**FULL PRESCRIBING INFORMATION**

SCEMBLIX 20 mg

SCEMBLIX 40 mg

Film coated tablets

**QUALITATIVE AND QUANTITATIVE COMPOSITION**

SCEMBLIX 20 mg: each film coated tablet contains 21.62 mg asciminib hydrochloride, equivalent to 20 mg asciminib.

Excipient with known effect

Each film-coated tablet contains 43 mg lactose monohydrate.

SCEMBLIX 40 mg: each film coated tablet contains 43.24 mg asciminib hydrochloride, equivalent to 40 mg asciminib.

Excipient with known effect

Each film-coated tablet contains 86 mg lactose monohydrate.

For the full list of excipients, see section 11.

## 1. INDICATIONS AND USAGE

- SCEMBLIX is indicated for the treatment of adult patients with: Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs).
- Ph+ CML in CP with the T315I mutation.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage in Patients with Ph+ CML-CP, Previously Treated with Two or More TKIs

The recommended dose of SCEMBLIX is 80 mg taken orally once daily at approximately the same time each day or 40 mg orally twice daily at approximately 12-hour intervals. The recommended dose of SCEMBLIX is taken orally without food. Avoid food consumption for at least 2 hours before and 1 hour after taking SCEMBLIX *[see Clinical Pharmacology (12.2)]*.

Continue treatment with SCEMBLIX as long as clinical benefit is observed or until unacceptable toxicity occurs.

### 2.2 Recommended Dosage in Patients with Ph+ CML-CP with the T315I Mutation

The recommended dose of SCEMBLIX is 200 mg taken orally twice daily at approximately 12-hour intervals. The recommended dose of SCEMBLIX is taken orally without food. Avoid food consumption for at least 2 hours before and 1 hour after taking SCEMBLIX *[see Clinical Pharmacology (12.2)]*.

### 2.3 Missed Dose

Once Daily Dosage Regimen: If a SCEMBLIX dose is missed by more than approximately 12 hours, skip the dose and take the next dose as scheduled.

Twice Daily Dosage Regimens: If a SCEMBLIX dose is missed by more than approximately 6 hours, skip the dose and take the next dose as scheduled.

## 2.4 Dosage Modifications

Dosage Modifications for Patients with Ph+ CML-CP, Previously Treated with Two or More TKIs

For the management of adverse reactions, reduce the SCEMBLIX dose as described in Table 1.

Dosage Modifications for Patients with Ph+ CML-CP with the T315I Mutation

For the management of adverse reactions, reduce the SCEMBLIX dose as described in Table 1.

**Table 1: Recommended Dosage Reductions for SCEMBLIX for Adverse Reactions**

| **Dosage Reduction** | **Dosage for Patients with CP-CML, Previously Treated with Two or More TKIs** | **Dosage for Patients with Ph+ CML-CP with the T315I Mutation** |
|---|---|---|
| First | • 40 mg once daily<br>OR<br>• 20 mg twice daily | 160 mg twice daily |
| Subsequent Reduction | Permanently discontinue SCEMBLIX in patients unable to tolerate 40 mg once daily OR 20 mg twice daily. | Permanently discontinue SCEMBLIX in patients unable to tolerate 160 mg twice daily. |

The recommended dosage modifications for the management of selected adverse reactions are shown in Table 2.

**Table 2: SCEMBLIX Dosage Modification for the Management of Adverse Reactions**

| **Adverse Reaction** | **Dosage Modification** |
|---|---|
| **Thrombocytopenia and/or neutropenia** *[see Warnings and Precautions (5.1)]* | |
| ANC less than 1.0 x $10^9$/L and/or PLT less than 50 x $10^9$/L | Withhold SCEMBLIX until resolved to ANC greater than or equal to 1 x $10^9$/L and/or PLT greater than or equal to 50 x $10^9$/L.<br>If resolved:<br>• Within 2 weeks: resume SCEMBLIX at starting dose.<br>• After more than 2 weeks: resume SCEMBLIX at reduced dose.<br>For recurrent severe thrombocytopenia and/or neutropenia, withhold SCEMBLIX until resolved to ANC greater than or equal to 1 x $10^9$/L and PLT greater than or equal to 50 x $10^9$/L, then resume at reduced dose. |
| **Asymptomatic amylase and/or lipase elevation** *[see Warnings and Precautions (5.2)]* | |
| Elevation greater than 2.0 x ULN | Withhold SCEMBLIX until resolved to less than 1.5 x ULN.<br>If resolved:<br>• Resume SCEMBLIX at reduced dose. If events reoccur at reduced dose, permanently discontinue SCEMBLIX.<br>If not resolved:<br>• Permanently discontinue SCEMBLIX. Perform diagnostic tests to exclude pancreatitis. |

| | |
|---|---|
| **Non-hematologic adverse reactions** *[see Warnings and Precautions (5.3, 5.4, 5.5)]* | |
| Grade 3[1] or higher | Withhold SCEMBLIX until recovery to Grade 1 or less.<br>If resolved:<br>• Resume SCEMBLIX at reduced dose.<br>If not resolved:<br>• Permanently discontinue SCEMBLIX. |
| Abbreviations: ANC, absolute neutrophil count; PLT, platelets; ULN, upper limit of normal.<br>[1]Based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. | |

### 2.5 Administration

Advise patients to swallow SCEMBLIX tablets whole. Do not break, crush, or chew the tablets.

## 3 DOSAGE FORMS AND STRENGTHS

20 mg asciminib film-coated tablets: pale yellow, unscored, round, biconvex, with beveled edges, of approximately 6.2 mm diameter film-coated tablet debossed with “20” on one side and the “Novartis” logo on the other side.

40 mg asciminib film-coated tablets: violet white, unscored, round, biconvex, with beveled edges, of approximately 8.2 mm

diameter film-coated tablet debossed with “40” on one side and the “Novartis” logo on the other side.

## 4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Myelosuppression

Thrombocytopenia, neutropenia, and anemia have occurred in patients receiving SCEMBLIX. Thrombocytopenia occurred in 98 of 356 (28%) patients receiving SCEMBLIX, with Grade 3 or 4 thrombocytopenia reported in 24 (7%) and 42 (12%) of patients, respectively. Among the patients with Grade 3 or 4 thrombocytopenia, median time to first occurrence of events was 6 weeks (range, 0.1 to 64 weeks). Of the 98 patients with thrombocytopenia, 7 (2%) patients permanently discontinued SCEMBLIX, while SCEMBLIX was temporarily withheld in 45 (13%) patients due to the adverse reaction.

Neutropenia occurred in 69 (19%) patients receiving SCEMBLIX, with Grade 3 and 4 neutropenia reported in 26 (7%) and 30 (8%) patients, respectively. Among the patients with Grade 3 or 4 neutropenia, median time to first occurrence of events was 6 weeks (range, 0.1 to 180 weeks). Of the 69 patients with neutropenia, 4 (1.1%) patients permanently discontinued SCEMBLIX, while SCEMBLIX was temporarily withheld in 34 (10%) patients due to the adverse reaction.

Anemia occurred in 46 (13%) patients receiving SCEMBLIX, with Grade 3 anemia occurring in 19 (5%) patients. Among the patients with Grade 3 or 4 anemia, median time to first occurrence of events was 30 weeks (range, 0.4 to 207 weeks). Of the 46 patients with anemia, SCEMBLIX was temporarily withheld in 2 (0.6%) patients due to the adverse reaction *[see Adverse Reactions (6.1)]*.

Perform complete blood counts every two weeks for the first 3 months of treatment and monthly thereafter or as clinically indicated. Monitor patients for signs and symptoms of myelosuppression.

Based on the severity of thrombocytopenia and/or neutropenia, reduce dose, temporarily withhold, or permanently discontinue SCEMBLIX *[see Dosage and Administration (2.4)]*.

### 5.2 Pancreatic Toxicity

Pancreatitis occurred in 9 of 356 (2.5%) patients receiving SCEMBLIX, with Grade 3 pancreatitis occurring in 4 (1.1%) patients. All cases of pancreatitis occurred in the Phase I study (X2101). Of the 9 patients with pancreatitis, two (0.6%) patients permanently discontinued SCEMBLIX, while SCEMBLIX was temporarily withheld in 4 (1.1%) patients due to

the adverse reaction. Asymptomatic elevation of serum lipase and amylase occurred in 76 of 356 (21%) patients receiving SCEMBLIX, with Grade 3 and Grade 4 pancreatic enzyme elevations occurring in 36 (10%) and 8 (2.2%) patients, respectively. Of the 76 patients with pancreatic enzymes elevated, SCEMBLIX was permanently discontinued in 8 (2.2%) patients due to the adverse reaction *[see Adverse Reactions (6.1)]*.

Assess serum lipase and amylase levels monthly during treatment with SCEMBLIX, or as clinically indicated. Monitor patients for signs and symptoms of pancreatic toxicity. Perform more frequent monitoring in patients with a history of pancreatitis. If lipase and amylase elevation are accompanied by abdominal symptoms, temporarily withhold SCEMBLIX and consider appropriate diagnostic tests to exclude pancreatitis *[see Dosage and Administration (2.4)]*.

Based on the severity of lipase and amylase elevation, reduce dose, temporarily withhold, or permanently discontinue SCEMBLIX *[see Dosage and Administration (2.4)]*.

### 5.3 Hypertension

Hypertension occurred in 68 of 356 (19%) patients receiving SCEMBLIX, with Grade 3 or 4 hypertension reported in 32 (9%) and 1 (0.3%) patients, respectively. Among the patients with Grade 3 or 4 hypertension, median time to first occurrence was 14 weeks (range, 0.1 to 156 weeks). Of the 68 patients with hypertension, SCEMBLIX was temporarily withheld in 3 (0.8%) patients due to the adverse reaction *[see Adverse Reactions (6.1)]*.

Monitor and manage hypertension using standard antihypertensive therapy during treatment with SCEMBLIX as clinically indicated; for Grade 3 or higher hypertension, temporarily withhold, reduce dose, or permanently discontinue SCEMBLIX depending on persistence of hypertension *[see Dosage and Administration (2.4)]*.

### 5.4 Hypersensitivity

Hypersensitivity occurred in 115 of 356 (32%) patients receiving SCEMBLIX, with Grade 3 or 4 hypersensitivity reported in 6 (1.7%) patients *[see Adverse Reactions (6.1)]*. Reactions included rash, edema, and bronchospasm. Monitor patients for signs and symptoms of hypersensitivity and initiate appropriate treatment as clinically indicated; for Grade 3 or higher hypersensitivity, temporarily withhold, reduce dose, or permanently discontinue SCEMBLIX depending on persistence of hypersensitivity *[see Dosage and Administration (2.4)]*.

### 5.5 Cardiovascular Toxicity

Cardiovascular toxicity (including ischemic cardiac and CNS conditions, arterial thrombotic and embolic conditions) and cardiac failure occurred in 46 (13%) and in 9 (2.5%) of 356 patients receiving SCEMBLIX, respectively *[see Adverse Reactions (6.1)]*. Grade 3 cardiovascular toxicity was reported in 12 (3.4%) patients, while Grade 3 cardiac failure was observed in 5 (1.4%) patients. Grade 4 cardiovascular toxicity occurred in 2 (0.6%) patients, with fatalities occurring in 3 (0.8%) patients. Permanent discontinuation of SCEMBLIX occurred in 3 (0.8%) patients due to cardiovascular toxicity and in 1 (0.3%) patient due to cardiac failure, respectively. Cardiovascular toxicity occurred in patients with pre-existing cardiovascular conditions or risk factors, and/or prior exposure to multiple TKIs.

Arrhythmia, including QTc prolongation, occurred in 24 of 356 (7%) patients receiving SCEMBLIX, with Grade 3 arrhythmia reported in 8 (2%) patients. QTc prolongation occurred in 3 of 356 (0.8%) patients receiving SCEMBLIX, with Grade 3 QTc prolongation reported in 1 (0.3%) patient *[see Adverse Reactions (6.1)]*.

Monitor patients with history of cardiovascular risk factors for cardiovascular signs and symptoms. Initiate appropriate treatment as clinically indicated; for Grade 3 or higher cardiovascular toxicity, temporarily withhold, reduce dose, or permanently discontinue SCEMBLIX depending on persistence of cardiovascular toxicity *[see Dosage and Administration (2.4)]*.

### 5.6 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, SCEMBLIX can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of asciminib to pregnant rats and rabbits during the period organogenesis caused adverse developmental outcomes, including embryo-fetal mortality and malformations at maternal exposures (AUC) equivalent to or less than those in patients at the recommended doses. Advise pregnant women and females of reproductive potential of the potential risk to a fetus if SCEMBLIX is used during pregnancy or if the patient becomes pregnant while taking SCEMBLIX. Verify the pregnancy status of females of reproductive potential prior to starting treatment with SCEMBLIX. Females of reproductive potential should use effective contraception during treatment with SCEMBLIX and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3)].*

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

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

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions can occur with SCEMBLIX and are discussed in greater detail in other sections of the labeling:

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Pancreatic Toxicity *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- Hypersensitivity *[see Warnings and Precautions (5.4)]*
- Cardiovascular Toxicity *[see Warnings and Precautions (5.5)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to SCEMBLIX at 10 mg to 200 mg orally twice daily (between 0.25 to 5 times the recommended dosage for the 80 mg daily dosage and between 0.05 times and up to the recommended dosage for the 200 mg twice daily dosage) in 356 patients enrolled in one of two clinical trials, including patients with Ph+ CML in CP receiving SCEMBLIX as monotherapy: study CABL001A2301 (ASCEMBL) and study CABL001X2101 *[see Clinical Studies (14)]*. Among the 356 patients receiving SCEMBLIX, the median duration of exposure to SCEMBLIX was 116 weeks (range, 0.1 to 342 weeks).

Adverse Reactions in Patients with Ph+ CML-CP, Previously Treated with Two or More TKIs

The clinical trial randomized and treated 232 patients with Ph+ CML-CP, previously treated with two or more TKIs to receive SCEMBLIX 40 mg twice daily or bosutinib 500 mg once daily (ASCEMBL) *[see Clinical Studies (14.1)]*. The safety population (received at least 1 dose of SCEMBLIX) included 156 patients with Ph+ CML-CP, previously treated with two or more TKIs. Among patients who received SCEMBLIX, 83% were exposed for 24 weeks or longer and 56% were exposed for 96 weeks or longer.

Serious adverse reactions occurred in 18% of patients who received SCEMBLIX. Serious adverse reactions in ≥ 1% included cardiac failure congestive (1.9%), pyrexia (1.9%), urinary tract infection (1.9%), headache (1.3%), and thrombocytopenia (1.3%). Two patients (1.3%) had a fatal adverse reaction, one each for mesenteric artery thrombosis and ischemic stroke.

Permanent discontinuation of SCEMBLIX due to an adverse reaction occurred in 8% of patients. Adverse reactions which resulted in permanent discontinuation of SCEMBLIX in > 2% of patients included thrombocytopenia (3.2%) and neutropenia (2.6%).

Dosage interruptions of SCEMBLIX due to an adverse reaction occurred in 41% of patients. Adverse reactions which required dosage interruption in > 5% of patients included thrombocytopenia (19%) and neutropenia (18%).

Dose reductions of SCEMBLIX due to an adverse reaction occurred in 6% of patients. Adverse reactions which required dose reductions in > 1% of patients included thrombocytopenia (4.5%) and neutropenia (1.3%).

The most common (≥ 20%) adverse reactions in patients who received SCEMBLIX were upper respiratory tract infections, musculoskeletal pain, headache, and fatigue.

The most common select laboratory abnormalities that worsened from baseline in ≥ 20% of patients who received SCEMBLIX were platelet count decreased, triglycerides increased, neutrophil count decreased, hemoglobin decreased, creatine kinase increased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, uric acid increased, and lymphocyte count decreased.

Table 3 summarizes the adverse reactions in ASCEMBL.

**Table 3: Adverse Reactions (≥ 10%) in Patients with Ph+ CML in CP, Previously Treated with Two or More TKIs Who Received SCEMBLIX in ASCEMBL**

| | **SCEMBLIX N = 156** | | **Bosutinib N = 76** | |
|---|---|---|---|---|
| **Adverse Reaction** | **All Grades %** | **Grade 3 or 4 %** | **All Grades %** | **Grade 3 or 4 %** |
| **Infections and infestations** | | | | |
| Upper respiratory tract infection[a] | 26 | 0.6 | 12 | 1.3 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Musculoskeletal pain[b] | 24 | 2.6 | 17 | 1.3 |
| Arthralgia | 13 | 0.6 | 3.9 | 0 |
| **Nervous system disorders** | | | | |
| Headache[c] | 21 | 1.9 | 16 | 0 |
| **General disorders and administration-site conditions** | | | | |
| Fatigue[d] | 20 | 0.6 | 11 | 1.3 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash[e] | 18 | 0.6 | 30 | 8 |
| **Vascular disorders** | | | | |
| Hypertension[f] | 14 | 7 | 5 | 3.9 |
| **Gastrointestinal disorders** | | | | |
| Diarrhea[g] | 13 | 0 | 72 | 11 |
| Nausea | 12 | 0.6 | 46 | 0 |
| Abdominal pain[h] | 14 | 0 | 24 | 2.6 |

Abbreviations: Ph+ CML in CP, Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP); TKIs, tyrosine kinase inhibitors.

[a]Upper respiratory tract infection includes: nasopharyngitis, upper respiratory tract infection, rhinitis, pharyngitis, respiratory tract infection, and pharyngotonsillitis.

[b]Musculoskeletal pain includes: pain in extremity, back pain, myalgia, non-cardiac chest pain, neck pain, bone pain, spinal pain, arthritis, musculoskeletal pain, and musculoskeletal chest pain.

[c]Headache includes: headache and post-traumatic headache.

[d]Fatigue includes: fatigue and asthenia.

[e]Rash includes: rash, rash maculopapular, dermatitis acneiform, rash pustular, eczema, dermatitis, skin exfoliation, dermatitis exfoliative generalized, rash morbilliform, drug eruption, erythema multiforme, and rash erythematous.

[f]Hypertension includes: hypertension and hypertensive crisis.

[g]Diarrhea includes: diarrhea and colitis.

[h]Abdominal pain includes: abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and epigastric discomfort.

Clinically relevant adverse reactions in < 10% of patients treated with SCEMBLIX in ASCEMBL included: cough, dyspnea, pleural effusion, dizziness, neuropathy peripheral, edema, pyrexia, vomiting, constipation, dyslipidemia, decreased appetite, pruritus, urticaria, lower respiratory tract infection, influenza, urinary tract infection, pneumonia, hemorrhage, arrhythmia (including electrocardiogram QT prolonged), palpitations, cardiac failure congestive, vision blurred, dry eye, hypothyroidism, and febrile neutropenia.

Table 4 summarizes the laboratory abnormalities in ASCEMBL.

**Table 4: Select Laboratory Abnormalities (≥ 10%) That Worsened from Baseline in Patients with Ph+ CML in CP, Previously Treated with Two or More TKIs Who Received SCEMBLIX in ASCEMBL**

| | SCEMBLIX[1] | | Bosutinib[1] | |
|---|---|---|---|---|
| **Laboratory Abnormality** | **All Grades %** | **Grade 3 or 4 %** | **All Grades %** | **Grade 3 or 4 %** |
| **Hematologic parameters** | | | | |
| Platelet count decreased | 46 | 24 | 36 | 12 |
| Neutrophil count decreased | 43 | 22 | 33 | 15 |
| Hemoglobin decreased | 37 | 2 | 54 | 5 |
| Lymphocyte count decreased | 20 | 3.3 | 34 | 2.6 |
| **Biochemical parameters** | | | | |
| Triglycerides increased | 44 | 5 | 30 | 2.6 |
| Creatine kinase increased | 30 | 2.6 | 24 | 5 |
| Alanine aminotransferase (ALT) increased | 26 | 0.6 | 50 | 16 |
| Aspartate aminotransferase (AST) increased | 21 | 1.9 | 46 | 7 |
| Uric acid increased | 21 | 6 | 18 | 2.6 |
| Phosphate decreased | 18 | 6 | 20 | 7 |
| Corrected calcium decreased | 16 | 0.6 | 22 | 0 |
| Lipase increased | 15 | 4.5 | 18 | 7 |
| Creatinine increased | 15 | 0 | 26 | 0 |
| Amylase increased | 13 | 1.3 | 13 | 0 |
| Alkaline phosphatase (ALP) increased | 13 | 0 | 12 | 0 |
| Bilirubin increased | 12 | 0 | 3.9 | 0 |
| Cholesterol increased | 12 | 0 | 8 | 0 |
| Potassium decreased | 11 | 0 | 9 | 0 |

[1]The denominator used to calculate the rate for SCEMBLIX and bosutinib varied from 152 to 156 and 75 to 76, respectively, based on the number of patients with a baseline value and at least one post-treatment value.
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Adverse Reactions in Patients with Ph+ CML-CP with the T315I Mutation

The single-arm clinical trial enrolled patients with Ph+ CML-CP with the T315I mutation *[see Clinical Studies (14.2)]*. The safety population (received at least 1 dose of SCEMBLIX) included 48 patients with Ph+ CML-CP with the T315I mutation who received 200 mg of SCEMBLIX twice daily. Among these patients, 83% were exposed for 24 weeks or longer, and 75% were exposed for 48 weeks or longer.

Serious adverse reactions occurred in 23% of patients who received SCEMBLIX. Serious adverse reactions in > 1% included abdominal pain (4.2%), vomiting (4.2%), pneumonia (4.2%), musculoskeletal pain (2.1%), headache (2.1%), hemorrhage (2.1%), constipation (2.1%), arrhythmia (2.1%), and pleural effusion (2.1%).

Permanent discontinuation of SCEMBLIX due to an adverse reaction occurred in 10% of patients. Adverse reactions which resulted in permanent discontinuation of SCEMBLIX in > 2% of patients included pancreatic enzymes increased (2.1%).

Dosage interruptions of SCEMBLIX due to an adverse reaction occurred in 31% of patients. Adverse reactions which required dosage interruption in > 5% of patients included pancreatic enzymes increased (17%) and thrombocytopenia (8%).

Dose reductions of SCEMBLIX due to an adverse reaction occurred in 23% of patients. Adverse reactions which required dose reductions in > 1% of patients included pancreatic enzymes increased (10%), abdominal pain (4.2%), anemia (2.1%), blood bilirubin increased (2.1%), dizziness (2.1%), fatigue (2.1%), hepatic enzymes increased (2.1%), musculoskeletal pain (2.1%), nausea (2.1%), neutropenia (2.1%), pruritus (2.1%), and thrombocytopenia (2.1%).

The most common (≥ 20%) adverse reactions in patients who received SCEMBLIX were musculoskeletal pain, fatigue, nausea, rash, and diarrhea.

The most common select laboratory abnormalities that worsened from baseline in ≥ 20% of patients who received SCEMBLIX were alanine aminotransferase (ALT) increased, lipase increased, triglycerides increased, hemoglobin decreased, neutrophil count decreased, lymphocyte count decreased, phosphate decreased, aspartate aminotransferase (AST) increased, amylase increased, platelet count decreased, and bilirubin increased.

Table 5 summarizes adverse reactions in study X2101.

**Table 5: Adverse Reactions (≥ 10%) in Patients with Ph+ CML in CP with the T315I Mutation Who Received SCEMBLIX in X2101**

| | **SCEMBLIX 200 mg twice daily N = 48** | |
|---|---|---|
| **Adverse reaction** | **All Grades %** | **Grade 3 or 4 %** |
| **Musculoskeletal and connective tissue disorders** | | |
| Musculoskeletal pain[a] | 42 | 4.2 |
| Arthralgia | 17 | 0 |
| **General disorders and administration-site conditions** | | |
| Fatigue[b] | 31 | 2.1 |
| Edema | 10 | 4.2 |
| **Gastrointestinal disorders** | | |
| Nausea | 27 | 0 |
| Diarrhea | 21 | 2.1 |
| Vomiting | 19 | 6 |
| Abdominal pain[c] | 17 | 8 |
| **Skin and subcutaneous tissue disorders** | | |
| Rash[d] | 27 | 0 |
| Pruritus | 13 | 0 |
| **Nervous system disorders** | | |
| Headache[e] | 19 | 2.1 |
| **Respiratory, thoracic, and mediastinal disorders** | | |
| Cough[f] | 15 | 0 |
| **Vascular disorders** | | |
| Hemorrhage[g] | 15 | 2.1 |
| Hypertension[h] | 13 | 8 |

| | | |
|---|---|---|
| **Infections and infestations** | | |
| Upper respiratory tract infection[i] | 13 | 0 |

[a]Musculoskeletal pain includes: pain in extremity, back pain, myalgia, musculoskeletal pain, non-cardiac chest pain, bone pain, arthritis, and musculoskeletal chest pain.

[b]Fatigue includes: fatigue and asthenia.

[c]Abdominal pain includes: abdominal pain and hepatic pain.

[d]Rash includes: rash, rash maculopapular, dermatitis acneiform, eczema, rash papular, skin exfoliation, and dyshidrotic eczema.

[e]Headache includes: headache and migraine.

[f]Cough includes: cough and productive cough.

[g]Hemorrhage includes: epistaxis, ear hemorrhage, mouth hemorrhage, post procedural hemorrhage, skin hemorrhage, and vaginal hemorrhage.

[h]Hypertension includes: hypertension and hypertensive crisis.

[i]Upper respiratory tract infection includes: upper respiratory tract infection, nasopharyngitis, rhinitis, and pharyngitis.

Clinically relevant adverse reactions in < 10% of patients treated with SCEMBLIX in X2101 included: constipation, pancreatitis, pyrexia, dizziness, neuropathy peripheral, pneumonia, lower respiratory tract infection, dyspnea, pleural effusion, dry eye, vision blurred, arrhythmia, palpitations, cardiac failure congestive, decreased appetite, dyslipidemia, hypersensitivity, and urticaria.

Table 6 summarizes laboratory abnormalities in X2101.

**Table 6: Select Laboratory Abnormalities (≥ 10%) That Worsened from Baseline in Patients with Ph+ CML in CP with the T315I Mutation in X2101**

| | **SCEMBLIX[1] 200 mg twice daily** | |
|---|---|---|
| **Laboratory Abnormality** | **All Grades %** | **Grade 3-4 %** |
| **Hematologic parameters** | | |
| Hemoglobin decreased | 44 | 4.2 |
| Neutrophil count decreased | 44 | 15 |
| Lymphocyte count decreased | 42 | 4.2 |
| Platelet count decreased | 25 | 15 |
| **Biochemical parameters** | | |
| Alanine aminotransferase (ALT) increased | 48 | 6 |
| Potassium increased | 48 | 2.1 |
| Triglycerides increased | 46 | 2.1 |
| Lipase increased | 46 | 21 |
| Phosphate decreased | 40 | 6 |
| Uric acid increased | 40 | 4.2 |
| Aspartate aminotransferase (AST) increased | 35 | 2.1 |
| Calcium corrected decreased | 33 | 0 |
| Creatinine increased | 31 | 0 |
| Amylase increased | 29 | 10 |
| Bilirubin increased | 23 | 0 |
| Cholesterol increased | 15 | 0 |
| Alkaline phosphatase (ALP) increased | 13 | 0 |

[1]The denominator used to calculate the rate was 48 based on the number of patients with a baseline value and at least one post-treatment value.

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**6.2 Effects on ability to drive and use machines**

Asciminib has no or negligible influence on the ability to drive and use machines.

However, it is recommended that patients experiencing dizziness, fatigue or other undesirable effects (see section 6) with a potential impact on the ability to drive or use machines safely should refrain from these activities as long as the undesirable effects persist.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

And to Novartis using the following email address: Safetydesk.israel@novaris.com

## 7 DRUG INTERACTIONS

### 7.1 Effect of Other Drugs on SCEMBLIX

Strong CYP3A4 Inhibitors

Asciminib is a CYP3A4 substrate. Concomitant use of SCEMBLIX with a strong CYP3A4 inhibitor increases both the asciminib $C_{max}$ and AUC, which may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*. Closely monitor for adverse reactions in patients treated with SCEMBLIX at 200 mg twice daily with concomitant use of strong CYP3A4 inhibitors.

Itraconazole Oral Solution Containing Hydroxypropyl-β-cyclodextrin

Concomitant use of SCEMBLIX with itraconazole oral solution containing hydroxypropyl-β-cyclodextrin decreases asciminib $C_{max}$ and AUC, which may reduce SCEMBLIX efficacy *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of SCEMBLIX at all recommended doses with itraconazole oral solution containing hydroxypropyl-β-cyclodextrin.

Strong CYP3A4 Inducers

Concomitant use of SCEMBLIX with strong CYP3A4 inducers decreases both the asciminib $C_{max}$ and AUC *[see Clinical Pharmacology (12.3)]*.

### 7.2 Effect of SCEMBLIX on Other Drugs

Certain CYP3A4 Substrates

Asciminib is a CYP3A4 inhibitor. Concomitant use of SCEMBLIX increases the $C_{max}$ and AUC of CYP3A4 substrates, which may increase the risk of adverse reactions of these substrates *[see Clinical Pharmacology (12.3)]*.

Closely monitor for adverse reactions in patients treated with SCEMBLIX at 80 mg total daily dose with concomitant use of certain CYP3A4 substrates, where minimal concentration changes may lead to serious adverse reactions. Avoid coadministration of SCEMBLIX at 200 mg twice daily with certain CYP3A4 substrates, where minimal concentration changes may lead to serious adverse reactions.

CYP2C9 Substrates

Asciminib is a CYP2C9 inhibitor. Concomitant use of SCEMBLIX increases the $C_{max}$ and AUC of CYP2C9 substrates, which may increase the risk of adverse reactions of these substrates *[see Clinical Pharmacology (12.3)]*.

Avoid coadministration of SCEMBLIX at 80 mg total daily dose with certain CYP2C9 substrates, where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, reduce the CYP2C9 substrate dosage as recommended in its prescribing information.

Avoid coadministration of SCEMBLIX at 200 mg twice daily with sensitive CYP2C9 substrates and certain CYP2C9 substrates, where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, consider alternative therapy with a non-CYP2C9 substrate.

Certain P-gp Substrates

Asciminib is a P-gp inhibitor. Concomitant use of SCEMBLIX increases the plasma concentrations of P-gp substrates, which may increase the risk of adverse reactions of these substrates *[see Clinical Pharmacology (12.3)]*.

Closely monitor for adverse reactions in patients treated with SCEMBLIX at all recommended doses with concomitant use of P-gp substrates, where minimal concentration changes may lead to serious toxicities.

Substrates of BCRP

Asciminib is a BCRP inhibitor. Concomitant use of SCEMBLIX may increase the plasma concentration of BCRP substrates. [see Clinical Pharmacology (12.3)], which may increase the risk of adverse reactions associated with these substrates.

Avoid coadministration of SCEMBLIX at all recommended doses with rosuvastatin . Closely monitor for adverse reactions in patients treated with SCEMBLIX at all recommended doses with concomitant use of other BCRP substrates. Reduce the dosage of the other BCRP substrates as recommended in their Prescribing Information when used concomitantly with SCEMBLIX at all recommended doses.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, SCEMBLIX can cause embryo-fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on SCEMBLIX use in pregnant women to evaluate a drug associated risk.

Animal reproduction studies in pregnant rats and rabbits demonstrated that oral administration of asciminib during organogenesis induced structural abnormalities, embryo-fetal mortality, and alterations to growth *(see Data)*.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

*Animal Data*

In embryo-fetal development studies, pregnant animals received oral doses of asciminib at 25, 150, and 600 mg/kg/day in rats and at 15, 50, and 300 mg/kg/day in rabbits during the period of organogenesis.

In rats, maternal toxicity at the asciminib dose of 600 mg/kg/day resulted in the early termination of the dose group; a complete embryo-fetal examination was not conducted for this group. Adverse embryo-fetal findings were observed at 25 and 150 mg/kg; these doses did not cause maternal toxicities. Increases in fetal weights at 25 and 150 mg/kg/day were observed, which may be related to increased ossification (i.e., increased rate of development). Malformations were evident at 150 mg/kg and included cleft palate, anasarca (edema), and cardiac abnormalities. Additional fetal findings included urinary tract and skeletal variations, observed primarily at 150 mg/kg/day. At the dose of 25 mg/kg/day, the area under the curve (AUC) exposures were equivalent to or below those achieved in patients at the 40 mg twice daily or 80 mg once daily doses, respectively. At the dose of 25 mg/kg/day, the AUC exposures were below those achieved in patients at the 200 mg twice daily dose.

In rabbits, maternal toxicities at the asciminib dose of 300 mg/kg/day resulted in the early termination of the dose group; a complete embryo-fetal examination was not conducted for this group. Adverse embryo-fetal findings were observed at 50 mg/kg; this dose did not cause maternal toxicities. Findings at the 50 mg/kg dose included increases in early resorptions and post-implantation loss, decreases in the number of live fetuses, and cardiac malformations. At the dose of 50

mg/kg/day, the AUC exposures were 4-fold those achieved in patients at the 40 mg twice daily or 80 mg once daily doses. At the dose of 50 mg/kg/day, the AUC exposures were below those achieved in patients at the 200 mg twice daily dose.

### 8.2 Lactation

Risk Summary

There are no data on the presence of asciminib or its metabolites in human milk, the effects on the breastfed child, or milk production.

Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with SCEMBLIX and for 1 week after the last dose.

### 8.3 Females and Males of Reproductive Potential

Based on findings from animal studies, SCEMBLIX can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with SCEMBLIX.

Contraception

*Females*

Females of reproductive potential should use effective contraception during treatment with SCEMBLIX and for 1 week after the last dose.

Infertility

Based on findings in animals, SCEMBLIX may impair fertility in females of reproductive potential *[see Nonclinical Toxicology (13.1)].* The reversibility of the effect on fertility is unknown.

### 8.4 Pediatric Use

SCEMBLIX is not indicated for children and adolescent under 18 years old.

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

### 8.5 Geriatric Use

In the ASCEMBL study, 44 of the 233 (19%) patients were 65 years of age or older and 6 (2.6%) were 75 years of age or older.

In the X2101 study, 16 of the 48 (33%) patients with the T315I mutation were 65 years of age or older and 4 (8%) were 75 years of age or older.

Overall, no differences in safety or efficacy of SCEMBLIX were observed between patients 65 years of age or older compared to younger patients. There is an insufficient number of patients 75 years of age or older to assess whether there are differences in safety or efficacy.

### 8.6 Renal Impairment

No dose adjustment is required for patients with mild to severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 89 mL/min/1.73 $m^2$) and not requiring dialysis receiving SCEMBLIX *[see Clinical Pharmacology (12.3)].*

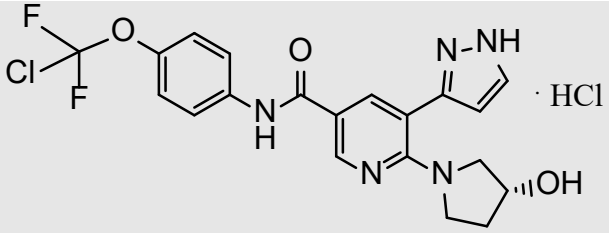
### 8.7 Hepatic Impairment

No dose adjustment is required for patients with mild [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin > 1 to 1.5 times ULN and any AST] to severe hepatic impairment (total bilirubin > 3 times ULN and any AST) receiving SCEMBLIX *[see Clinical Pharmacology (12.3)].*

## 11 DESCRIPTION

SCEMBLIX (asciminib) is a kinase inhibitor. The chemical name of the drug substance is *N*-[4-(Chlorodifluoromethoxy)phenyl]-6-[(3*R*)-3-hydroxypyrrolidin-1-yl]-5-(1*H*-pyrazol-3-yl)pyridine-3-carboxamide-hydrogen chloride (1/1). Asciminib hydrochloride is a white to slightly yellow powder. The molecular formula of

asciminib hydrochloride is $C_{20}H_{18}ClF_2N_5O_3$.HCl, and the relative molecular mass is 486.30 g/mol for the hydrochloride salt and 449.84 g/mol for the free base. The chemical structure of asciminib hydrochloride is shown below:




SCEMBLIX film-coated tablets are supplied for oral use with two strengths that contain 20 mg and 40 mg of asciminib (equivalent to 21.62 mg and 43.24 mg, respectively, of asciminib hydrochloride). The tablets contain lactose monohydrate, microcrystalline cellulose (E460i), hydroxypropylcellulose, low-substituted (E463),croscarmellose sodium (E468),polyvinyl alcohol (E1203),titanium dioxide (E171),magnesium stearate, talc (E553b), colloidal silicon dioxide, lecithin (E322), xanthan gum (E415),iron oxide red (E172)

Scemblix 20 mg film-coated tablets only -iron oxide yellow (E172)
Scemblix 40 mg film-coated tablets only -iron oxide black (E172)

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Asciminib is an ABL/BCR-ABL1 tyrosine kinase inhibitor. Asciminib inhibits the ABL1 kinase activity of the BCR-ABL1 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.

### 12.2 Pharmacodynamics

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EA06

Exposure-Response Relationships

Over asciminib dosages of 10 mg to 200 mg twice daily (0.25 to 5 times the recommended 80 mg daily dosage), a lower exposure was associated with a smaller decrease in BCR-ABL1 level and a lower MMR rate at Week 24.

Over asciminib dosages of 10 mg to 280 mg twice daily (0.25 to 7 times the recommended 80 mg daily dosage), a higher exposure was associated with slightly higher incidence of some adverse reactions (e.g., Grade ≥ 3 lipase increase, Grade ≥ 3 hemoglobin decrease, Grade ≥ 2 ALT increase, Grade ≥ 2 AST increase, Grade ≥ 2 bilirubin increase, and any grade lipase increase).

Cardiac Electrophysiology

Asciminib does not cause a large mean increase in QTc interval (i.e., > 20 msec) at the maximum recommended clinical dosage (200 mg twice daily). Based on available clinical data, small mean QTc increase (< 10 msec) cannot be excluded.

### 12.3 Pharmacokinetics

Asciminib steady-state exposure (AUC and $C_{max}$) increase slightly more than dose proportional across the dose range of 10 to 200 mg (0.25 to 5 times the recommended 80 mg daily dosage) administered once or twice daily.

Pharmacokinetic parameters are presented as geometric mean (CV%) unless otherwise stated. The steady state $C_{max}$ and $AUC_{tau}$ of asciminib at recommended dosages are listed in Table 7.

**Table 7: Steady State[a] Asciminib Exposure at Recommended Dosages**

| Asciminib Dosage | $C_{max}$ (ng/mL) | $AUC_{tau}$[b] (ng*h/mL) | Accumulation Ratio |
|---|---|---|---|
| 80 mg once daily | 1781 (23%) | 15112 (28%) | 1.30 |

| | | | |
|---|---|---|---|
| 40 mg twice daily | 793 (49%) | 5262 (48%) | 1.65 |
| 200 mg twice daily | 5642 (40%) | 37547 (41%) | 1.92 |
| [a]Steady state is achieved within 3 days.<br>[b]$AUC_{tau}$ represents $AUC_{0\text{-}12h}$ for twice daily dosing and $AUC_{0\text{-}24h}$ for once daily dosing. | | | |

Absorption

The median (range) $T_{max}$ of asciminib is 2.5 hours (2 to 3 hours).

*Effect of Food*

The AUC and $C_{max}$ of asciminib decreased by 62% and 68%, respectively, with a high-fat meal (1000 calories, 50% fat) and by 30% and 35%, respectively, with a low-fat meal (400 calories, 25% fat) compared to the fasted state following administration of SCEMBLIX.

Distribution

The apparent volume of distribution of asciminib at steady state is 151 L (135%). Asciminib is the main circulating component in plasma (93% of the administered dose).

Asciminib is 97% bound to human plasma proteins *in vitro*.

Elimination

The total apparent clearance of asciminib is 6.7 L/hour (48%) at 40 mg twice daily and 80 mg once daily, and 4.1 L/hour (38%) at 200 mg twice daily. The terminal elimination half-life of asciminib is 5.5 hours (38%) at 40 mg twice daily and 80 mg once daily, and 9.0 hours (33%) at 200 mg twice daily.

*Metabolism*

Asciminib is metabolized by CYP3A4-mediated oxidation, UGT2B7- and UGT2B17-mediated glucuronidation.

*Excretion*

Eighty percent (57% as unchanged) and 11% (2.5% as unchanged) of the asciminib dose were recovered in the feces and in the urine of healthy subjects, respectively, following oral administration of a single 80 mg dose of radio-labeled asciminib.

Asciminib is eliminated by biliary secretion via breast cancer-resistant protein (BCRP).

Specific Populations

No clinically significant differences in the pharmacokinetics of asciminib were observed based on sex, age (20 to 88 years), race (Asian 20%, White 70%, Black/African American 4%), or body weight (42 - 184 kg), mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 $m^2$), or mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST) to moderate (total bilirubin > 1.5 to 3 times ULN and any AST) hepatic impairment.

*Patients with Renal Impairment*

Asciminib $AUC_{inf}$ and $C_{max}$ are increased by 57% and 6%, respectively, in subjects with eGFR between 13 to < 30 mL/min/1.73 $m^2$ and not requiring dialysis compared to subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 $m^2$) following oral administration of a single 40 mg dose of SCEMBLIX. The exposure changes in patients with severe renal impairment are not considered clinically meaningful.

*Patients with Hepatic Impairment*

Asciminib $AUC_{inf}$ and $C_{max}$ are increased by 33% and 4%, respectively, in subjects with severe hepatic impairment (total bilirubin > 3 times ULN and any AST), compared to subjects with normal hepatic function (total bilirubin ≤ ULN and AST ≤ ULN) following oral administration of a single 40 mg dose of SCEMBLIX. The exposure changes are not considered clinically meaningful.

Drug Interaction Studies

*Clinical Studies and Model-Informed Approaches*

Drugs That Affect Asciminib Plasma Concentration

*Strong CYP3A Inhibitors:* The asciminib $AUC_{inf}$ and $C_{max}$ increased by 36% and 19%, respectively, following coadministration of a single SCEMBLIX dose of 40 mg with a strong CYP3A4 inhibitor (clarithromycin). No clinically significant differences in the pharmacokinetics of asciminib were observed when coadministered with itraconazole, which is also a strong CYP3A4 inhibitor.

*Strong CYP3A Inducers:* The asciminib $AUC_{inf}$ decreased by 34% and $C_{max}$ decreased by 22% following coadministration of a single SCEMBLIX dose of 200 mg with a strong CYP3A4 inducer (phenytoin) 100 mg three times daily. The asciminib $AUC_{inf}$ decreased by 15% while $C_{max}$ increased by 9%, following coadministration of a single SCEMBLIX dose of 40 mg with a strong CYP3A4 inducer (rifampicin).

*Itraconazole Oral Solution*: Coadministration of multiple doses of itraconazole oral solution containing hydroxypropyl-β-cyclodextrin with a single SCEMBLIX dose of 40 mg decreased asciminib $AUC_{inf}$ and $C_{max}$ by 40% and 50%, respectively. Concomitant use of oral products containing hydroxypropyl-β-cyclodextrin with SCEMBLIX other than itraconazole oral solution has not been fully characterized.

*Imatinib:* The asciminib $AUC_{inf}$ and $C_{max}$ increase by 108% and 59%, respectively following coadministration of a single SCEMBLIX dose of 40 mg with imatinib (an inhibitor of BCRP, CYP3A4, UGT2B17, and UGT1A3/4). The exposure changes are not considered clinically meaningful. Concomitant use of imatinib with SCEMBLIX at 200 mg twice daily has not been fully characterized.

*Other Drugs:* No clinically significant differences in the pharmacokinetics of asciminib were observed when coadministered with rabeprazole (acid-reducing agent) and quinidine (P-gp inhibitor).

Drugs That are Affected by Asciminib

*CYP3A4 Substrates:* The midazolam $AUC_{inf}$ and $C_{max}$ increased by 28% and 11%, respectively, following coadministration of a CYP3A4 substrate (midazolam) with SCEMBLIX 40 mg twice daily. The midazolam $AUC_{inf}$ and $C_{max}$ increased by 24% and 17%, respectively, following coadministration with SCEMBLIX at 80 mg once daily and 88% and 58%, respectively, at 200 mg twice daily.

*CYP2C9 Substrates:* The S-warfarin $AUC_{inf}$ and $C_{max}$ increased by 41% and 8%, respectively, following coadministration of CYP2C9 substrate (warfarin) with SCEMBLIX at 40 mg twice daily. The S-warfarin $AUC_{inf}$ and $C_{max}$ increased by 52% and 4%, respectively, following coadministration with SCEMBLIX at 80 mg once daily and 314% and 7%, respectively, at 200 mg twice daily.

*CYP2C8 Substrates:* The repaglinide (substrate of CYP2C8, CYP3A4, and OATP1B) $AUC_{inf}$ and $C_{max}$ increased by 8% and 14%, respectively, following coadministration of repaglinide with SCEMBLIX 40 mg twice daily. The repaglinide $AUC_{inf}$ and $C_{max}$ increased by 12% and 8%, respectively, following coadministration with SCEMBLIX at 80 mg once daily and 42% and 25%, respectively, at 200 mg twice daily. The rosiglitazone (substrate of CYP2C8 and CYP2C9) $AUC_{inf}$ and $C_{max}$ increased by 20% and 3%, respectively, following coadministration of rosiglitazone with SCEMBLIX 40 mg twice daily. The rosiglitazone $AUC_{inf}$ and $C_{max}$ increased by 24% and 2%, respectively, following coadministration with SCEMBLIX at 80 mg once daily and 66% and 8%, respectively, at 200 mg twice daily.

*P-gp Substrates*: Coadministration of SCEMBLIX with a drug that is a substrate of P-gp may result in a clinically relevant increase in the plasma concentrations of P-gp substrates, where minimal concentration changes may lead to serious toxicities.

*OATP1B Substrates:* The atorvastatin (substrate of OATP1B, CYP3A4, and P-gp) $AUC_{inf}$ and $C_{max}$ increased by 14% and 24%, respectively, following coadministration of atorvastatin with SCEMBLIX 80 mg once daily.

*In Vitro Studies*

*CYP450 and UGT Enzymes*

Asciminib may reversibly inhibit UGT1A1 at plasma concentrations reached at a total daily dose of 80 mg and 200 mg twice daily. In addition, asciminib may reversibly inhibit CYP2C19 at concentrations reached at 200 mg twice daily dose.

*Transporter Systems*

Asciminib is a substrate of BCRP and P-gp. Asciminib inhibits BCRP, P-gp, OATP1B1, OATP1B3, and OCT1.

Asciminib may increase the exposure of BCRP substrates in a dose dependent manner.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, rats were administered oral doses of asciminib at 20, 66, and 200 mg/kg/day in males and 10, 30, and 66 mg/kg/day in females. Asciminib induced a statistically significant increase in the incidence of benign Sertoli cell tumors in the ovaries of high-dose females. The exposures to asciminib (AUC) in female rats at 66 mg/kg/day were approximately 8-fold or 6-fold higher than the exposure (AUC) achieved in patients at the dose of 40 mg twice daily or 80 mg once daily, respectively, and equivalent to those achieved in patients at the dose of 200 mg twice daily. The clinical relevance of these findings is currently unknown.

Asciminib was not genotoxic in an *in vitro* bacterial mutagenicity (Ames) assay, an *in vitro* micronucleus assay in human peripheral blood lymphocytes (HPBL), or an *in vivo* rat peripheral blood reticulocyte micronucleus assay.

In a combined male and female fertility and early embryonic development study in rats, animals were administered asciminib doses of 10, 50, or 200 mg/kg/day orally. Male animals were dosed once daily for at least 28 days prior to mating, during the 2-week mating period, and until terminal necropsy (Days 63- to 67). Female animals were dosed once daily for the 2-week premating period, during the 2-week mating period, and through gestation day (GD) 6. Decreased sperm count and motility were observed at 200 mg/kg/day. While there were no effects on fertility indices or conception rates, a decreased mean number of live embryos was observed at 200 mg/kg/day and was attributed to a lower number of implantations and an increased number of early resorptions. Increased early resorptions were also observed in the embryo-fetal development study in rabbits *[see Use in Specific Populations (8.1)]*.

At the dose of 200 mg/kg, the AUC exposures were approximately 19-fold, 13-fold, or 2-fold higher than those achieved in patients at the 40 mg twice daily, 80 mg once daily, or 200 mg twice daily doses, respectively.

## 14 CLINICAL STUDIES

### 14.1 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 TKIs was evaluated in the multi-center, randomized, active-controlled, and open-label study ASCEMBL (NCT03106779).

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 40 mg twice daily (N = 157) or bosutinib 500 mg once daily (N = 76). 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 103 weeks (range, 0.1 to 201 weeks) for patients receiving SCEMBLIX and 31 weeks (range, 1 to 188 weeks) for patients receiving bosutinib.

The main efficacy outcomes from ASCEMBL are summarized in Table 8.

**Table 8: Efficacy Results in Patients with Ph+ CML-CP, Previously Treated with Two or More TKIs (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<br>25<br>(19, 33) | N = 76<br>13<br>(6.5, 23) | 12[a]<br>(2.2, 22) | 0.029[b] |

| | | | | |
|---|---|---|---|---|
| **MMR rate, % (95% CI) at 96 weeks** | N = 157<br>38<br>(30, 46) | N = 76<br>16<br>(8, 26) | 22[a]<br>(11, 33) | 0.001[b] |
| **CCyR rate, % (95% CI) at 24 weeks** | N = 103[c]<br>41<br>(31, 51) | N = 62[c]<br>24<br>(14, 37) | 17<br>(3.6, 31) | |
| **CCyR rate, % (95% CI) at 96 weeks** | N = 103[c]<br>40<br>(30, 50) | N = 62[c]<br>16<br>(8, 28) | 24[a]<br>(10, 37) | |

Abbreviations: MMR, major molecular response (*BCR-ABL1*$^{IS}$ ≤ 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 Cochran-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.

With a median duration of follow-up of 28 months (range: 1 day to 45 months), the median duration of response for patients treated with SCEMBLIX had not yet been reached.

### 14.2 Ph+ CML-CP with the T315I Mutation

The efficacy of SCEMBLIX in the treatment of patients with Ph+ CML-CP with the T315I mutation was evaluated in a multi-center open-label study CABL001X2101 (NCT02081378). Testing for T315I mutation utilized a qualitative p210 BCR-ABL1 mutation test on peripheral blood 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% were male and 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).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

SCEMBLIX is supplied in PCTFE/PVC/Alu blisters Packs.

Packs containing 20 or 60 film-coated tablets.
Not all pack sizes may be marketed.

- SCEMBLIX (asciminib) 20 mg film-coated tablets are supplied as pale yellow, unscored, round, biconvex, with beveled edges, of approximately 6.2 mm diameter film-coated tablets containing 20 mg of asciminib (equivalent to 21.62 mg of asciminib HCl). Each tablet is debossed with “20” on one side and the “Novartis” logo on the other side.
- SCEMBLIX (asciminib) 40 mg film-coated tablets are supplied as violet white, unscored, round, biconvex, with beveled edges, of approximately 8.2 mm diameter film-coated tablets containing 40 mg of asciminib (equivalent to 43.24 mg of asciminib HCl). Each tablet is debossed with “40” on one side and the “Novartis” logo on the other side.

Storage

Do not store above 25°C. Store in the original container in order to protect from moisture.

Shelf life

The expiry date of the product is indicated on the packaging materials.

## 17 LICENSE HOLDER AND IMPORTER

Novartis Israel Ltd., P.O.B 9240, Tel Aviv.

## 18 REGISTRATION NUMBER

SCEMBLIX 20MG: 172-84-37483-99

SCEMBLIX 40MG: 172-85-37484-99

Revised in December 2025.