RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	INQOVI®
Generic Name	decitabine and cedazuridine
Drug Manufacturer	OTSUKA

New Drug Approval

FDA Approval Date: 7/7/2020
Review Designation: Orphan
Type of Review: New Drug Application 212576

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Myelodysplastic Syndromes (MDS) are a group of diverse bone marrow disorders in which the bone marrow does not produce enough healthy blood cells. MDS is often referred to as a "bone marrow failure disorder". MDS is primarily a disease of the elderly (most patients are older than age 65), but MDS can affect younger patients as well.

The annual age-adjusted incidence in the United States is approximately 4.0/100,000 persons, and the incidence substantially rises with age. Beyond age, other risk factors include male gender, obesity, smoking, and prior receipt of radiotherapy or chemotherapy, but most cases remain idiopathic in nature. The overall 5-year survival probability remains relatively poor at approximately 31% without a clear temporal improvement in outcomes despite the approval of three MDS-specific therapies since 2004 and increasing use of allogeneic hematopoietic stem cell transplantation.

Efficacy

INQOVI® was evaluated in Study ASTX727-01-B, an open-label, randomized, 2-cycle, 2-sequence crossover study (NCT02103478) that included 80 adult patients with MDS (International Prognostic Scoring System [IPSS] Intermediate-1, Intermediate-2, or high-risk) or CMML. Patients were randomized 1:1 to receive INQOVI® (35 mg decitabine and 100 mg cedazuridine) orally in Cycle 1 and decitabine 20 mg/m2 intravenously in Cycle 2 or the reverse sequence. Both INQOVI® and intravenous decitabine were administered once daily on Days 1 through 5 of the 28-day cycle. Starting with Cycle 3, all patients received INQOVI® orally once daily on Days 1 through 5 of each 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by IPSS risk level. Twelve (15%) of the 80 patients went on to stem cell transplantation following INQOVI® treatment.

Safety

ADVERSE EVENTS

Most common adverse reactions (incidence ≥ 20%) are fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and hemoglobin decreased.

WARNINGS & PRECAUTIONS

- **Myelosuppression**: Fatal and serious myelosuppression and infectious complications can occur. Obtain complete blood cell counts prior to initiation of INQOVI®, prior to each cycle, and as clinically indicated to

monitor for response and toxicity. Delay the next cycle and resume at the same or reduced dose as recommended.

- **Embryo-Fetal Toxicity**: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Decitabine is a nucleoside metabolic inhibitor that is believed to exert its effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation and/or apoptosis. Decitabine inhibits DNA methylation in vitro, which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in cancer cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation.

Dose & Administration

ADULTS

The recommended dosage of INQOVI® is 1 tablet (35 mg decitabine and 100 mg cedazuridine) taken orally once daily on Days 1 through 5 of each 28-day cycle.

PEDIATRICS

The safety and effectiveness of INQOVI® have not been established in pediatric patients.

GERIATRICS

No overall differences in safety or effectiveness were observed between patients age 65 years and older, 75 years and older, and younger patients.

RENAL IMPAIRMENT

No dosage modification of INQOVI® is recommended for patients with mild or moderate renal impairment. INQOVI® has not been studied in patients with severe renal impairment or end-stage renal disease.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 35 mg decitabine and 100 mg cedazuridine.