Melphalan flufenamide (Pepaxti®) with dexamethasone for the treatment of multiple myeloma (MM)

General information

Drug description [1]	Indication [2]
Melphalan flufenamide (melflufen, Pepaxti®) is a first-in-class peptide-drug conjugate that targets aminopeptidases and rapidly and selectively releases alkylating agents into tumour cells.	Melphalan flufenamide (Pepaxti®) is indicated, in combination with dexamethasone, for the treatment of adult patients with MM 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.

Current treatment [3]

- NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM:
  - Lenalidomide in combination with dexamethasone for adults who have received 2 or more prior therapies.
  - Ixazomib, with lenalidomide and dexamethasone, for adults who have already had 2 or 3 lines of therapy.
  - Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent.
  - Pomalidomide, in combination with low-dose dexamethasone for adults at third or subsequent relapse: that is, after 3 previous treatments including both lenalidomide and bortezomib.
  - Daratumumab monotherapy for adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after three previous therapies.

Regulatory status

EMA [2, 4]	FDA [5, 6]
Approval status for this indication: On 23 June 2022, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Pepaxti®. **UPDATE**: Date of issue of marketing authorisation valid throughout the European Union: 17/08/2022 The full indication is: ❖ Pepaxti® is indicated, in combination with dexamethasone, for the treatment of adult patients with MM 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. **Other indications**: none ✓ **Orphan status**	**Approval status for this indication**: not approved **Other indications:** On 26 February 2021, the FDA granted accelerated approval to melphalan flufenamide (Pepaxto®) in combination with dexamethasone for adult patients with relapsed or refractory MM who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD-38 directed monoclonal antibody. Limitations of Use: Pepaxto® is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials.

Costs

Currently, no cost information is available.

Warnings and precautions [5, 7]

- **Thrombocytopenia**
  - Monitor platelets counts at baseline, during treatment, and as clinically indicated.
  - Dose delay or dose reduction may be required to allow recovery of platelets.
- **Neutropenia**
  - Monitor neutrophil counts at baseline, during treatment and as clinically indicated.

- Monitor patients with neutropenia for signs of infection.
- Dose delay or dose reduction may be required to allow recovery of neutrophils.

❖ **Anaemia**
- Monitor red blood cell counts at baseline, during treatment, and as clinically indicated.

❖ **Infections**
- Monitor for signs/symptoms of infection and treat promptly.

❖ **Gastrointestinal events**
- Nausea and diarrhoea are very common and vomiting is common during treatment with Pepaxti®. Prophylaxis with anti-emetic agents should be considered prior to and during infusion with melphalan flufenamide.

❖ **Thromboembolic events**
- Venous thromboembolic events have been observed in patients receiving Pepaxti® in combination with dexamethasone. 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.

❖ **Increased risk of mortality with Pepaxto® at dosages higher than the recommended dosage**
- Dosages exceeding the recommended dose for Pepaxto® may be associated with mortality.

❖ **Carcinogenicity**
- **Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)**
  - AML and MDS have occurred in patients with MM who have received Pepaxti®.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®. 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 MM. Melphalan flufenamide is not indicated in combination with lenalidomide or thalidomide.
- Patients should be monitored closely before and during treatment for occurrence of SPM.
- Monitor patients long-term for the development of secondary malignancies.

❖ **Embryo-foetal toxicity**
- Can cause foetal harm.
- Advise patients of reproductive potential of the potential risk to a foetus and to use effective contraception.

❖ **Prior autologous stem cell transplant**
- Pepaxti® is not recommended in patients who have progressed within 36 months after an ASCT. This is based on results from study OP-103 (OCEAN), a randomised phase 3 trial in patients with relapsed or refratory MM following 2 to 4 lines of prior therapy and refractory to lenalidomide and the last line of therapy.

❖ **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.

❖ **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.

Study characteristics: HORIZON trial [1]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)

HORIZON, OP-106 NCT02963493	157[1]	melflufen 40 mg IV on day 1 of each 28-day cycle plus once weekly oral dexamethasone at a dose of 40 mg (20 mg in patients older than 75 years)	-	ORR (partial response or better)[2]	single-arm, multicenter, phase II study[3]	-	Oncopeptides AB	[1]
Efficacy							**Safety (n=157)**	
<u>Efficacy among patients of the all-treatment population, n=157 (data cutoff date January 14, 2020)</u> **ORR** per investigator assessment: 29% (95% CI, 22%-37%) **ORR** per independent review committee: 30% (95% CI, 23%-38%) **sCR**: 1% **VGPR**: 11% **PR:** 18% **Minimal response**: 16% **CBR**: 45% (95% CI, 37%-53%) **Median time to PR or better**: 1.9 months (range, 1.0-7.4 months) **Median duration of PR or better**: 5.5 months (95% CI, 3.9-7.6 months) **Median PFS**: 4.2 months (95%CI, 3.4-4.9 months) **Median OS:** 11.6 months (95% CI, 9.3-15.4 months); with an estimated 1-year event-free rate of 48.8% (95% CI, 39.6%-57.4%) **<u>Efficacy among patients of the triple-class–refractory population, n=119</u>** **ORR** per investigator assessment: 26% (95% CI, 18%-35%) **ORR** per independent review committee: 26% (95% CI, 18%-35%) **VGPR:** 11% **PR**:15% **Minimal response**: 13% **CBR**: 39% (31%-49%) **Median time to PR or better**: 1.9 months (range, 1.0-6.1 months) **Median duration of PR or better**: 4.4 months (95% CI, 3.4-7.6 months) **Median PFS:** 3.9 months (95%CI, 3.0-4.6 months) **Median OS**: 11.2 months (95%CI, 7.7-13.2 months); with an estimated 1-year event-free rate of 41.9% (95% CI, 31.6%-51.8%) **<u>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 (n=52, investigator-assessed)</u> [7]:** **ORR:** 28.8% (95% CI, 17.1%, 43.1%)							**TEAES**: n=157/157 (100%) in the all-treated population **Patients reporting at least one melflufen-related TEAE**: n=149/157 (95%) **TEAEs grade ≥3**: n=150/157 (96%) **Serious TEAEs**: n=77/157 (49%) **Deaths due to TEAEs**: n=10/157 (6%)[4] **Patients who had least one TEAE leading to melflufen treatment discontinuation**: n=34/157 (22%)	

[1] At baseline, patients had received a median of **5** prior lines of therapy; 98% had disease that was refractory to the last line of therapy received; 76% had triple-class–refractory disease; 59% had MM that was refractory to prior alkylator therapy.
[2] Assessed by the investigator and confirmed by independent review.
[3] The primary analysis is complete with long-term follow-up ongoing.
[4] None of the deaths were considered related to melflufen.

Stringent complete response: 0
Complete response: 0
VGPR: 9.6%
PR: 19.2%
Median duration of response: 7.6 months (95% CI, 3.0-12.3)
Median time to response: 2.3 months (range, 1.0-10.5)

Risk of bias - study level (case series) [8]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	no	yes	yes	yes	yes

Overall risk of bias: moderate

Study characteristics: OCEAN trial [9-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
OCEAN, Study OP-103 NCT03151811	495 (1:1)	40 mg melflufen IV on day 1 and 40 mg dexamethasone orally on days 1, 8, 15 and 22 of each 28-day cycle[5]	4 mg pomalidomide capsules orally on days 1–21 and 40 mg dexamethasone orally on days 1, 8, 15 and 22 of each 28-day cycle[6]	PFS	ongoing[7], randomised, head-to-head, superiority, open-label, global, phase III trial	-	Oncopeptides AB.	[10]

Efficacy (I vs. C), ITT population: n=495

As of **data cutoff (3 Feb 2021),** 51% of patients in the melflufen group and 52% in the pomalidomide group were **alive** and ongoing in the study.
Median PFS: 6.8 months (95% CI, 5.0–8.5; 67% of patients had an event) vs. 4.9 months (4.2–5.7; 76% of patients had an event); HR 0.79 (95% CI, 0.64–0.98); log-rank p=0.032; at a median follow-up of 15.5 months (IQR 9.4–22.8) vs. 16.3 months (10.1–23.2)

Safety (I vs. C), safety population: n=474[8]

Serious TEAEs: n=95/228 (42%) vs. n=113/246 (46%)[9]
Treatment discontinuation due to a TEAE: n=60/228 (26%) vs. n=54/246 (22%)

[5] For patients aged ≥75 years, the dexamethasone dose in both arms will be reduced from 40 mg to 20 mg on days 1, 8, 15 and 22 of each 28-day cycle.
[6] For patients aged ≥75 years, the dexamethasone dose in both arms will be reduced from 40 mg to 20 mg on days 1, 8, 15 and 22 of each 28-day cycle.
[7] The OCEAN trial is currently ongoing; estimated study completion date is 09/2024.
[8] Patients who received at least one dose of study drug.
[9] 18% vs. 21% were considered to be treatment related.

ORR: 33% (95% CI, 27–39) vs. 27% (22–33); p=0.16 **CR**: 3% vs. 1% **VGPR**: 9% vs. 7% **PR**: 20% vs. 18% **Median OS:** 19.8 months (95% CI, 15.1–25.6) at a median follow-up of 19.8 months (IQR 12.0–25.0) vs. 25.0 months (95% CI, 18.1–31.9) at a median follow-up of 18.6 months (IQR 11.8–23.7); HR 1.10 (95% CI, 0.85–1.44); p=0.47 **Time to first confirmed response**: 2.1 months (IQR 1.1–3.7) vs. 2.0 months (1.1–2.9) **Time to best confirmed response** (post-hoc analysis): 3.2 months (IQR 1.9–5.9) vs. 2.8 months (1.2–5.6)	**AEs leading to death:** n=27/228 (12%) vs. n=32/246 (13%)[10] **TEAEs leading to death** were considered possibly related to treatment with melflufen in 2 patients (1 patient with acute myeloid leukaemia and in 1 with pancytopenia and acute cardiac failure) and pomalidomide in 4 patients (2 patients with pneumonia, 1 with myelodysplastic syndromes, and 1 with COVID-19 pneumonia). **Overall deaths in the safety population:** n=106/228 (46%) vs. n=106/246 (43%)[11]

Risk of bias (RCT) [12]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	no	unclear[12]	yes[13]	unclear

Additional information [13]

28 July 2021: FDA is alerting patients and healthcare professionals that a clinical trial (OCEAN, Study OP-103) evaluating Pepaxto® (melphalan flufenamide) with dexamethasone to treat patients with MM showed an increased risk of death

- The trial compared Pepaxto® with low-dose dexamethasone to pomalidomide with low-dose dexamethasone in patients with relapsed or refractory (resistant) MM following 2-4 lines of prior therapy and in patients who were resistant to lenalidomide in the last line of therapy.
- FDA encourages healthcare professionals to review patients' progress on Pepaxto® and discuss the risks of continued administration with each patient in the context of other treatments. Patients currently receiving Pepaxto® should also discuss with their healthcare professional the risks and benefits of receiving Pepaxto®.
- In February 2021, FDA approved Pepaxto® under Accelerated Approval for use in combination with dexamethasone to treat adult patients with relapsed or refractory MM who have received at least four prior lines of therapy and whose disease was refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody. The manufacturer, Oncopeptides AB, was required to conduct the OCEAN trial as a post-approval requirement under the accelerated approval program.
- Due to the detrimental effect on OS in the OCEAN trial, FDA is requiring the manufacturer suspend enrollment in the trial. FDA has also suspended enrollment in other ongoing Pepaxto® clinical trials. Patients receiving clinical benefit from Pepaxto® may continue treatment in the OCEAN trial provided they are informed of the risks and sign a revised written informed consent.
- FDA continues to evaluate the OCEAN trial results and may hold a future public meeting to discuss these safety findings and explore the continued marketing of Pepaxto®. The agency will update patients and healthcare professionals when new information is available.

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CBR=clinical benefit rate, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete respons, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, IV=intravenously, MG=median gain, MM=multiple myeloma, n=number of patients, NICE=National Institute for Health and Care Excellence, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, sCR=stringent complete response, ST=standard treatment, TEAE=treatment-emergent adverse event, VGPR=very good partial response

References:

[10] Most commonly COVID-19 pneumonia (3% vs. 2%), pneumonia (1% vs. 2%), and multiorgan dysfunction syndrome (1% vs. 1%).

[11] 23 (10%) patients in the melflufen group and 33 (13%) in the pomalidomide group died within 30 days of receiving their last dose of study drug.

[12] The OCEAN trial is currently ongoing.

[13] The study was designed by the funder together with key advisors in the MM community. Study data were collected by site staff and study investigators. The funders compiled and maintained the data collected by the investigators. Data were analysed by the study sponsor. All authors and the sponsor participated in the interpretation of the data and writing and reviewing of the manuscript.

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