Report XPOVIO™ - Selinexor

Product Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Selinexor **Brand Name:** - Xpovio™ (US)[1]; - Nexpovio (EU) [2] **Originator/licensee:** Karyopharm Therapeutics **Classification:** NCE **ATC code:**L01XX66 **Orphan Status:** **EU:**Yes **USA:**Yes **Mechanism of action:** reversible covalent selective inhibitor of nuclear export (SINE) that specifically blocks exportin 1 (XPO1).[1]	**Authorized Indication** Selinexor is indicated in combination with dexamethasone, for the treatment of pts with relapsed refractory MM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an antiCD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.[1] **Route of administration:**OS **Licensing status** **EU CHMP P. O. date:**28/01/2021 **FDA M.A. date:**03/07/2019 **EU Speed Approval Pathway:**Yes **FDA Speed Approval Pathway:**Yes --- **ABBREVIATIONS:** **BCLPD-R:** bortezomib, carfilzomib,lenalidomide, pomalidomide, daratumumab refractory; **CHMP**: Committee for Medicinal Products for Human Use **ITT:** Intention to Treat; **M.A.**: Marketing Authorization **MM**: Multiple Myeloma **ORR:** Overall Response Rate; **Pts**: patients **TEAE:** Treatment Emergent Adverse Event; **Vd:** bortezomib and dexamethasone.	**Summary of clinical EFFICACY:** ***Pivotal:*** **KCP-330-012 (STORM)Part 2(NCT02336815):**single-arm, open-label, multi-centre, international, phase 2b study that enrolled 123 adult pts who previously had received more than 3 anti-MM regimens and had penta-exposed, triple class-refractory MM (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab). Oral selinexor (80 mg) in combination with dexamethasone (20 mg) was administered on days 1 and 3, weekly, in 4-week cycles (28-days cycle – 8 doses per cycle) until disease progression, unacceptable toxicity or death. The primary endpoint was ORR, defined as a confirmed partial response (≥50% reduction in the serum level of myeloma protein) or better, with response adjudicated by Independent Review Committee.A total of 122 pts were included in the modified ITT population and ORR was 26% (95% CI, 19%-35%), including 2 stringent complete responses.[1][3][4] ***Supportive:*** **KCP-330-012 (STORM)Part 1(NCT02336815):** single-arm, open-label, multi-centre, international, phase 2b study that enrolled 78 adult pts with quad-exposed, double-class-refractory (i.e.previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, but not an anti-CD38 mab) and penta-exposed, triple-class-refractory MM (i.e.previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab). Oral selinexor (80 mg) in combination with dexamethasone (20 mg) was given twice weekly on days 1, 3, 8, 10, 15, and 17 (six doses per cycle of each 28-day cycle) until disease progression unacceptable toxicity or death. The primary endpoint was ORR (partial response or better). The ORR was 21% (95% CI, 13% to 31%).[3][5] **Summary of clinical SAFETY** Approximately 94% of pts in both the overall STORM population and the BCLPD-R subpopulation experienced at least one severe (Grade 3-4) TEAE. The most common severe TEAEs (occurring in at least 10% of patients) in the BCLPD-R subpopulation were anemia (44.6%), leukopenia (15.7%), lymphopenia (10.8%), neutropenia (24.1%), thrombocytopenia (59%), nausea (10.8%), fatigue (25.3%), and hyponatremia (21.7%).[1] **Ongoing studies:** • ***For the same indication:***Yes • ***For other indications:***Yes [Phase III, but if it is an O/OE drug, also Phase II] **Discontinued studies (for the same indication):** No	**Economic impact:** $22.977,50for 12 tablets/pack (20 mg) – US [7]. *Price for 28-day cycle:* $61.273,33 **Epidemiology:** MM is a plasma cell neoplasm that accounts for 1%-1.8% of all cancers and is the second most common haematological malignancy with an estimated incidence in Europe of 4.5-6.0/100,000/year. Despite the significant improvement in patients' survival over the past 20 years, only 10%-15% of pts achieve or exceed expected survival compared with the matched general population.[8] --- **POSSIBLE PLACE IN THERAPY:** currently, pts with triple-classrefractory MM have notreatment options with proven clinical benefit[9][10]. Belantamab mafodotin monotherapy or selinexor dexamethasone (Sd) may be suitable options.[11] **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** **BOSTON (NCT03110562):** phase III study that compared the efficacy of selinexor in combination with Vd (SVd) vs. Vd in pts who received 1-3 prior lines of therapy.[12] **OTHER INDICATIONS IN DEVELOPMENT:** Liposarcoma; Thymoma; COVID-19; Myelofibrosis; Myeloid Leukemia; Breast Cancer; Diffuse Large B-cell Lymphoma; Glioblastoma; other[13] **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** belantamab mafodotin[13] *Service reorganization: No *Possible off label use: Yes --- **References:** **[1].** https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212306Orig1s000MultidisciplineR.pdf **[2].** https://www.ema.europa.eu/en/medicines/human/summaries-opinion/nexpovio **[3].**https://clinicaltrials.gov/ct2/show/study/NCT02336815 **[4].** Chari A, Vogl DT, Gavriatopoulou M et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple M Engl J Med. 2019 Aug 22;381(8):727-738. **[5].**Vogl DT, Dingli D, Cornell RF, et al. Selective Inhibition of Nuclear Export With Oral Selinexor for Treatment of Re Refractory Multiple Myeloma. J Clin Oncol. 2018;36(9):859-866. **[7].** https://www.drugs.com/price-guide/xpovio **[8].** Usmani S.Z. Hoering A. Cavo M. et al. Clinical predictors of long-term survival in newly diagnosed transpla multiple myeloma - an IMWG Research Project. Blood Cancer J. 2018; 8: 123 **[9]**. Pick M, Vainstein V, Goldschmidt N, et al. Daratumumab resistance is frequent in advanced-stage multiple patients irrespective of CD38 expression and is related to dismal prognosis. Eur J Haematol 2018;100: 494-501. **[10].**Usmani S, Ahmadi T, Ng Y, et al. Analysis of real-world data on overall survival in multiple myeloma patients with ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or double refra PI and an IMiD. Oncologist 2016; 21: 1355-61. **[11].** M.A. Dimopoulos, P. Moreau, E. Terpos et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for treatment and follow-up†, Annals of Oncology, Volume 32, Issue 3, 2021, Pages 309-322 **[12].**Dimopoulos M, Delimpasi S, Simonova M, et al. Weekly selinexor, bortezomib, and dexamethasone (SVd) ve weekly bortezomib and dexamethasone (Vd) in patients with multiple myeloma (MM) after one to three prior therap results of the phase III BOSTON study. J Clin Oncol. 2020;38 **[13].**https://clinicaltrials.gov/ct2/results?term=selinexor&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply

Issued on February 2021