NEW DRUG APPROVAL

Brand Name	Scemblix®
Generic Name	asciminib
Drug Manufacturer	Novartis Pharmaceuticals Corporation

New Drug Approval

FDA Approval Date: October 29, 2021
Review Designation: Priority; Orphan
Type of Review: Type 1 - New Molecular Entity; New Drug Application (NDA): 215358
Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Chronic myelogenous leukemia (CML) is an uncommon type of cancer of the bone marrow — the spongy tissue inside bones where blood cells are made. CML causes an increased number of white blood cells in the blood.

The chromosomes in the blood cells swap sections with each other. A section of chromosome 9 switches places with a section of chromosome 22, creating an extra-short chromosome 22 and an extra-long chromosome 9.

The extra-short chromosome 22 is called the Philadelphia chromosome, named for the city where it was discovered. The Philadelphia chromosome is present in the blood cells of 90 percent of people with chronic myelogenous leukemia.

The Philadelphia chromosome creates a new gene. Genes from chromosome 9 combine with genes from chromosome 22 to create a new gene called *BCR-ABL*. The *BCR-ABL* gene contains instructions that tell the abnormal blood cell to produce too much of a protein called tyrosine kinase. Tyrosine kinase promotes cancer by allowing certain blood cells to grow out of control.

About 15% of all leukemia is CML. This year, an estimated 9,110 people (5,150 men and 3,960 women) in the United States will be diagnosed with CML. Most of these will be adults, with an average age of diagnosis at 64 years. About 50% of cases are found in people older than 64. CML is rare in children.
It is estimated that 1,220 deaths (680 men and 540 women) from this disease will occur this year.

Efficacy

Ph+ CML-CP, Previously Treated with Two or More TKIs

The efficacy of Scemblix® in the treatment of patients with Ph+ CML in chronic phase (Ph+ CML-CP), previously treated with two or more tyrosine kinase inhibitors was evaluated in the multi-center, randomized, active-controlled, and open-label study ASCEMBL (NCT 03106779).
In this study, a total of 233 patients were randomized in a 2:1 ratio and stratified according to major cytogenetic response (MCyR) status to receive either Scemblix® or bosutinib.
Patients continued treatment until unacceptable toxicity or treatment failure occurred. Patients were 52% female and 48% male with a median age of 52 years (range, 19 to 83 years). Of the 233 patients, 19% were 65 years or older, while 2.6% were 75 years or older. Patients were White (75%), Asian (14%), and Black or African American (4.3%). Of the 233 patients, 81% and 18% had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, respectively. Patients who had previously received 2, 3, 4, or 5 or more prior lines of TKIs were 48%, 31%,

15%, and 6%, respectively. The median duration of treatment was 67 weeks (range, 0.1 to 162 weeks) for patients receiving Scemblix® and 30 weeks (range, 1 to 149 weeks) for patients receiving bosutinib.

Table: Efficacy Results in Patients with Ph+ CML-CP, Previously Treated with Two or More Tyrosine Kinase Inhibitors (ASCEMBL)

	SCEMBLIX 40 mg twice daily	Bosutinib 500 mg once daily	Difference (95% CI)	p-value
MMR rate, % (95% CI) at 24 weeks	N = 157 25 (19, 33)	N = 76 13 (6.5, 23)	12[a] (2.2, 22)	0.029[b]
CCyR rate, % (95% CI) at 24 weeks	N = 103[c] 41 (31, 51)	N = 62[c] 24 (14, 37)	17 (3.6, 31)	

Abbreviations: MMR, major molecular response (*BCR-ABL1*$^{IS} \leq 0.1\%$); CCyR, complete cytogenetic response (0% of Philadelphia-positive metaphases in bone marrow aspirate with at least 20 examined).
[a]Estimated using a common risk difference stratified by baseline major cytogenetic response status.
[b]Estimated using a Cochrane-Mantel-Haenszel two-sided test stratified by baseline major cytogenetic response status.
[c]CCyR analysis based on patients who were not in CCyR at baseline.

The MMR rate at 48 weeks was 29% (95% CI: 22, 37) in patients receiving Scemblix® and 13% (95% CI: 6.5, 23) in patients receiving bosutinib. With a median duration of follow-up of 20 months (range: 1 day to 36 months), the median duration of response had not yet been reached for patients with MMR at any time.

Ph+ CML-CP with the T315I mutation

The efficacy was evaluated in a multi-center open-label study CABL001X2101 (NCT02081378). Testing for T315I mutation utilized a qualitative p210 BCR-ABL mutation test using Sanger Sequencing.

Efficacy was based on 45 patients with Ph+ CML-CP with the T315I mutation who received Scemblix® at a dose of 200 mg twice daily. Patients continued treatment until unacceptable toxicity or treatment failure occurred.

Of the 45 patients (80% male,20% female) 31% were 65 years or older, while 9% were 75 years or older with a median age of 54 years (range, 26 to 86 years). The patients were White (47%), Asian (27%), and Black or African American (2.2%), and 24% were unreported or unknown. Seventy-three percent and 27% of patients had ECOG performance status 0 and 1, respectively. Patients who had previously received 1, 2, 3, 4, and 5 or more TKIs were 18%, 31%, 36%, 13%, and 2.2%, respectively. MMR was achieved by 24 weeks in 42% (19/45, 95% CI: 28% to 58%) of the 45 patients treated with Scemblix®.

MMR was achieved by 96 weeks in 49% (22/45, 95% CI: 34% to 64%) of the 45 patients treated with Scemblix®. The median duration of treatment was 108 weeks (range, 2 to 215 weeks).

Safety

ADVERSE EVENTS

Most common adverse reactions (≥ 20%) are upper respiratory tract infections, musculoskeletal pain, fatigue, nausea, rash, and diarrhea.

Most common laboratory abnormalities (≥ 20%) are platelet count decreased, triglycerides increased, neutrophil count decreased, hemoglobin decreased, creatine kinase increased, alanine aminotransferase increased, lipase increased, and amylase increased.

WARNINGS & PRECAUTIONS

- **Myelosuppression**: Severe thrombocytopenia and neutropenia events may occur. Monitor complete blood counts regularly during therapy and manage by treatment interruption or dose reduction.
- **Pancreatic Toxicity**: Monitor serum lipase and amylase. Interrupt, then resume at reduced dose or discontinue Scemblix® based on severity. Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms.
- **Hypertension**: Monitor blood pressure and manage hypertension as clinically indicated. Interrupt, dose reduce, or stop Scemblix® if hypertension is not medically controlled.
- **Hypersensitivity**: May cause hypersensitivity reactions. Monitor patients for signs and symptoms and initiate appropriate treatment as clinically indicated.
- **Cardiovascular Toxicity**: Cardiovascular toxicity may occur. Monitor patients with history of cardiovascular risk factors for cardiovascular signs and symptoms. Initiate appropriate treatment as clinically indicated.
- **Embryo-Fetal Toxicity**: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Asciminib is an ABL/BCR-ABL1 tyrosine kinase inhibitor. Asciminib inhibits the ABL1 kinase activity of the BCRABL1 fusion protein, by binding to the ABL myristoyl pocket. In studies conducted in vitro or in animal models of CML, asciminib showed activity against wild-type BCR-ABL1 and several mutant forms of the kinase, including the T315I mutation.

Dose & Administration

ADULTS

- Recommended Dosage in Ph+ CML in CP: 80 mg orally once daily or 40 mg twice daily.
- Recommended Dosage in Ph+ CML in CP with the T315I Mutation: 200 mg orally twice daily.

PEDIATRICS

The safety and efficacy of Scemblix® in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustment is necessary.

HEPATIC IMPAIRMENT

No dosage adjustment is necessary.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Film-coated tablets: 20 mg and 40 mg.