syndrome |
| MM | Multiple myeloma |
| NDA | New drug application |
| OS | Overall survival |
| PADER | Periodic adverse drug experience report |
| PI | Proteasome inhibitor |
| PL | Package leaflet |
| PSUR | Periodic safety update report |
| QPPV | Qualified person responsible for pharmacovigilance |
| RMP | Risk management plan |
| SD | Standard deviation |
| SEER | Surveillance, Epidemiology, and End Results |
| SIR | Standardised incidence ratio |
| SmPC | Summary of product characteristics |
| SP | Safety population |
| TEAE | Treatment-emergent adverse event |
| TSP | Targeted safety population |
| UK | United Kingdom |
| USA | United States of America |

# Part I: Product overview

| | |
|---|---|
| **Active substance (INN or common name)** | Melphalan flufenamide |
| **Pharmacotherapeutic group(s) (ATC Code)** | L01AA10 |
| **Marketing authorisation applicant** | Oncopeptides AB (publ) |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name in the EEA** | Pepaxti |
| **Marketing authorisation procedure** | Centralised |
| **Brief description of the product**<br>• Chemical class<br>• Summary of mode of action<br>• Important information about its composition | Melphalan flufenamide, hereinafter referred to as melflufen, is a peptide-conjugated alkylating drug. The drug is composed of a dipeptide and an alkylating moiety of the nitrogen mustard analogues group. Similar to other nitrogen mustard drugs, crosslinking of DNA is probably the most important factor for the cytotoxic effect of melflufen. Due to its high lipophilicity, melflufen is passively and rapidly distributed into cells, where it is metabolised by esterases to a desethyl metabolite and subsequently or directly by aminopeptidases to melphalan. These metabolites have the same alkylating moiety as melflufen. In cellular assays, melflufen inhibited proliferation and induced apoptosis of haematopoietic and solid tumour cells. Additionally, melflufen showed synergistic cytotoxicity with dexamethasone in melphalan-resistant and nonresistant multiple myeloma cell lines. |
| **Hyperlink to the product information** | Proposed product information (in the eCTD sequence) |
| **Indication in the EEA** | Current:<br>Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 2 prior lines of therapies, and whose disease is refractory to lenalidomide and the last line of therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation. |
| | Proposed:<br>Melflufen is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 3 prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immuno-modulatory 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. |
| **Dosage in the EEA** | Current:<br>Melflufen is for intravenous use and should be administered as a 30-minute infusion via a peripheral venous route or a central venous access device after reconstitution and dilution.<br>The recommended starting dose of melflufen is 40 mg administered 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. Treatment may continue until disease progression or until unacceptable toxicity occurs. For additional information regarding administration of melflufen, see the corresponding summary of product characteristics (SmPC).<br>For dose and schedule of dexamethasone, see the corresponding SmPC. |
| | Proposed:<br>Not applicable. |
| **Pharmaceutical form(s) and strengths** | Powder for concentrate for solution for infusion (powder for concentrate).<br>One vial of powder contains 20 mg of melphalan flufenamide (as hydrochloride), which is a lyophilised white to off-white powder. |
| **Is/will the product be subject to additional monitoring in the EU?** | No |

# Part II: Safety specification

## Module SI: Epidemiology of the indication and target population

### Indication

Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 3 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.**Incidence and prevalence of multiple myeloma**

Multiple myeloma (MM), although a rare disease, accounts for 1%–2% of all new cancer cases and is the second most common haematologic malignancy, with a global incidence rate of 1.7 per 100,000 and an age-standardised incidence rate of 2.1–3.4 per 100,000 in France, Germany, Italy, Spain, and the UK (WHO IARC 2018). An estimated 35,842 patients were diagnosed in the 27 European Union countries during 2020, with an estimated 23,275 deaths due to the disease (ECIS 2020). Data from Sweden and Denmark suggest a 3-fold increase in the prevalence of MM from 1980 to 2014 (Turesson et al. 2018).

### Demographics of the population in the multiple myeloma indication – age, gender, racial and/or ethnic origin and risk factors for the disease

MM is primarily a disease of the elderly with a steep increase in incidence with advancing age (Kyle et al. 2004, Turesson et al. 2010). MM is most frequently diagnosed among people aged 65 to74 years with a median age of 72 years at diagnosis in Europe (Palumbo et al. 2011) and 69 years in the US (SEER 2019). The disease is extremely rare in those less than 30 years of age with a reported frequency of 0.02% to 0.3% (Blade et al. 1996, SEER 2019). MM is more common in men than women (ECIS 2020), and, in the US, twice as common in African Americans than in other races and ethnicities (SEER 2019). In general, MM is not considered to be a genetic disease, however familial cases, albeit rare, do exist (Lynch et al. 2001).

MM is a multifactorial disease with a wide variety of risk factors. Despite the growing interest in the field, the aetiology of MM is poorly understood. However, many risk factors have been implicated, with variable levels of evidence (Wang et al. 2012, Sergentanis et al. 2015).
Risk factors for MM include:

- Age: The incidence of cancer in general and haematologic malignancies increases with age.
- Sex: Most but not all registries show a higher incidence of MM in men.
- Race: Ethnic pattern with myeloma occurring around twice as frequently in African Americans as Caucasians (SEER 2019).
- Family history: Myeloma risk is 2.3 times higher in people with a first-degree relative (parent, sibling, or child) with myeloma compared with the general population, a cohort study showed (Frank et al. 2014).
- Obesity: Four meta-analysis have shown a positive association between obesity and MM risk (Larsson et al. 2007, Renehan et al. 2008, Ríos-Tamayo et al. 2011, Wallin et al. 2011).
- Occupational MM: A meta-analysis on occupational exposure to dichloromethane, a widespread used solvent, showed an excess risk of MM (Liu et al. 2013).

- Precursor disease: MM is almost always preceded by a precursor disease. Several precursor diseases can progress to MM, such as monoclonal gammopathy of undetermined significance (Kyle et al. 2006), smouldering MM (Kyle et al. 2007), or solitary plasmacytoma (Katodritou et al. 2014).

**Main existing treatment options**

Current treatment of MM includes glucocorticoids (dexamethasone, prednisolone, methylprednisolone), chemotherapy (primarily alkylating agents), including high-dose chemotherapy followed by autologous stem cell transplantation, proteasome inhibitors (PIs) (such as bortezomib, carfilzomib, and ixazomib), immunomodulatory agents (IMiDs) (such as thalidomide, lenalidomide, and pomalidomide), monoclonal antibodies (such as daratumumab, isatuximab, and elotuzumab), the histone deacetylase inhibitor panobinostat, the XPO1 inhibitor selinexor, the autologous chimeric antigen receptor (CAR) T-cell products idecabtagene vicleucel and ciltacabtagene autoleucel, and the bispecific antibody teclistamab.

In general, patients with MM receive several different regimens during their lifespan (Palumbo et al. 2011, Kumar et al. 2017) . The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy, and the type of relapse (Moreau et al. 2017).

In the RRMM setting, the duration of treatment-free intervals (TFIs) and time to progression (TTP) decreases with later treatment lines, indicating progressively shorter remission and survival with each subsequent treatment line (Yong et al. 2016). Data from a multi-country European real-world study (N=4,997) provide a glimpse into the rate of relapse in MM (Yong et al. 2016). This observational study was a retrospective chart review conducted in Belgium, France, Germany, Italy, Spain, Switzerland, and the UK. Authors found that 95% of patients had received first-line, 61% had received second-line, 38% had received third-line, 15% had received fourth-line and 1% had received fifth-line or later treatment. Of interest is that the median time to progression decreased from 18 months in first line to 13, 7, and 5 months through lines 2, 3 and 4, respectively. In the 3rd line of treatment, patients have generally been exposed to all 5 drugs that have demonstrated single-agent efficacy (with or without glucocorticoids), including bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab.

**Natural history of the indicated condition in the multiple myeloma population, including mortality and morbidity**

The disease course for MM varies with the disease stage at diagnosis, cytogenetic profile, as well as age and patient comorbidities. Patients with MM may have symptom-free periods, but the disease always relapses, and patients may become refractory to all available treatment options due to mutations and/or clonal evolution of the tumour cells. While the advent of novel treatment regimens has translated into improvements in outcomes over the past 15 years (Sonneveld 2017), the disease is ultimately fatal, with a 5-year survival slightly over 50% (SEER 2019). The presence of extramedullary disease is a poor prognostic marker in patients both with newly diagnosed and relapsed MM (Usmani et al. 2012).

According to the International Myeloma Working Group criteria (IMWG) (Rajkumar et al. 2011), relapsed-refractory MM is defined as disease that is nonresponsive while on salvage

therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously, before then progressing in their disease course.

**Important comorbidities**

Comorbidities are common in older patients (≥65 years). As MM is predominantly a disease of the elderly, patients with MM will have age-related conditions concomitantly with symptoms of MM. A Danish study showed increased risk for comorbidities in MM patients compared with population controls (OR 1.4 [1.1-1.7]). In particular, the risk for renal disease was very high (OR 11.0 [8.1-14.9]), but the risk for other comorbidities, including congestive heart failure, chronic pulmonary disease, ulcer disease, and diabetes mellitus with chronic complications, was also significantly higher than in the background population. Patients with registered comorbidity also had increased mortality compared with patients without comorbidity (Gregersen et al. 2017).

MM can present with an abundance of clinical features, including anaemia, renal dysfunction, bone pain, hypercalcaemia, spinal cord compression, fatigues, and recurrent bacterial infections (Kyle et al. 2003, Palumbo et al. 2011). Anaemia is one of the hallmark symptoms of MM, present in 35%–73% at diagnosis (Palumbo et al. 2011). Between 20% and 50% of newly diagnosed patients with MM also have renal impairment, with about 5% needing dialysis (Alexanian et al. 1990, Knudsen et al. 1994, Blade et al. 1998, Knudsen et al. 2000), both groups with significantly shorter survival compared to the entire study population. Osteolytic bone disease is already present at the time of MM diagnosis in 70%–80% of patients (Terpos et al. 2013), and it increases their risk of skeletal-related fractures and spinal cord compression (Coleman 1997).

Patients with MM are at increased risk of venous thromboembolism (Srkalovic et al. 2004). Venous thromboembolism is more common with increasing age, and the use of IMiDs in combination with dexamethasone or chemotherapeutic agents produces a risk of venous thromboembolism of up to 70% in the absence of anticoagulation (Palumbo et al. 2008). Many patients will have received prior therapy with drug combinations and may have residual toxicity such as neuropathy, induced by bortezomib and thalidomide, and myelosuppression, induced by alkylating agents (Sonneveld 2017).

## Module SII: Nonclinical part of the safety specification

Melflufen is a novel peptide-drug conjugate with identical bis-(2-chloroethyl)amino alkylating function as cyclophosphamide, chloroambucil, bendamustine, and melphalan. The high lipophilicity of melflufen provides for a rapid inflow of alkylator into tissues. This is followed by rapid intracellular hydrolysis of the peptide bond, present in melflufen as well as in its de-esterified metabolite, the net result being immediate attainment of high intracellular concentration of particularly the hydrophilic metabolite melphalan. This description of melflufen's disposition, i.e. rapid tissue uptake and a primarily peptidase-governed metabolism, explains the beneficial cytotoxic activities *in vitro* and is considered responsible for the favourable *in vivo* antitumour activity compared to melphalan.

*In vitro* studies conducted with melflufen in a panel of human tumour cell lines, including MM cells, have shown that melflufen expresses similar patterns of activity as melphalan, but with much improved potency. In MM cell lines, the $IC_{50}$ of melflufen was at least 10-fold lower than that of melphalan. The desethyl metabolite showed similar cytotoxic activity as melphalan.

In the rat, intravenous infusion of melflufen at a dose level close to the lethal dose results in a short-lasting but significant stimulatory action on respiration and heart rate. This could be explained as a stress reaction to local irritation and pain; effects commonly associated with high-dose chemotherapeutic regimens. A preliminary in vitro screening assay indicated hERG blocking activity. However, Holter monitoring in a single-dose study in dogs and ECGs taken in a repeat-dose study in dogs revealed no propensity for any QT prolongation or other ECG abnormalities.

Single- and repeat-dose toxicity of melflufen has been investigated in mice, rats, and dogs. In the single-dose studies, $LD_{50}$ values in rodents were similar to those reported for melphalan. Histologic examinations showed the expected organ damage for a bisfunctional alkylator with effects on the bone marrow, lymphoid organs, and testes. Target organs were essentially the same in the repeat-dose studies as those observed in the single-dose studies. At higher dose levels, damage to the gastrointestinal epithelium, a common finding with alkylators, was observed in dogs.

Dogs were intravenously administered a single dose of melflufen (17.5 mg/kg) or an equimolar dose of melphalan; these dose levels were representative of dosages needed for myeloablation. Increased mortality was observed in dogs administered melflufen despite similar melphalan exposure in animals administered melflufen or melphalan.

Local tolerance information from central vein infusions with clinically relevant concentrations of melflufen in dogs did not show any melflufen-related local tissue damage. Peripheral vein infusion in mice (single- and repeat-dose studies) was associated with haematoma and necrosis of the injection site (tail vein) at all dose levels, whereas such findings were only seen in high-dose rats. When dogs were administered melflufen and melphalan via the cephalic vein, tissue changes seen 2 days after infusion were somewhat more pronounced with melflufen than with melphalan. However, no difference in tissue damage between the compounds was observed in samples taken 30 days after infusion. A comparative intradermal study in mice gave no evidence of any worse local toxicity of melflufen compared with that of melphalan and bendamustine. The overall local tolerance data from animal studies should thus support the testing of peripheral vein administration of melflufen in the clinical setting.

No genotoxicity, carcinogenicity, or reproduction toxicity studies have been conducted with melflufen. This is justified considering that melflufen is an alkylating agent and thus per definition is a genotoxic and embryolethal substance. Melflufen is indicated for late-stage anticancer treatment in patients with few treatment options. The molecule has identical alkylating functions as cyclophosphamide, bendamustine, chloroambucil, and melphalan, compounds with documented carcinogenic and teratogenic activity. These properties are expected also for melflufen.

No phototoxic potential of melflufen was identified.

**Key safety findings**

Key safety findings from nonclinical studies and relevance to human usage are presented in Table 1

**Table 1 Key safety findings and relevance to human usage**

| Key safety findings (from nonclinical studies) | Relevance to human usage |
|---|---|
| Alkylator toxicity | Target organs of toxicity are those expected of an alkylator, i.e. the bone marrow, lymphoid organs, and testes, and at higher doses the gastrointestinal epithelium. |
| Cardiac effects | High-dose melflufen given to rats resulted in a minor effect on heart rate, but in the absence of any ECG alterations from Holter monitoring in dogs, the rat data are not considered indicative of a clinical risk. |

## Module SIII: Clinical trial exposure

Exposure to melflufen in clinical trials included in the integrated summary of safety (ISS) is provided in Table 2. The clinical trials included are:

- OP-107 (BRIDGE): data lock point 5 April 2021
- OP-103 (OCEAN): data lock point 3 February 2021
- OP-106 (HORIZON): data lock point 31 March 2020
- O-12-M1: data lock point 9 November 2017

Clinical data from melflufen treatment are available from 491 patients with relapsed-refractory MM who received treatment with melflufen as a single-agent (at a dose of 40 mg) or in combination with dexamethasone (at doses ranging from 15 to 55 mg) (safety population [SP]) (Table 2).

The targeted safety population (TSP) includes the 431 patients who received a starting dose of melflufen 30 or 40 mg on Day 1 of their first 28-day cycles in combination with dexamethasone.

Presentation of safety concerns (i.e. important identified risks, important potential risks, and missing information) in the risk management plan (RMP) focuses on patients receiving melflufen plus dexamethasone in the TSP. The rationale for this focus is that this population comprises patients on the same starting dose and dosing regimen as the intended treatment regimen.

**Table 2 Exposure to melflufen in clinical trials included in the ISS**

| **Treatment** | **Number of patients** | | **Treated cycles median (min, max)** |
|---|---|---|---|
| Melflufen (multiple myeloma patients) | SP | TSP | TSP |
| Melflufen single-agent[a] | 13 | 0 | - |
| **Melflufen plus dexamethasone** | 478 | 431[b] | 5.0 (1, 40) |
| Total | 491 | 431 | 5.0 (1, 40) |

ISS integrated summary of safety; max maximum; min minimum; SP safety population; TSP targeted safety population.
[a] Single-agent in Phase II of Study O-12-M1.
[b] Focus is on the targeted safety population/melflufen plus dexamethasone when presenting safety concerns in Part II: Module SVII – Identified and potential risks.
The table includes data from Studies O-12-M1, OP-103, OP-106, and OP-107.
Source: ISS Table 18.1.1.1, ISS Table 18.1.1.2, ISS Table 18.1.12.2 and CSR O-12-M1 Table 12.

Duration, dose, age and sex, and racial origin in the TSP are provided in Table 3 to Table 7.

**Table 3 Treatment duration and number of cycles of melflufen (targeted safety population)**

| **Duration of treatment (weeks)[a]** | |
|---|---|
| N | 431 |
| Median (min, max) | 21.6 (4, 164) |
| **Total number of treated cycles[b]** | |
| N | 431 |
| Median (min, max) | 5.0 (1, 40) |

max maximum; min minimum.
[a] Calculated as (date of last dose of melflufen + 21 [or 28 ] - date of first dose of melflufen + 1) / 7.
[b] Calculated as the sum of the number of cycles where a patient has received at least 1 dose of melflufen during a cycle.
The table includes data from Studies O-12-M1, OP-103, OP-106, and OP-107.
Source: ISS Table 18.1.12.2

**Table 4 Relative dose intensity of melflufen (targeted safety population)**

| **Relative dose intensity of melflufen (%)[a]** | **n[b]** | **Mean (SD)** |
|---|---|---|
| | 374 | 92.4 (12.52) |
| **Relative dose intensity of melflufen (%) by cycle[c]** | | |
| Cycle 1 | 374 | 91.1 (15.28) |
| Cycle 2 | 308 | 86.8(18.59) |
| Cycle 3 | 249 | 81.3 (23.76) |
| Cycle 4 | 216 | 80.1 (23.79) |
| Cycle 5 | 184 | 75.3 (26.34) |
| Cycle 6 | 155 | 74.5 (25.83) |
| Cycle 7 | 139 | 71.6 (26.48) |
| Cycle 8 | 117 | 71.3 (25.50) |
| Cycle 9 | 100 | 70.3 (27.91) |
| Cycle 10 | 85 | 68.7 (27.44) |
| Cycle 11 | 72 | 67.4 (27.55) |
| Cycle 12 | 60 | 65.0 (26.88) |
| Cycle 13 | 50 | 66.3 (26.36) |
| Cycle 14 | 41 | 61.2 (26.34) |
| Cycle 15 | 32 | 65.3 (26.08) |
| Cycle 16 | 24 | 62.3 (25.57) |
| Cycle 17 | 17 | 60.1 (25.43) |
| Cycle 18 | 13 | 61.7 (24.36) |
| Cycle 19 | 11 | 58.8 (28.61) |
| Cycle 20 | 9 | 54.5 (27.45) |

SD standard deviation.
[a] Calculated as (actual dose intensity [mg/cycle] / planned dose intensity [mg/cycle] x 100%.
[b] Only patients with completed cycles were included in this calculation. If no subsequent dose of melflufen was administered, the cycle was not considered complete.
[c] Calculated as (actual dose intensity of melflufen by cycle [mg/length of the actual cycle in days] / planned dose intensity of melflufen by cycle [mg/length of the planned cycle in days]) × 100%.
The table includes data from Studies O-12-M1, OP-103, OP-106, and OP-107.
Source: ISS Table 18.1.12.2

**Table 5 Exposure to melflufen by age and sex (targeted safety population)**

| Age group (years)[a] | Number of patients (%) |
|---|---|
| <65 | 177 (41.1) |
| ≥65 – ≤75 | 188 (43.6) |
| >75 | 66 (15.3) |
| **Total** | 431 |
| **Sex** | |
| Male | 246 (57.1) |
| Female | 185 (42.9) |
| **Total** | 431 |

[a] Age (years) calculated as [(date of informed consent) – (date of birth) / 365.25].
The table includes data from Studies O-12-M1, OP-103, OP-106, and OP-107.
Source: ISS Table 18.1.2.2

**Table 6 Exposure to melflufen by racial group (targeted safety population)**

| Racial group | Number of patients (%) |
|---|---|
| Asian | 7 (1.6) |
| Black or African American | 16 (3.7) |
| Native Hawaiian or other Pacific Islander | 1 (0.2) |
| Caucasian/white | 388 (90.0) |
| Other | 2 (0.5) |
| Not reported | 2 (0.5) |
| Unknown | 15 (3.5) |
| **Total** | 431 |

The table includes data from Studies O-12-M1, OP-103, OP-106, and OP-107.
Source: ISS Table 18.1.2.2

**Table 7 Exposure to melflufen by weight and body surface area (targeted safety population)**

| | |
|---|---|
| **Weight (kg)** | |
| N | 429 |
| Median (min, max) | 74.0 (40.0, 140.0) |
| **Weight category** (kg), n (%) | |
| <60 | 49 (11.4) |
| ≥60 to <75 | 170 (39.4) |
| ≥75 to <95 | 155 (36.0) |
| ≥95 | 55 (12.8) |
| Missing | 2 (0.5) |
| **Body surface area ($m^2$)[a]** | |
| N | 421 |
| Median (min, max) | 1.847 (1.26, 2.71) |
| **Body surface area category** ($m^2$), n (%) | |
| <1.60 | 45 (10.4) |
| ≥1.60 to <1.85 | 170 (39.4) |
| ≥1.85 to <2.15 | 158 (36.7) |
| ≥2.15 | 48 (11.1) |
| Missing | 10 (2.3) |

[a] Body surface area is computed using the Mosteller formula: ([height (cm) x weight (kg] / 3600)$^{0.5}$.
The table includes data from Studies O-12-M1, OP-103, OP-106, and OP-107.
Source: ISS Table 18.1.2.2

# Module SIV: Populations not studied in clinical trials

## SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

| Criterion | Reason for exclusion | Missing information | Rationale |
|---|---|---|---|
| Evidence of mucosal or internal bleeding and/or platelet transfusion refractory | To allow unconfounded assessment of risk for bleeding. | No | Bone marrow suppression with thrombocytopenia and bleeding included in SmPC section 4.4. |
| Known active infection requiring parenteral or oral anti-infective treatment | To allow unconfounded assessment of risk for infection. | No | Bone marrow suppression with neutropenia and infection included in SmPC section 4.4. |
| Other malignancy within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix | To allow unconfounded assessment of the disease under study relative to potential impact on overall survival, the need for other anticancer treatment, or concomitant complication of the other primary tumour that could impact endpoints of the study. | No | Interfere with assessment of risk for second primary malignancies with melflufen. |
| Pregnant or breast-feeding females | Melflufen is an alkylating agent, per definition genotoxic, and can cause chromatid or chromosome damage in humans. | No | Pregnancy and breast-feeding included in SmPC section 4.6. |
| Known HIV or hepatitis B or C viral infection | Risk for transmission of infection at blood test. Suspicion of possible risk for activation of chronic infection. | No | Patients with active hepatitis may receive melflufen with relevant prophylaxis if the treatment benefit outweighs the risk.<br>Reactivation of hepatitis has not been reported in clinical trials. |

## SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions that develop after longer exposure time than in the present clinical development programme, or adverse reactions associated with impaired renal function developing during the course of the MM disease.

### SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

**Table 8 Exposure of special populations included or not in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| Pregnant women | Not included in the clinical development programme |
| Breast-feeding women | |
| Patients with relevant comorbidities:<br>• Patients with hepatic impairment<br>• Patients with renal impairment[a]<br>• Patients with severe cardiovascular impairment[b]<br>• Immunocompromised patients<br>• Patients with a disease severity different from inclusion criteria in clinical trials | <br>Not included in the clinical development programme<br>Number of patients: 123 (of 431) patients<br>Not included in the clinical development programme<br>Patients with MM are immunocompromised due to the disease and previous treatment(s)<br>Not included in the clinical development programme |
| Population with relevant different ethnic origin | Number of patients by race:<br>Asian 7<br>Black or African American 16<br>Native Hawaiian or Other Pacific Islander 1<br>Caucasian/white 388<br>Other 2<br>Not reported 2<br>Unknown 15<br>Total 431 |
| Subpopulations carrying relevant genetic polymorphisms | The metabolism of melflufen indicates that polymorphisms in the different enzyme systems have no significant impact, and thus, subpopulation studies have not been performed. |

[a] Defined as estimated glomerular filtration rate ≥15 to <60 mL/min.
[b] Defined as a significant history of cardiovascular disease (e.g. myocardial infarction, significant conduction system abnormalities, uncontrolled hypertension, ≥Grade 3 thromboembolic event in the last 6 months).

## Module SV: Postauthorisation experience including European EAP program

Melflufen (Pepaxto®) was approved by the Food and Drug Administration (FDA) on 26 February 2021. After interactions and dialogue with the FDA, Oncopeptides decided to withdraw the New Drug Application (NDA) on 22 October 2021. On 13 January 2022 Oncopeptides requested to rescind the 22 October 2021 letter, and discussions between Oncopeptides and FDA regarding Pepaxto and the NDA 214383 is currently ongoing.

Postauthorisation safety information received by Oncopeptides for the period of 26 February 2021 to 27 August 2022 has been summarised in Periodic Adverse Drug Experience Reports (PADERs) and submitted to the FDA.

Market experience with melflufen corresponds to approximately 1100 treatment cycles distributed for commercial use in the USA. In addition, melflufen corresponding to

approximately 300 treatment cycles has been distributed for use in a Managed Access Program in Europe. Up to 31 December 2021, 57 case reports with a total of 139 events have been received by Oncopeptides; 18 of the case reports contained SAEs. In the majority of case reports information was limited. There were 8 patients with fatal events, 1 patient with thrombocytopenia experienced a fatal bleeding after surgery, 1 patient with a suspected progression and neutropenia died due to pleural effusion and pyrexia. In the remaining 6 fatal cases information is very limited; 1 patient died from unspecified hematotoxicity, 1 from General physical health deterioration, 1 from disease progression and in the remaining 3 cases the only event term reported was Death. No new safety findings have been identified during safety surveillance. Next detailed safety data summary will be provided in next PSUR submission.

Overall the safety profile noted in case reports from post marketing use is similar to what is seen in the clinical studies, with thrombocytopenia/platelet count decreased being the most reported events.

In summary, no new safety concerns have been identified based on review of all postauthorisation spontaneous and solicited reports received up to 27 August 2022
The reported ADEs are consistent with the known safety profile of melflufen and/or are indicative of the underlying disease.

# Module SVI: Additional EU requirements for the safety specification

### Potential for misuse for illegal purposes

Melflufen is administered in the hospital or office-based settings; hence, the potential for misuse for illegal purposes is considered low.

### Potential for off-label use

The safety of melflufen at doses required for myeloablation has not been studied in humans. Nonclinical safety studies in dogs administered melflufen at dosages exceeding the recommended dose for relapsed and refractory MM was associated with mortality. Therefore, the SmPC section 4.4 includes a warning to not use melflufen for conditioning treatment prior to stem cell transplantation.

# Module SVII: Identified and potential risks

## SVII.1: Identification of safety concerns in the initial RMP submission

### SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

**Reasons for not including an identified or potential risk in the list of safety concerns in the RMP**

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

The following nonhaematological treatment-emergent adverse events (TEAEs) were reported by >15% of 431 patients treated with melflufen plus dexamethasone in the TSP in melflufen clinical trials. All TEAEs are considered adverse drug reactions (ADRs) and are included in the SmPC section 4.8:

- Nausea was reported in 88 patients (20.4%); 3 events (0.7%) were treatment-related Grade 3/4, and none was serious. Antiemetic prophylaxis is given according to instructions in the SmPC section 4.2.
- Fatigue was reported in 87 patients (20.2%); 5 events (1.2%) were treatment-related Grade 3/4, and 2 events (0.5%) were serious.
- Asthenia was reported in 83 patients (19.3%); 6 events (1.4%) were treatment-related Grade 3/4, and 1 event (0.2%) was serious.
- Diarrhoea was reported in 82 patients (19.0%); 2 events (0.5%) were treatment-related Grade 3/4, and 3 events (0.7%) were serious. Diarrhoea is treated according to standard clinical practice.
- Pyrexia was reported in 74 patients (17.2%); 3 events (0.7%) were treatment-related Grade 3/4, and 7 events (1.6%) were serious. Pyrexia is treated according to standard clinical practice.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

The following haematological TEAEs were reported by >15% of 431 patients treated with melflufen plus dexamethasone in the TSP in melflufen clinical trials. All TEAEs are considered ADRs and are included in the SmPC section 4.8:

- Anaemia was reported in 288 patients (66.8%); 171 events (39.7%) were treatment-related Grade 3/4, and 11 events (2.6%) were serious.
- Thrombocytopenia was reported in 285 patients (66.1%); 249 events (57.8%) were treatment-related Grade 3/4, and 14 events (3.2%) were serious.
  Platelet count decreased was reported in 79 patients (18.3%); 68 events (15.8%) were treatment-related Grade 3/4, and 9 events (2.1%) were serious.
- Neutropenia was reported in 247 patients (57.3%); 225 events (52.2%) were treatment-related Grade 3/4, and 8 events (1.9%) were serious.
  Neutrophil count decreased was reported in 74 patients (17.2%); 65 events (15.1%) were treatment-related Grade 3/4, and 2 events (0.5%) were serious.
  White blood cell count decreased was reported in 72 patients (16.7%); 56 events (13.0%) were treatment-related Grade 3/4, and none was serious.

### SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

For details on important identified risks, important potential risks, and missing information, see Section SVII.3.

### SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

### SVII.3 Details of important identified risks, important potential risks, and missing information

### SVII.3.1 Presentation of important identified risks and important potential risks

Not applicable.

### SVII.3.2 Presentation of the missing information

Not applicable

## Module SVIII: Summary of the safety concerns

Not applicable

# Part III: Pharmacovigilance plan (including postauthorisation safety studies)

## III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities (adverse reactions reporting and signal detection) are sufficient to manage the safety concerns of the medicinal product.

## III.2 Additional pharmacovigilance activities

None

## III.3 Summary table of additional pharmacovigilance activities

None

# Part IV: Plans for postauthorisation efficacy studies

There are no planned postauthorisation efficacy studies.

# Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

## V.1 Routine risk minimisation measures

None.

## V.2 Additional risk minimisation measures

None

## V.3 Summary of risk minimisation measures

None.

# Part VI: Summary of the risk management plan

# Summary of risk management plan for Pepaxti® (melphalan flufenamide)

This is a summary of the risk management plan (RMP) for Pepaxti. The RMP details important risks of Pepaxti, how these risks can be minimised, and how more information will be obtained about Pepaxti's risks and uncertainties (missing information).

Pepaxti's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Pepaxti should be used.

This summary of the RMP of Pepaxti should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European public assessment report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Pepaxti's RMP.

## I. The medicine and what it is used for

Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 3 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 SmPC for the full indication).

It contains melphalan flufenamide as the active substance, and it is given by intravenous infusion after reconstitution and dilution.

Further information about the evaluation of Pepaxti's benefits can be found in Pepaxti's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary>.

## II Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Pepaxti, together with measures to minimise such risks and the proposed studies for learning more about melphalan flufenamide's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Pepaxti is not yet available, it is listed under 'missing information' below.

## II.A List of important risks and missing information

Important risks of Pepaxti are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Pepaxti. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. use in patients with severely impaired kidney function).

| **List of important risks and missing information** | |
|---|---|
| Missing information | None |

## II.B Summary of important risks

None.

## II.C Postauthorisation development plan

### II.C.1 Studies which are conditions of the marketing authorisation

There are no planned studies which are conditions of the marketing authorisation or specific obligation of Pepaxti.

### II.C.2 Other studies in postauthorisation development plan

None

# Annexes

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## Annex 4 Specific adverse drug reaction follow-up forms

Not applicable

# Annex 6 Details of proposed additional risk minimisation activities

Not applicable