RXADVANCE
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NEW DRUG APPROVAL

Brand Name	XPOVIO®
Generic Name	selinexor
Drug Manufacturer	Karyopharm Therapeutics Inc.

New Drug Approval

XPOVIO® is a nuclear export inhibitor.

XPOVIO® in combination with dexamethasone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma 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 anti-CD38 monoclonal antibody.

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.

FDA Approval Date: June 22, 2020

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Multiple myeloma is a form of cancer. It develops when abnormal plasma cells grow out of control. Plasma cells are a type of white blood cell that is made in the soft tissue inside the bones (bone marrow). They are part of the body's disease-fighting system (immune system).

Multiple myeloma damages bones and causes other health problems because of its effect on blood cells. Abnormal plasma cells produce monoclonal proteins (M proteins) and interfere with many important functions that normal cells perform in the body. The disease gets worse over time (progresses) and reduces the body's ability to fight infections.

Multiple myeloma affects thousands of people worldwide and is the second most common cancer of the blood only to non-Hodgkin's lymphoma. Multiple myeloma accounts for around 1% of all cancers worldwide and for about 2% of cancer-related deaths. The most common age of onset is between 65 and 70 years.

Male gender increases the risk for multiple myeloma, which is slightly more prevalent in men than women. African Americans appear to be at the highest risk for the disease, while Asians are at the lowest risk. One study demonstrated that the incidence of myeloma in African Americans is 9.5 per 100,000 people while among Caucasian Americans, the rate is 4.1 per 100,000 individuals. In the African American population, myeloma is among the top ten cancers to cause death.

Efficacy

Relapsed or Refractory Multiple Myeloma

The efficacy of XPOVIO® plus dexamethasone was evaluated in STORM (KCP-330-012; NCT02336815). STORM was a multicenter, single-arm, open-label study of adults with relapsed or refractory multiple myeloma (RRMM). STORM Part 2 included 122 patients with RRMM who had previously received three or more antimyeloma treatment regimens, and an anti-CD38 monoclonal antibody; and whose myeloma was documented to be refractory to glucocorticoids, a proteasome inhibitor, an immunomodulatory agent, an anti-CD38 monoclonal antibody, and to the last line of therapy.

In STORM Part 2, a total of 122 patients received XPOVIO® 80 mg orally in combination with dexamethasone 20 mg orally on Days 1 and 3 of every week. Eighty-three patients had RRMM that was refractory to bortezomib,

carfilzomib, lenalidomide, pomalidomide, and daratumumab. Efficacy was based on overall response rate (ORR), as assessed by an Independent Review Committee (IRC) based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. The approval of XPOVIO® was based upon the efficacy and safety in a prespecified subgroup analysis of the 83 patients whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, as the benefit-risk ratio appeared to be greater in this more heavily pretreated population than in the overall trial population. The median time to first response was 4 weeks (range: 1 to 10 weeks). The median duration of response was 3.8 months (95% CI: 2.3, not estimable).

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

The efficacy of XPOVIO® monotherapy was evaluated in SADAL (KCP-330-009; NCT02227251). SADAL was a multicenter, single-arm, open-label study of adults with relapsed or refractory DLBCL, not otherwise specified (NOS), after 2 to 5 systemic regimens. Eligible patients were not candidates for autologous hematopoietic stem cell transplantation (HSCT). The study required a minimum of 60 days since last systemic therapy, with a minimum of 98 days in patients with refractory disease (defined as less than partial response) to last systemic therapy. Patients received XPOVIO® 60 mg orally on Days 1 and 3 of each week. Treatment continued until disease progression or unacceptable toxicity.

Of 134 patients evaluated, the median age was 67 years (range: 35-91), 59% were male, 79% were White, and 7% were Asian. Most patients (88%) had an ECOG performance status of 0 or 1. The diagnosis was de novo DLBCL not otherwise specified (NOS) in 75% and transformed DLBCL in 23%. The median number of prior systemic therapies was 2 (range: 1-5), with 63% of patients receiving 2 prior systemic therapies, 24% receiving 3 prior therapies, and 10% receiving 4 or 5 prior therapies. Twenty-eight percent had documented refractory disease to the most recent therapy; 30% had prior autologous HSCT. The median time from last systemic therapy to the start of XPOVIO® was 5.4 months overall and 3.6 months in the patients with refractory disease. Efficacy was based on overall response rate (ORR) and duration of response as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria. The median time to first response was 8.1weeks (range: 6.7-16.4 weeks).

Safety

ADVERSE EVENTS

The most common adverse reactions (incidence ≥20%) in patients with multiple myeloma are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection.

The most common adverse reactions (incidence ≥20%) in patients with DLBCL, excluding laboratory abnormalities, are fatigue, nausea, diarrhea, appetite decrease, weight decrease, constipation, vomiting, and pyrexia. Grade 3-4 laboratory abnormalities (≥15%) are thrombocytopenia, lymphopenia, neutropenia, anemia, and hyponatremia.

WARNINGS & PRECAUTIONS

- **Thrombocytopenia**: Monitor platelet counts throughout treatment. Manage with dose interruption and/or reduction and supportive care.
- **Neutropenia:** Monitor neutrophil counts throughout treatment. Manage with dose interruption and/or reduction and granulocyte colony stimulating factors.
- **Gastrointestinal Toxicity:** Nausea, vomiting, diarrhea, anorexia, and weight loss may occur. Provide antiemetic prophylaxis. Manage with dose interruption and/or reduction, antiemetics, and supportive care.

- **Hyponatremia:** Monitor serum sodium levels throughout treatment. Correct for concurrent hyperglycemia and high serum paraprotein levels. Manage with dose interruption, reduction, or discontinuation, and supportive care.
- **Serious Infection:** Monitor for infection and treat promptly.
- **Neurological Toxicity:** Advise patients to refrain from driving and engaging in hazardous occupations or activities until neurological toxicity resolves. Optimize hydration status and concomitant medications to avoid dizziness or mental status changes.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential and males with a female partner of reproductive potential, of the potential risk to a fetus and use of effective contraception.

CONTRAINDICATIONS

Specific contraindications have not been determined.

Clinical Pharmacology

MECHANISMS OF ACTION

Selinexor reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). XPO1 inhibition by selinexor leads to accumulation of TSPs in the nucleus and reductions in several oncoproteins, such as c-myc and cyclin D1, cell cycle arrest, and apoptosis of cancer cells. Selinexor demonstrated pro-apoptotic activity in vitro in multiple myeloma cells and showed anti-tumor activity in murine xenograft models of multiple myeloma and diffuse large B cell lymphoma.

Dose & Administration

ADULTS

Multiple Myeloma: Recommended dosage of XPOVIO® is 80 mg in combination with dexamethasone taken orally on Days 1 and 3 of each week.
DLBCL: Recommended dosage of XPOVIO® is 60 mg taken orally on Days 1 and 3 of each week.

PEDIATRICS

Safety and effectiveness have not been established in pediatric patients.

GERIATRICS

No overall difference in effectiveness was observed in patients over 65 years of age, including patients over 75 years of age, when compared with younger patients.

RENAL IMPAIRMENT

No clinically significant differences in the pharmacokinetics of selinexor were observed based on age (18 to 94 years old), sex, body weight (36 to 168 kg), ethnicity, mild to severe renal impairment (CL_{CR}: 15 to 89 mL/min, estimated by the Cockcroft-Gault equation), and disease type (hematological non-DLBCL, solid tumor, DLBCL).

HEPATIC IMPAIRMENT

Mild hepatic impairment had no clinically significant effect on the pharmacokinetics of selinexor. The effect of moderate and severe hepatic impairment on selinexor pharmacokinetics is unknown.

NEW DRUG APPROVAL

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets for oral use: 20 mg