Selinexor (Nexpovio®) in combination with dexamethasone for the treatment of relapsed and refractory multiple myeloma (MM)

General information

Drug description [1]	Indication [2]
Selinexor (Nexpovio®) is a selective inhibitor of nuclear export compound that blocks exportin 1 and forces nuclear accumulation and activation of tumour suppressor proteins, inhibits nuclear factor κB, and reduces oncoprotein messenger RNA translation.	Selinexor (Nexpovio®) is indicated in combination with dexamethasone for the treatment of MM in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors (PIs), two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Current treatment

❖ According to the EHA-ESMO Clinical Practice Guideline [3], the following is recommended for patients at third and subsequent lines of treatment:

- For patients who have been exposed or are refractory to both bortezomib and lenalidomide:
  - DaraKd (daratumumab/carfilzomib/dexamethasone; I, A)
  - IsaPd (Isatuximab/pomalidomide/dexamethasone; I, A),
  - IsaKd (Isatuximab/carfilzomib/dexamethasone; I, A) and
  - EloPd (elotuzumab/pomalidomide/dexamethasone; II, B) are recommended.
- Patients with t(11;14), who are refractory to lenalidomide and are PI-sensitive may be treated with
  - VenVd (venetoclax/bortezomib/dexamethasone; I, A) if available.
- For triple-class refractory patients, Sd (selinexor/dexamethasone) or belantamab mafodotin monotherapy is recommended (II, B), if available.
- Results of phase III studies of melflufen, TCEs and CAR-Ts in triple-class refractory patients are awaited.

❖ NICE guidelines [4] recommend the use of a number of possible sequences of treatments for relapsed or refractory MM:

- Ixazomib, with lenalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating MM in adults only if they have already had 2 or 3 lines of therapy and the conditions in the managed access agreement for ixazomib are followed.
- Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of MM only in people who have received two or more prior therapies. The drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the manufacturer.
- Panobinostat in combination with bortezomib and dexamethasone is recommended, within its marketing authorisation, as an option for treating MM, that is, for 'adult patients with relapsed and/or refractory MM who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent' when the company provides panobinostat with the discount agreed in the patient access scheme.
- Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory MM in 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 3 previous therapies and the conditions in the managed access agreement are followed.
- Pomalidomide, in combination with low-dose dexamethasone, is recommended as an option for treating MM in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib, only when the company provides pomalidomide with the discount agreed in the patient access scheme.

Regulatory status

EMA [2, 5]	FDA [6, 7]
Approval status for this indication: On 28 January 2021, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Nexpovio® intended for the treatment of relapsed and refractory MM. The full indication is: ❖ Nexpovio® is indicated in combination with dexamethasone for the treatment of MM in adult patients who have received at least four prior therapies and whose disease is refractory to at least two PIs, two immunomodulatory	**Approval status for this indication**: On 3 July 2019, the FDA granted accelerated approval to selinexor (Xpovio®) in combination with dexamethasone for adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two PIs, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. **Other indications**: Selinexor is indicated: ❖ in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy.

agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 26/03/2021

This product is no longer an orphan medicine. It was originally designated an orphan medicine on 19 November 2014. Product was withdrawn from the Union Register of Orphan Medicinal Products by the European Commission in February 2021 upon request of the marketing authorisation holder at the time of the granting of a marketing authorisation.

Other indications:

- ❖ Nexpovio® is indicated in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy.

✓ **Medicine under additional monitoring**

- ❖ for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy (accelerated approval).

✓ **Fast track designation**
✓ **Orphan drug designation**

Costs

16 Nexpovio® tablets 20 mg = € 7,912.10 (ex-factory price) [8]

Posology [6]

- ❖ Advise patients to maintain adequate fluid and caloric intake throughout treatment. Consider intravenous hydration for patients at risk of dehydration.
- ❖ Provide prophylactic antiemetics. Administer a 5-HT3 receptor antagonist and other anti-nausea agents prior to and during treatment with selinexor.

Warnings and precautions for use [9]

❖ **Haematology**

- Patients should have their complete blood counts assessed at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment.
- Thrombocytopenia
  - o Thrombocytopenic events (thrombocytopenia and platelet count decreased) were frequently reported in patients receiving selinexor which can be severe (Grade 3/4).
  - o Grade 3/4 thrombocytopenia can sometimes lead to clinically significant bleeding and in rare cases may lead to potentially fatal haemorrhage.
  - o Thrombocytopenia can be managed with dose interruptions, modifications, platelet transfusions, and/or other treatments as clinically indicated. Patients should be monitored for signs and symptoms of bleeding and evaluating promptly.
- Neutropenia
  - o Neutropenia including severe neutropenia (Grade 3/4) has been reported with selinexor. In a few cases concurrent infections occurred in patients with Grade 3/4 neutropenia.
  - o Patients with neutropenia should be monitored for signs of infection and evaluated promptly.
  - o Neutropenia can be managed with dose interruptions, modifications, and colony-stimulating factors as per medical guidelines.

❖ **Gastrointestinal toxicity**

- Nausea, vomiting, diarrhoea, which sometimes can be severe and require the use of anti-emetic and anti-diarrhoeal medicinal products.
- Prophylaxis with 5HT3 antagonists and/or other anti-nausea agents should be provided prior to and during treatment with selinexor. Fluids with electrolytes should be administered to prevent dehydration in patients at risk.
- Nausea/vomiting can be managed by dose interruption, reduction and/or discontinuation, and/or initiation of other antiemetics medicinal products as clinically indicated.
- Diarrhoea can be managed with dose modification or administration of anti-diarrhoea medicinal products.

❖ **Weight loss and anorexia**

- Selinexor can cause weight loss and anorexia. Patients should have their body weight, nutritional status and volume checked at baseline, during treatment, and as clinically indicated.

- Monitoring should be more frequent during the first two months of treatment. Patients experiencing new or worsening decreased appetite and weight may require dose modification, appetite stimulants, and nutritional consultations.

❖ **Confusional state and dizziness**

- Selinexor can cause confusional state and dizziness. Patients should be instructed to avoid situations where dizziness or confusional state may be a problem and to not take other medicinal products that may cause dizziness or confusional state without adequate medical advice. Patients should be advised not to drive or operate heavy machinery until symptoms resolve.

❖ **Hyponatraemia**

- Selinexor can cause hyponatraemia. Patients should have their sodium levels checked at baseline, during treatment, and as clinically indicated. Monitoring should be more frequent during the first two months of treatment. Correct sodium levels for concurrent hyperglycaemia (serum glucose >150 mg/dL) and high serum paraprotein levels.
- Hyponatraemia should be treated as per medical guidelines (intravenous sodium chloride solution and/or salt tablets), including dietary review.
- Patients may require selinexor dose interruption and/or modification.

❖ **Cataract**

- Selinexor can cause new onset or exacerbation of cataract. Ophthalmologic evaluation may be performed as clinically indicated. Cataract should be treated as per medical guidelines, including surgery if warranted.

❖ **Tumour lysis syndrome (TLS)**

- TLS has been reported in patients receiving therapy with selinexor. Patients at a high risk for TLS should be monitored closely. Treat TLS promptly in accordance with institutional guidelines.

❖ **Women of childbearing potential/contraception in males and females**

- Women of childbearing potential should be advised to avoid becoming pregnant or abstain from sexual intercourse while being treated with selinexor and for at least 1 week following the last dose of selinexor.
- Women of childbearing potential and male patients of reproductive potential should be advised to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with selinexor and for at least 1 week following the last dose of selinexor.

❖ **Excipients:**

- This medicinal product contains less than 1 mmol sodium (23 mg) per 20 mg tablet, that is to say essentially 'sodium-free'.

Study characteristics [1, 10, 11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
STORM NCT02336815	122 (ITT-population)	oral selinexor (80 mg) plus dexamethasone (20 mg) twice weekly	-	Overall response[1]	phase 2b, multi-centre, open-label study	XPO1	Karyopharm Therapeutics	[1]

Efficacy (I vs. C)

PR or better: in 26% of patients (95% CI, 19-35), including 2 stringent **CRs** (in 2% of the patients), 6 **very good PRs** (in 5%), and 24 **PRs** (in 20%)
Both patients with **relapse after CAR-T therapy** had a PR.
Minimal response (according to IMWG criteria): in16 patients (13%),
Stable disease: in 48 patients (39%)
Progressive disease or disease that could not be evaluated for response: 26 patients (21%)
Median time to a partial response or better: was 4.1 weeks (range, 1-14)
Minimal response or better: in 39% of patients (95% CI, 31-49).
Median duration of response: 4.4 months (95% CI, 3.7-10.8)
Median PFS: 3.7 months (95% CI, 3.0-5.3)
Median OS: 8.6 months (95% CI, 6.2-11.3)

Safety[2] (I vs. C)

Patients with ≥1 AE: n=123/123 (100%)
Patients with ≥1 treatment-emergent SAE: n=78/123 (63%)
Patients with ≥1 treatment-related[3] SAE: n=39/123 (32%)
Death[4]: n=12/123 (8%)
Discontinuation[5]: n=22/123 (18%)

[1] Overall response was defined as a partial response or better, with response assessed by an independent review committee.
[2] Safety population: n=123
[3] Subset of treatment-emergent events. Relatedness per investigator assessment.
[4] Death due to AE(s); In the 12 patients with these AEs, 2 events were assessed by the investigator as being related to treatment.
[5] Because of an adverse event considered by the investigator to be related to selinexor or dexamethasone

Median OS in patients who had a PR or better or a minimal response or better: 15.6 months **QoL:** 88 patients had sufficient data to be included in longitudinal QoL analyses. Most patients did not experience QoL decline during the early cycles of selinexor treatment during the trial. The MCID decline, evaluated by two approaches, was greater among treatment non-responders than responders. A DID approach demonstrated greater decline between baseline and end of treatment for non-responders. **Efficacy results** (by Independent Review Committee) from the 83 patients whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab **(penta-refractory) [9]:** **Overall response rate** (includes sCR + VGPR + PR): 25.3%; 95% CI 16.4-36 **sCR, MRD negative**: 1.2% **CR**: 0 **VGPR:** 4.8% **PR:** 19.3% **Minimal response**: 12.0 **Stable disease**: 38.6% **Progressive disease/not evaluable**: 24.1% **Median time to first response**: 3.9 months **Median duration of response**: 3.8 months	

Risk of bias (study level) [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**
no	no	no, open-label	yes	yes[6]	High risk

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CAR-T=chimeric antigen receptor T, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, DID=difference-in-difference, DLBCL=diffuse large B-cell lymphoma, EHA=European Hematology Association, 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, MCID=minimal clinically important differences, MG=median gain, n=number of patients, MRD=minimal residual disease, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PI=proteasome inhibitor, PM=preliminary grade, PR=partial response, QoL=quality of life, RNA=ribonucleic acid, SAE=serious adverse event, sCR=stringent complete response, ST=standard treatment, TCE=T-cell engagers, TLS= tumour lysis syndrome, VGPR=very good partial response

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[6] The study was designed by the sponsor. The sponsor collected the data and analysed them in conjunction with the authors. A professional medical writer, funded by the sponsor, wrote the first draft of the manuscript under close direction of the authors.

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