Myeloma Patients Europe

FACTSHEET

MYELOMA PATIENTS EUROPE

MELPHALAN FLUFENAMIDE (MELFLUFEN, PEPAXTI®)

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MPE
Myeloma
Patients
Europe

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Myeloma Patients Europe (MPE) has developed a series of factsheets for patients and patient advocates, providing an overview of available treatment options for myeloma and covering some topics related to the disease.

The factsheets cover important issues around the treatment, so that patients can feel safe and ask their doctor specific questions.

For each of the available therapies, the following topics will be addressed:

- What is myeloma?
- What is the particular treatment?
- How does the treatment work?
- What are the benefits?
- What are the side-effects?
- How and when is the treatment given?

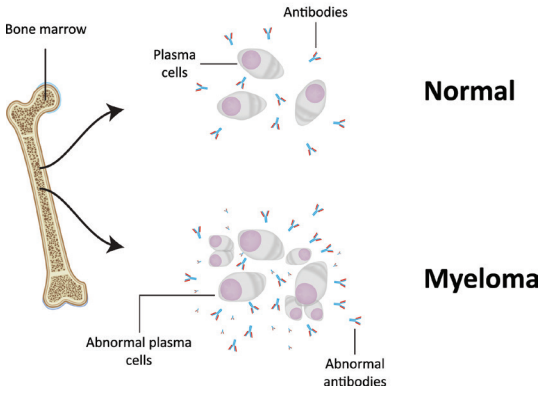
Myeloma treatment is constantly evolving and the factsheets will be updated regularly to reflect the latest developments.

What is myeloma?

Myeloma is a rare cancer of the bone marrow that causes the formation of abnormal plasma cells, known as cancerous myeloma cells, which divide uncontrollably. Usually, plasma cells help the body fight infections by making antibodies that recognise and attack viruses, bacteria, and other cancer cells. Myeloma affects multiple places in the body (this is why it is sometimes referred to as 'multiple myeloma') where bone marrow is normally active, such as the bones of the spine, pelvis, rib cage, and the areas around the shoulders and hips.

Myeloma causes pain, anaemia (low red blood cells), fatigue, fractures, recurring infections, bruising, and high blood calcium (hypercalcaemia). These symptoms usually require treatment. After treatment, most myeloma symptoms may subside and not require treatment (also known as remission). Many patients may also be on treatment during remission to ensure their myeloma is kept at bay (known as maintenance treatment). After some time, the patient's symptoms may reappear, requiring treatment (also known as relapse). Myeloma usually occurs with periods of remission and relapse, and after some time, the patient's disease no longer responds to treatment (known as refractory myeloma).

Treatment may involve combining more drugs, often three or four, which is considered more effective than a single drug. Myeloma generally cannot be cured, but survival rates are increasing due to the availability of new treatments, and many patients can enjoy a good quality of life. Several new therapies have recently been approved or are under consideration for use following relapse or refractory myeloma.



What is melphalan flufenamide (melflufen, Pepaxti®)?

Melphalan flufenamide (also known as melflufen, trade names Pepaxti®, Pepaxto®) is derived from the chemotherapeutic agent melphalan manufactured by Oncopeptides AB. Melflufen is indicated for treating adult myeloma patients with dexamethasone. Patients who are given melflufen have received at least three prior lines of therapies and have myeloma refractory to at least one proteasome inhibitor, one immunomodulatory agent and one anti-CD38 monoclonal antibody. Also, patients being administered melflufen have progressed on or after their previous treatment line. Patients who have received an autologous stem cell transplant should be three years or more from transplantation[1].

Melflufen was granted "orphan drug designation" by the European Commission in 2015. An orphan drug designation is a status assigned to medicines developed for rare disease conditions that affect fewer than five patients per 10,000 inhabitants in the EU. On 23 June 2022, the Committee for Medicinal Products for Human Use (CHMP) recommended granting marketing authorisation in Europe for using melflufen in treating myeloma[2]. Melflufen was authorised by the European Medicines Agency (EMA) in August 2022.

How does melphalan flufenamide (melflufen, Pepaxti®) work?

Melflufen is a first-in-class peptide drug conjugate – a treatment that combines a chemotherapy drug (melphalan) and a peptide (a small protein). Melphalan is an older and widely used chemotherapy drug commonly employed to treat multiple myeloma. Melflufen is a modified version of melphalan. Specifically, adding a peptide to melphalan helps the melphalan more rapidly and efficiently find and enter myeloma cells, resulting in a more effective drug[3].

Once melfuflen is inside myeloma cells, it is broken down into its active form by peptidases (enzymes inside cells) to release the chemotherapy drug melphalan. Melphalan then acts as an alkylating agent – a class of compounds that causes changes to the structure of DNA, which prevents the cells from replicating and ultimately leads to myeloma cell death[4].

What are the benefits of melphalan flufenamide (melflufen, Pepaxti®)?

The safety and efficacy of melflufen were evaluated in the phase 2 HORIZON study in 157 relapsed/refractory multiple myeloma patients who were refractory to pomalidomide and/or an anti-CD38 monoclonal antibody. Of the 157 patients enrolled, 29% of those who received treatment had a response (a reduction in signs and symptoms of myeloma). In addition, the progression-free survival (the time from treatment to the progression of disease or death) was 4.2 months and overall survival (the median time patients lived after treatment) was 11.6 months[5].

Additionally, the phase 3 OCEAN trial investigated treatment with melfufen in 495 relapsed/refractory multiple myeloma patients who received 2-4 lines of prior therapy and were refractory to lenalidomide[6]. This study compared the efficacy of pomalidomide with melflufen. Thus far, the results suggest that treatment with melflufen lengthens the time before disease progression or death compared to pomalidomide[7]. Further developments are likely available in the future. The estimated completion date of the OCEAN trial is September 2024.

Although melflufen is approved by the EMA, it is important to note that in 2021, the FDA suspended enrolment in the Phase 3 OCEAN trial of melflufen in the United States, as the trial showed an increased risk of death in patients receiving melflufen[8]. Specifically, the study was suspended because statistical calculations (the "hazard ratio") showed patients were more likely to die while receiving the melflufen than pomalidomide[1]. Oncopeptides AB stopped marketing melflufen in the United States on October 22, 2021[9].

How is melphalan flufenamide (melflufen, Pepaxti®) given?

Melflufen is administered through an infusion (drip) for over 30 minutes into a vein and is usually given once every 28 days. The specific dose of melflufen

may vary depending on your body weight, any side effects that you may experience and your response to the medication.

Patients receiving melflufen will also receive dexamethasone (40 mg by mouth, or 20mg by mouth, if older than 75) on days 1, 8, 15 and 22 of each 28-day cycle.

What are the side-effects of teclistamab?[1]

The safety of melflufen was evaluated in the HORIZON trial of 157 patients. The most common laboratory abnormalities (changes in the blood) that occurred in >50% of patients were[5]:

- Leukopenia (decreased leukocytes, a type of immune/white blood cell; 99%),
- Thrombocytopenia (decreased platelets, needed for blood clotting; 99%),
- Lymphopenia (decreased lymphocytes, a type of immune/white blood cell; 97%),
- Neutropenia (decreased neutrophils, a type of immune/white blood cell; 95%),
- Anaemia (decreased red blood cells; 84%)
- Increased creatinine (indication of kidney dysfunction; 68%)

Changes in blood levels can be seen throughout treatment and will likely require frequent monitoring. Taking melflufen may increase your risk of infection, and therefore you may be advised to take precautions to prevent infection such as handwashing, wearing a mask and avoiding large crowds. Your provider may also recommend that you be up to date on vaccinations before treatment. In addition, you may be advised to take precautions to limit your risk of falling (e.g., removing trip hazards from your home), as low platelets can increase your risk of bleeding.

As well as changes in the blood, the other most common adverse reactions seen with melflufen (occurring in > 10% of patients) were[5]:

- Nausea (32%)
- Fatigue (29%)
- Weakness/loss of energy (27%)
- Diarrhoea (27%)

- Fever (24%)
- Cough (17%)
- Upper respiratory tract infections (16%)
- Constipation (15%)
- Decreased appetite (14%)
- Peripheral oedema (swelling of the extremities e.g., legs and ankles) (14%)
- Headache (13%)
- Vomiting (13%)
- Bone pain (13%)
- Pain in the extremities (13%)
- Pneumonia (13%)
- Back pain (12%)
- Insomnia (11%)
- Dizziness (11%)
- Shortness of breath (dyspnoea) (11%)
- Joint pain (arthralgia) (10%)
- Changes in electrolytes e.g., low potassium (14%) or low calcium (10%)

In the HORIZON trial, 49% of patients experienced serious adverse events: the most frequent of which were pneumonia (10%), respiratory tract infection (6%) and thrombocytopenia (5%). Second primary cancers (a longer-tem side effect) also occurred in five of the 157 patients (~3%)[5].

Side effects related to melflufen can occur at any time throughout treatment. Some side effects may be managed with observation, blood product replacement, or growth stimulation drugs. Also, supportive care and other symptom-specific treatments (e.g., antibiotics for bacterial infections, antinausea drugs, or diarrhoea medications) can be prescribed. It is important to communicate with your doctor regarding any symptoms you are experiencing so that they may treat your side effects appropriately.

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MPE is a network of European myeloma patient organisations. It supports national patient organisations to improve treatment and access for patients in their countries and helps inform and raise awareness on a European level through its educational programmes. Please note, this information does not replace the information provided by your doctor. If there is anything that is not clear to you, please always ask your clinical team.

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