

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr**SCSEMBLIX™**

asciminib tablets

Tablets, 20 mg and 40 mg, asciminib (as asciminib hydrochloride), Oral

Antineoplastic Agent

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SCSEMBLIX is a trademark

## RECENT MAJOR LABEL CHANGES

|                            |         |
|----------------------------|---------|
| 7 Warnings and Precautions | 07/2023 |
|----------------------------|---------|

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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

SCEMBLIX™ (asciminib tablets) 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.

#### **1.1 Pediatrics**

Paediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for SCEMBLIX for pediatric use.

#### **1.2 Geriatrics**

Geriatrics (≥ 65 years of age): No overall differences in the safety or efficacy of SCEMBLIX were observed between patients of 65 years of age or above and younger patients (see [7.1.4 Geriatrics](#) and [14 CLINICAL TRIALS](#)).

### **2 CONTRAINDICATIONS**

SCEMBLIX is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 Dosage forms, strengths, composition and packaging](#).

### **4 DOSAGE AND ADMINISTRATION**

#### **4.1 Dosing Considerations**

Treatment with SCEMBLIX should be initiated by a physician experienced in the use of anticancer therapies.

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with SCEMBLIX.

#### **4.2 Recommended Dose and Dosage Adjustment**

The recommended total daily dose of SCEMBLIX is 80 mg. SCEMBLIX can be taken orally either as 80 mg once daily at approximately the same time each day, or as 40 mg twice daily at approximately 12-hour intervals.

Patients changing from 40 mg twice daily to 80 mg once daily should start taking SCEMBLIX once daily approximately 12 hours after the last twice-daily dose, and then continue at 80 mg once daily.

Patients changing from 80 mg once daily to 40 mg twice daily should start taking SCEMBLIX twice daily approximately 24 hours after the last once-daily dose and then continue at 40 mg twice daily at approximately 12-hour intervals.

Any change in the dosage regimen is at the prescriber's discretion, as necessary for the management of the patient.

Treatment with SCEMBLIX should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

## Dosage Modifications

For the management of adverse reactions, SCEMBLIX dose can be reduced based on individual safety and tolerability, as described in Table 1. If adverse reactions are effectively managed, SCEMBLIX may be resumed as described in Table 1.

SCEMBLIX should be permanently discontinued in patients unable to tolerate a total daily dose of 40 mg.

**Table 1 SCEMBLIX dosage modification**

| Starting dose     | Reduced dose      | Resumed dose      |
|-------------------|-------------------|-------------------|
| 80 mg once daily  | 40 mg once daily  | 80 mg once daily  |
| 40 mg twice daily | 20 mg twice daily | 40 mg twice daily |

The recommended dosage modification for the management of selected adverse reactions is shown in Table 2.

**Table 2 SCEMBLIX dosage modification for the management of selected adverse reactions**

| Adverse reaction                                      | Dosage modification   |
|---|---|
| <b>Thrombocytopenia and/or neutropenia</b>            |   |
| ANC $<1 \times 10^9/L$ and/or PLT $<50 \times 10^9/L$ | Withhold SCEMBLIX until resolved to ANC $\geq 1 \times 10^9/L$ and/or PLT $\geq 50 \times 10^9/L$ .<br>If resolved: <ul style="list-style-type: none"><li>• Within 2 weeks: resume SCEMBLIX at starting dose.</li><li>• After more than 2 weeks: resume SCEMBLIX at reduced dose.</li></ul> For recurrent severe thrombocytopenia and/or neutropenia, withhold SCEMBLIX until resolved to ANC $\geq 1 \times 10^9/L$ and PLT $\geq 50 \times 10^9/L$ , then resume at reduced dose. |
| <b>Asymptomatic amylase and/or lipase elevation</b>   |   |
| Elevation $>2 \times ULN$                             | Withhold SCEMBLIX until resolved to $<1.5 \times ULN$ . <ul style="list-style-type: none"><li>• If resolved: resume SCEMBLIX at reduced dose. If events reoccur at reduced dose, permanently discontinue SCEMBLIX.</li><li>• If not resolved: permanently discontinue SCEMBLIX. Perform diagnostic tests to exclude pancreatitis.</li></ul>   |
| <b>Non-hematologic adverse reactions</b>              |   |
| Grade 3 or higher <sup>1</sup> adverse reactions      | Withhold SCEMBLIX until resolved to grade 1 or lower. <ul style="list-style-type: none"><li>• If resolved: resume SCEMBLIX at a reduced dose.</li><li>• If not resolved: permanently discontinue SCEMBLIX.</li></ul>  |

| Adverse reaction  | Dosage modification |
|---|---------------------|
| Abbreviations: ANC, absolute neutrophil count; PLT, platelets; ULN, upper limit of normal<br><sup>1</sup> Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.03. |                     |

## Special populations

**Pediatrics (<18 years of age):** Health Canada has not authorized an indication for pediatric use.

**Geriatrics (≥ 65 years):** No dose adjustment is required in patients 65 years of age or above (see [7.1.4 Geriatrics](#) and [10.3 Pharmacokinetics](#)).

**Renal impairment:** No dose adjustment is required in patients with mild, moderate or severe renal impairment not requiring dialysis (absolute Glomerular Filtration Rate (aGFR) ≥15 mL/min) receiving SCEMBLIX (see [10.3 Pharmacokinetics](#)). SCEMBLIX has not been studied in subjects with end stage renal disease requiring dialysis.

**Hepatic impairment:** No dose adjustment is required in patients with mild, moderate or severe hepatic impairment receiving SCEMBLIX (see [10.3 Pharmacokinetics](#)).

## 4.4 Administration

SCEMBLIX should be taken orally without food. Food consumption should be avoided for at least 2 hours before and 1 hour after taking SCEMBLIX (see [9 DRUG INTERACTIONS](#) and [10 CLINICAL PHARMACOLOGY](#)).

SCEMBLIX tablets should be swallowed whole and should not be broken, crushed or chewed.

## 4.5 Missed Dose

**Once-daily dosage regimen:** If a SCEMBLIX dose is missed by more than approximately 12 hours, it should be skipped and the next dose should be taken as scheduled.

**Twice-daily dosage regimen:** If a SCEMBLIX dose is missed by more than approximately 6 hours, it should be skipped and the next dose should be taken as scheduled.

## 5 OVERDOSAGE

There is limited experience of SCEMBLIX overdose. In clinical studies, SCEMBLIX has been administered at doses up to 280 mg twice daily with no evidence of increased toxicity. General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition                                     | Non-medicinal Ingredients   |
|-------------------------|--|---|
| Oral                    | Tablet<br>20 mg and 40 mg<br>asciminib (as asciminib<br>hydrochloride) | Colloidal silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, iron oxide (yellow and red for the 20 mg tablet and black and red for the 40 mg tablet), lactose monohydrate, lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide, xanthan gum. |

Each 20 mg film-coated SCEMBLIX tablet contains 21.62 mg asciminib hydrochloride, which is equivalent to 20 mg asciminib.

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

Each 40 mg film-coated SCEMBLIX tablet contains 43.24 mg asciminib hydrochloride, which is equivalent to 40 mg asciminib.

40 mg film-coated SCEMBLIX tablets: violet white, round, biconvex with beveled edges, approximately 8.2 mm diameter, unscored, debossed with “Novartis” logo on one side and “40” on the other side.

SCEMBLIX 20 mg and 40 mg tablets are supplied in blister pack (10 blisters/card, 6 cards/carton).

## 7 WARNINGS AND PRECAUTIONS

### Cardiovascular

#### **Cardiovascular toxicity**

Cardiovascular toxicity (including ischemic cardiac and CNS conditions, arterial thrombotic and embolic conditions) and cardiac failure occurred in 29 (8.1%) and in 11 (3.1%) of 356 patients receiving SCEMBLIX, respectively. Grade 3 cardiovascular toxicity was reported in 11 (3.1%) patients, while grade 3 cardiac failure was observed in 8 (2.2%) patients. Grade 4 cardiovascular toxicity occurred in 1 (0.3%) patient, with fatalities occurring in 2 (0.6%) patients. Grade 4 cardiac failure was observed in 1 (0.3%) patients.

Permanent discontinuation of SCEMBLIX occurred in 2 (0.6%) due to cardiovascular toxicity and in 1 (0.3%) patient due to cardiac failure. Cardiovascular toxicity occurred in patients with pre-existing cardiovascular conditions or risk factors, and/or prior exposure to multiple TKIs.

## **Arrhythmias**

Arrhythmia, including QTc prolongation, occurred in 24 of 356 (7%) patients receiving SCEMBLIX, with Grade 3 arrhythmia reported in 8 (2.2%) patients. Electrocardiogram QTc prolongation occurred in 3 of 356 (0.8%) patients receiving SCEMBLIX, with Grade 3 QTc prolongation reported in 1 out of 356 (0.3%) patients (see [8 ADVERSE REACTIONS and Monitoring and Laboratory Tests](#)).

In the ASCEMBL clinical study, one patient had a prolonged QTcF greater than 500 ms together with more than 60 ms QTcF increase from baseline and one patient had prolonged QTcF with more than 60 ms QTcF increase from baseline.

Caution should be exercised when administering SCEMBLIX concomitantly with medicinal products with known risk of torsades de pointes (see [9 DRUG INTERACTIONS](#) and section [10 CLINICAL PHARMACOLOGY](#)).

## **Hypertension**

Hypertension occurred in 66 of 356 (18.5%) patients receiving SCEMBLIX, with grade 3 and 4 reactions reported in 30 (8.4%) and 1 (0.3%) patients, respectively. Among the patients with hypertension  $\geq$  grade 3, the median time to first occurrence of reactions was 14 weeks (range: 0.1 to 156 weeks). Of the 66 patients with hypertension, SCEMBLIX was temporarily withheld in 3 (0.8%) patients due to the adverse reaction.

## **Hematologic**

### **Myelosuppression**

Thrombocytopenia, neutropenia and anemia occurred in patients receiving SCEMBLIX. Severe (NCI CTCAE grade 3 or 4) thrombocytopenia and neutropenia were reported during treatment with SCEMBLIX (see [8 ADVERSE REACTIONS](#)). Myelosuppression was generally reversible and managed by temporarily withholding SCEMBLIX (see [Monitoring and Laboratory Tests](#)).

Thrombocytopenia occurred in 98 of 356 (27.5%) patients receiving SCEMBLIX, with grade 3 and 4 reactions reported in 24 (6.7%) and 42 (11.8%) of patients, respectively. Among the patients with thrombocytopenia  $\geq$  grade 3, the median time to first occurrence of reactions was 6 weeks (range: 0.1 to 64 weeks) with median duration of any occurring reaction of 1.71 weeks (95% CI, range: 1.43 to 2 weeks). Of the 98 patients with thrombocytopenia, 7 (2%) permanently discontinued SCEMBLIX, while SCEMBLIX was temporarily withheld in 45 (12.6%) patients due to the adverse reaction.

Neutropenia occurred in 69 of 356 (19.4%) patients receiving SCEMBLIX, with grade 3 and 4 reactions reported in 26 (7.3%) and 30 (8.4%) patients, respectively. Among the patients with neutropenia  $\geq$  grade 3, the median time to first occurrence of reactions was 6 weeks (range: 0.14 to 180 weeks) with median duration of any occurring reaction of 1.79 weeks (95% CI, range: 1.29 to 2 weeks). Of the 69 patients with neutropenia, 4 (1.1%) permanently discontinued SCEMBLIX, while SCEMBLIX was temporarily withheld in 34 (9.6%) patients due to the adverse reaction.

Anemia occurred in 46 of 356 (12.9%) patients receiving SCEMBLIX, with grade 3 reactions occurring in 19 (5.3%) patients. Among the patients with anemia grade 3, the median time to first occurrence of reactions was 30 weeks (range: 0.4 to 207 weeks) with median duration of any



occurring reaction of 0.9 weeks (95% CI, range: 0.43 to 2.14 weeks). Of the 46 patients with anemia, SCEMBLIX was temporarily withheld in 2 (0.6%) patients due to the adverse reaction.

Based on the severity of thrombocytopenia and/or neutropenia, the SCEMBLIX dose should be reduced, temporarily withheld or permanently discontinued as described in Table 2 (see [4 DOSAGE AND ADMINISTRATION](#)).

## **Hepatic/Biliary/Pancreatic**

### ***Pancreatic toxicity***

Pancreatitis occurred in 9 of 356 (2.5%) patients receiving SCEMBLIX, with grade 3 reactions occurring in 4 (1.1%) patients. Of the 9 patients with pancreatitis, 2 (0.6%) 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 (21.3%) patients receiving SCEMBLIX, with grade 3 and 4 reactions occurring in 36 (10.1%) and 8 (2.2%) patients, respectively. Of the 76 patients with pancreatic enzymes elevation, SCEMBLIX was permanently discontinued in 8 (2.2%) patients due to the adverse reaction (see [Monitoring and Laboratory Tests](#)).

If serum lipase and amylase elevation are accompanied by abdominal symptoms, treatment should be temporarily withheld and appropriate diagnostic tests should be considered to exclude pancreatitis (see [4 DOSAGE AND ADMINISTRATION](#)).

Based on the severity of serum lipase and amylase elevation, the SCEMBLIX dose should be reduced, temporarily withheld or permanently discontinued as described in Table 2 (see [4 DOSAGE AND ADMINISTRATION](#)).

## **Immune**

### ***Hepatitis B reactivation***

Reactivation of hepatitis B virus (HBV) has occurred in patients who are chronic carriers of this virus following administration of other BCR::ABL1 tyrosine kinase inhibitors (TKIs). Patients should be tested for HBV infection before the start of treatment with SCEMBLIX (see [Monitoring and Laboratory Tests](#)).

### ***Hypersensitivity***

Hypersensitivity events occurred in 111 of 356 (31.2%) patients receiving SCEMBLIX, with ≥grade 3 events reported in 6 (1.7%) patients (see [Monitoring and Laboratory Tests](#)).

## **Monitoring and Laboratory Tests**

It is recommended that an electrocardiogram is performed prior to the start of treatment with SCEMBLIX and monitored during treatment as clinically indicated. Hypokalemia and hypomagnesemia should be corrected prior to SCEMBLIX administration and monitored during treatment as clinically indicated.

Hypertension should be monitored and managed using standard antihypertensive therapy during treatment with SCEMBLIX as clinically indicated.

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with SCEMBLIX.

Complete blood counts should be performed every two weeks for the first 3 months of treatment and monthly thereafter, or as clinically indicated. Patients should be monitored for signs and symptoms of myelosuppression.

Serum lipase and amylase levels should be assessed monthly during treatment with SCEMBLIX, or as clinically indicated. Patients should be monitored for signs and symptoms of pancreatic toxicity. More frequent monitoring should be performed in patients with a history of pancreatitis. HBV carriers who require treatment with SCEMBLIX should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Patients should be monitored for signs and symptoms of hypersensitivity and appropriate treatment should be initiated as clinically indicated.

## **Reproductive Health: Female and Male Potential**

### **Fertility**

Based on findings in animals, SCEMBLIX may impair fertility. There are no data on the effect of SCEMBLIX on human fertility (see [16 NON-CLINICAL TOXICOLOGY](#)).

### **Teratogenic risk**

Based on findings from animal studies, SCEMBLIX can cause fetal harm when administered to a pregnant woman. Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus if SCEMBLIX is used during pregnancy or if the patient becomes pregnant while taking SCEMBLIX.

Sexually-active females and males of reproductive potential should use effective contraception (in addition to a barrier method) during treatment with SCEMBLIX and for at least 7 days after the last dose (see Pregnant Women and [Monitoring and Laboratory Tests](#)).

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

Based on findings from animal studies, SCEMBLIX can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk.

Animal reproduction studies in pregnant rats and rabbits demonstrated that oral administration of asciminib during organogenesis induced embryotoxicity, fetotoxicity and teratogenicity. Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus if SCEMBLIX is used during pregnancy or if the patient becomes pregnant while taking SCEMBLIX (see [Reproductive Health: Female and Male Potential](#)) and [16 NON-CLINICAL TOXICOLOGY](#)).

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with SCEMBLIX.

### 7.1.2 Breast-feeding

It is unknown whether SCEMBLIX is excreted in human milk. Because of the potential for serious adverse reactions in the breastfed child, breast-feeding is not recommended during treatment with SCEMBLIX and for at least 7 days after the last dose.

### 7.1.3 Pediatrics

#### Pediatrics (< 18 years):

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for SCEMBLIX for pediatric use.

### 7.1.4 Geriatrics

#### Geriatrics (≥ 65 years):

In ASCEMBL, 44 of the 233 (18.9%) patients were 65 years or older, while 6 (2.6%) were 75 years or older.

No overall differences in the safety or efficacy of SCEMBLIX were observed between patients of 65 years of age or above and younger patients. There is an insufficient number of patients of 75 years of age or above to assess whether there are differences in safety or efficacy.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

The overall safety profile of SCEMBLIX has been evaluated in 356 patients with Ph+ CML in chronic (CP) and accelerated (AP) phases receiving SCEMBLIX as monotherapy. It is based on the safety pool of the pivotal phase III study A2301 (ASCSEMBL) (N=156 Ph+ CML-CP patients) and the phase I study X2101, including patients with:

Ph+ CML-CP (N=115),

Ph+ CML-CP harboring the T315I mutation (N=70),

Ph+ CML-AP (N=15).

The safety pool (N=356) includes patients receiving SCEMBLIX at doses ranging from 10 to 200 mg twice daily and 80 to 200 mg once daily. In the pooled dataset, the median duration of exposure to SCEMBLIX was 116 weeks (range: 0.1 to 342 weeks).

The most common adverse reactions of any grade (incidence ≥20%) in patients receiving SCEMBLIX were musculoskeletal pain (38.8%), upper respiratory tract infections (28.1%), thrombocytopenia (27.5%), fatigue (27.2%), headache (24.2%), arthralgia (21.6%) increased pancreatic enzymes (21.3%), abdominal pain (21.3%), diarrhea (20.5%), and nausea (20.2%). The most common adverse reactions of ≥ grade 3 (incidence ≥5%) in patients receiving SCEMBLIX were thrombocytopenia (18.5%), neutropenia (15.7%), increased pancreatic enzymes (12.4%), hypertension (8.7%) and anemia (5.3%).

Clinically relevant adverse reactions (incidence <20%) in patients receiving SCEMBLIX included hypersensitivity (0.3%).

Serious adverse reactions occurred in 12.4% of patients receiving SCEMBLIX. The most frequent serious adverse reactions (incidence  $\geq 1\%$ ) were pleural effusion (2.5%), lower respiratory tract infections (2.2%), thrombocytopenia (1.7%), pyrexia (1.4%), pancreatitis (1.1%), musculoskeletal pain (1.7%) and vomiting (1.1%).

## 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse reactions in real-world use.

In the ASCEMBL randomized study, the safety population (patients receiving at least 1 dose of SCEMBLIX) included 156 patients with Ph+ CML-CP, previously treated with two or more TKIs, and treated with SCEMBLIX 40 mg twice daily or bosutinib 500 mg once daily (see [14 Clinical Trials](#)). In the asciminib arm, 83% of patients were exposed for at least 24 weeks and 67% were exposed for 48 weeks or longer.

The most common ( $\geq 20\%$ ) adverse reactions in patients who received SCEMBLIX were upper respiratory tract infections (24%), fatigue (20%), headache (20%) and musculoskeletal pain (21.8%).

Serious adverse events occurred in 18% of patients who received SCEMBLIX. Serious adverse events in  $\geq 1\%$  included urinary tract infection (1.9%), pyrexia (1.3%), cardiac failure (1.3%) and thrombocytopenia (1.3%). Two patients (1.3%) had a fatal adverse event, one each for mesenteric artery thrombosis and ischemic stroke.

Permanent discontinuation of SCEMBLIX due to an adverse reaction occurred in 5.8% of patients. Adverse reactions which resulted in permanent discontinuation of SCEMBLIX in  $\geq 2\%$  of patients included thrombocytopenia (3.2%) and neutropenia (2.6%).

Dosage interruptions of SCEMBLIX due to an adverse reaction occurred in 35.9% of patients. Adverse reactions which required dosage interruption in  $\geq 5\%$  of patients included thrombocytopenia (18.6%) and neutropenia (17.3%).

Dose reductions of SCEMBLIX due to an adverse reaction occurred in 5.8% of patients. Adverse reactions which required dose reductions in  $\geq 1\%$  of patients included thrombocytopenia (4.5%) and neutropenia (1.3%).

Adverse reactions from the phase III clinical study A2301 (ASCEMBL) (Table 4) are listed by MedDRA system organ class and ranked by frequency within each system organ class.

**Table 4 Summary of adverse reactions (≥ 10%) observed with SCEMBLIX in ASCEMBL**

| Adverse reactions   | SCEMBLIX 40 mg BID <sup>1</sup><br>N=156<br>% |           | Bosutinib 500 mg QD <sup>2</sup><br>N=76<br>% |           |
|---|---|-----------|---|-----------|
|   | All grades                                    | Grade 3/4 | All grades                                    | Grade 3/4 |
| <b>Gastrointestinal disorders</b>                           |   |           |   |           |
| Diarrhea  | 13  | 0         | 72  | 11        |
| Nausea  | 12  | 0.6       | 46  | 0         |
| Abdominal pain <sup>3</sup>                                 | 13  | 0         | 22  | 3         |
| <b>General disorders and administration site conditions</b> |   |           |   |           |
| Fatigue <sup>4</sup>  | 20  | 0.6       | 11  | 1         |
| <b>Infections and infestations</b>                          |   |           |   |           |
| Upper respiratory tract infection <sup>5</sup>              | 24  | 0.6       | 9   | 0         |
| <b>Musculoskeletal and connective tissue disorders</b>      |   |           |   |           |
| Musculoskeletal pain <sup>6</sup>                           | 22  | 3         | 16  | 1         |
| Arthralgia  | 13  | 0.6       | 4   | 0         |
| <b>Nervous system disorders</b>                             |   |           |   |           |
| Headache  | 20  | 2         | 16  | 0         |
| <b>Skin and subcutaneous tissue disorders</b>               |   |           |   |           |
| Rash <sup>7</sup>   | 14  | 0         | 25  | 5         |
| <b>Vascular disorders</b>                                   |   |           |   |           |

| Adverse reactions         | SCEMBLIX 40 mg BID <sup>1</sup><br>N=156<br>% |           | Bosutinib 500 mg QD <sup>2</sup><br>N=76<br>% |           |
|---------------------------|---|-----------|---|-----------|
|                           | All grades                                    | Grade 3/4 | All grades                                    | Grade 3/4 |
| Hypertension <sup>8</sup> | 14  | 6         | 5   | 4         |

<sup>1</sup>SCEMBLIX median duration of exposure: 103 weeks (range: 0.1 to 201 weeks) with 53.57% of patients ongoing treatment.

<sup>2</sup>Bosutinib median duration of exposure: 31 weeks (range: 1 to 188 weeks) with 19.7% of patients ongoing treatment.

<sup>3</sup>Abdominal pain includes: abdominal pain and abdominal pain upper;

<sup>4</sup>Fatigue includes: fatigue and asthenia;

<sup>5</sup>Upper respiratory tract infection includes: upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis;

<sup>6</sup>Musculoskeletal pain includes: pain in extremity, back pain, myalgia, non-cardiac chest pain, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain, musculoskeletal discomfort;

<sup>7</sup>Rash includes: rash and rash maculopapular;

<sup>8</sup>Hypertension includes: hypertension and blood pressure increased;

### 8.3 Less Common Clinical Trial Adverse Reactions

Other clinically significant adverse reactions reported in < 10% of patients in the SCEMBLIX arm (all grades) are presented below.

**Blood and lymphatic system disorders:** Febrile neutropenia (0.6%)

**Cardiac disorders:** Palpitations (3%)

**Eye disorders:** Vision blurred (3%), dry eye (2%)

**Gastrointestinal disorders:** Vomiting (8%)

**General disorders and administration site conditions:** Edema (8%), pruritus (5%), pyrexia (4%)

**Immune system disorders:** Hypersensitivity (0.3%)

**Infections and infestations:** Lower respiratory tract infection (4%), influenza 3%)

**Investigations:** Electrocardiogram QT prolonged (1.3%) **Metabolism and nutrition disorders:** Dyslipidemia (6%), Decreased appetite (5%)

**Nervous system disorders:** Dizziness (7%)

**Respiratory, thoracic and mediastinal disorders:** Cough (8%), dyspnea (5%), pleural effusion (1%)

**Skin and subcutaneous tissue disorders:** Urticaria (1%)

#### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

**Table 5** Clinically relevant or  $\geq 10\%$  new or worsened laboratory abnormalities in adult patients with Ph+ CML in CP, previously treated with two or more tyrosine kinase inhibitors in ASCEMBL

| Laboratory Abnormality                     | SCEMBLIX <sup>1</sup><br>40 mg BID<br>N = 156 |                | Bosutinib <sup>1</sup><br>500 mg QD<br>N = 76 |                |
|--|---|----------------|---|----------------|
|  | All Grades %                                  | Grade 3 or 4 % | All Grades %                                  | Grade 3 or 4 % |
| <b>Hematologic parameters</b>              |   |                |   |                |
| 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            |
| <b>Biochemical parameters</b>              |   |                |   |                |
| 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              |
| Lipase increased                           | 15  | 5              | 18  | 7              |

|                                      |    |     |     |   |
|--------------------------------------|----|-----|-----|---|
| Corrected Calcium decreased          | 16 | 0.6 | 22  | 0 |
| 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   | 4.0 | 0 |
| Cholesterol increased                | 12 | 0   | 8   | 0 |
| Potassium decreased                  | 11 | 0   | 9   | 0 |

<sup>1</sup> 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.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

#### Drugs that may alter asciminib plasma concentrations

*CYP3A4 inducers:* Concomitant administration of SCEMBLIX with strong CYP3A4 inducers reduces asciminib plasma concentrations, which may reduce SCEMBLIX efficacy.

*Itraconazole oral solution containing hydroxypropyl-β-cyclodextrin:* Concomitant administration of SCEMBLIX with an itraconazole oral solution containing hydroxypropyl-β-cyclodextrin decreases asciminib plasma concentrations, which may reduce SCEMBLIX efficacy. Avoid concomitant use of itraconazole oral solution containing hydroxypropyl-β-cyclodextrin.

#### Drugs that may have their plasma concentrations altered by asciminib

*CYP3A4 substrates:* Concomitant administration of SCEMBLIX with CYP3A4 substrates increases plasma concentrations of these substrates and may result in increased risk of adverse reactions to these agents.

*CYP2C9 substrates:* Concomitant administration of SCEMBLIX with CYP2C9 substrates increases plasma concentrations of these substrates and may result in increased risk of adverse reactions to these agents.

*P-gp substrates:* Concomitant administration of SCEMBLIX with P-gp substrates may increase plasma concentrations of these substrates and result in increased risk of adverse reactions to these agents.

#### Drugs that may have a pharmacodynamic interaction with asciminib

*Drugs with known risk of torsades de pointes:* Medicinal products with known risk of torsades de pointes may interact with asciminib.



## 9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 6 - Established or Potential Drug-Drug Interactions**

| [Proper/Common name]   | Source of Evidence | Effect  | Clinical comment  |
|--|--------------------|---|---|
| Strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin or St. John's wort). | CT                 | Co-administration of a strong CYP3A4 inducer (rifampicin) decreased asciminib AUC <sub>inf</sub> by 14.9%, while increasing asciminib C <sub>max</sub> by 9% in healthy subjects receiving a single SCEMBLIX dose of 40 mg.<br><br>The effect of strong CYP3A4 inducers on a SCEMBLIX dose of 80 mg has not been characterized. | Caution should be exercised during concomitant administration of SCEMBLIX with strong CYP3A4 inducers.                |
| Itraconazole oral solution containing hydroxypropyl-β-cyclodextrin                                     | CT                 | Co-administration of the strong CYP3A4 inhibitor itraconazole as an oral solution containing hydroxypropyl-β-cyclodextrin decreased asciminib AUC <sub>inf</sub> by 40% and C <sub>max</sub> by 50% in healthy subjects receiving a single SCEMBLIX dose of 40 mg.  | Avoid concomitant administration of SCEMBLIX with itraconazole oral solution containing hydroxypropyl-β-cyclodextrin. |

|   |              |   |   |
|---|--------------|---|---|
| <p>CYP3A4 substrates (e.g., fentanyl, alfentanil, dihydroergotamine, or ergotamine)</p> | <p>CT, T</p> | <p>Co-administration of asciminib with a CYP3A4 substrate (midazolam) increased midazolam AUC<sub>inf</sub> and C<sub>max</sub> by 28% and 11%, respectively, in healthy subjects receiving SCEMBLIX 40 mg twice daily.</p> <p>PBPK models predict that co-administration of asciminib at 80 mg once daily would increase midazolam AUC<sub>inf</sub> and C<sub>max</sub> by 24% and 17%, respectively.</p> | <p>Caution should be exercised during concomitant administration of SCEMBLIX with CYP3A4 substrates known to have a narrow therapeutic index.</p>   |
| <p>CYP2C9 substrates (e.g., phenytoin or warfarin)</p>                                  | <p>CT, T</p> | <p>Co-administration of asciminib with a CYP2C9 substrate (warfarin) increased S-warfarin AUC<sub>inf</sub> and C<sub>max</sub> by 41% and 8%, respectively, in healthy subjects receiving SCEMBLIX 40 mg twice daily.</p> <p>PBPK models predict that co-administration of asciminib at 80 mg once daily would increase S-warfarin AUC<sub>inf</sub> and C<sub>max</sub> by 52% and 4%, respectively.</p>  | <p>Caution should be exercised during concomitant administration of SCEMBLIX with CYP2C9 substrates known to have a narrow therapeutic index.</p> <p>Consider dose adjustment of CYP2C9 substrates as per their Product Monographs.</p> |
| <p>P-gp substrates (e.g., digoxin, dabigatran)</p>                                      | <p>T</p>     | <p>PBPK models predict that co-administration of asciminib with a P-gp substrate (digoxin) would increase digoxin AUC<sub>inf</sub> and C<sub>max</sub>.</p>  | <p>Caution should be exercised during concomitant administration of SCEMBLIX with P-gp substrates known to have a narrow therapeutic index.</p>   |

|  |    |  |  |
|--|----|--|--|
| Agents/medicinal products with known risk of torsades de pointes (e.g., bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozone) | CT | Events of arrhythmia, including QTc prolongation, were observed in patients receiving SCEMBLIX in clinical studies (see <a href="#">7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY</a> ). | Caution should be exercised during concomitant administration of SCEMBLIX and medicinal products known to cause torsades de pointes. |
|--|----|--|--|

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### Clinical studies

*Effect of CYP3A4 inhibitors on asciminib:* Co-administration of a strong CYP3A4 inhibitor, clarithromycin, with a single SCEMBLIX dose of 40 mg increased asciminib AUC by 36% and Cmax by 20%. The exposure changes are not considered clinically meaningful.

*Effect of acid-reducing agents on asciminib:* Co-administration of a proton pump inhibitor, rabeprazole, had no effect on the AUC and Cmax of asciminib.

*Effect of P-gp inhibitors on asciminib:* Co-administration of a P-gp inhibitor, quinidine, had no effect on the AUC and Cmax of asciminib.

*Effect of combined inhibitors of BCRP, CYP3A4, and UGT2B17 on asciminib:* Co-administration of imatinib, an inhibitor of BCRP, CYP3A4, and UGT2B17, increased asciminib AUC by 108% and Cmax by 59%. The exposure changes are not considered clinically meaningful.

*Effect of asciminib on CYP2C8 substrates:* Co-administration of asciminib with a CYP2C8 substrate, repaglinide, had no effect on the AUC and Cmax of repaglinide.

### In vitro studies

*Asciminib and CYP/UGT enzymes:* At plasma concentrations reached at a total daily dose of 80 mg, asciminib is a reversible inhibitor of UGT1A1 and a weak inducer of CYP1A2.

Asciminib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2D6, CYP2E1, or UGT2B7 at clinically relevant plasma concentrations.

*Asciminib and transporters:* At plasma concentrations reached at a total daily dose of 80 mg, asciminib is an inhibitor of BCRP, OATP1B1, and OATP1B3. Asciminib is a substrate of BCRP and P-gp.

Asciminib is not an inhibitor of BSEP, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2-K at clinically relevant plasma concentrations.

## 9.5 Drug-Food Interactions

The bioavailability of asciminib decreases on consumption of food (see [4 DOSAGE AND ADMINISTRATION](#) and [10 CLINICAL PHARMACOLOGY](#)).

## 9.6 Drug-Herb Interactions

St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A4 that may increase the metabolism of asciminib and hence decrease asciminib blood levels and caution should be

exercised during concomitant administration of SCEMBLIX with strong CYP3A4 inducers.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Asciminib is an oral inhibitor of ABL/BCR::ABL1 tyrosine kinase. Asciminib inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein, by specifically targeting the ABL myristoyl pocket (STAMP).

### 10.2 Pharmacodynamics

*In vitro*, asciminib inhibits the tyrosine kinase activity of ABL1 at mean IC<sub>50</sub> values below 3 nanomolar. In patient-derived cancer cells, asciminib specifically inhibits the proliferation of cells harboring BCR::ABL1 with IC<sub>50</sub> values between 1 and 25 nanomolar. In cells expressing the wild-type form of BCR::ABL1, asciminib inhibits cell growth with mean IC<sub>50</sub> values of 0.61 ±0.21 nanomolar.

In mouse xenograft models of CML, asciminib dose-dependently inhibited the growth of tumors harbouring the wild-type form of BCR::ABL1, with tumor regression being observed at doses above 7.5 mg/kg twice daily.

### Cardiac electrophysiology

SCEMBLIX treatment is associated with an exposure-related prolongation of the QT interval. The correlation between asciminib concentration and the estimated maximum mean change from baseline of the QT interval with Fridericia's correction ( $\Delta$ QTcF) was evaluated in 239 patients with Ph+ CML or Ph+ acute lymphoblastic leukemia (ALL). Asciminib is not predicted to cause large mean increases in QTcF interval (i.e., >20 msec) following a total daily dose of 80 mg.

### 10.3 Pharmacokinetics

Asciminib exhibits a slight dose over-proportional increase in steady-state exposure (AUC and C<sub>max</sub>) across the dose range of 10 to 200 mg (0.25 to 5 times the recommended 80 mg total daily dose) administered once or twice daily. Steady-state conditions are achieved within 3 days. Table 7 summarizes the steady state asciminib exposures and accumulation ratios in patients at the recommended dosages under fasting condition.

**Table 7: Steady State Asciminib Exposure (Geometric Mean (CV%)) and Accumulation Ratios at Recommended Dosages**

| Asciminib Dose    | C <sub>max</sub><br>(ng/mL) | AUC <sub>tau</sub><br>(ng*h/mL) | Accumulation<br>Ratio |
|-------------------|-----------------------------|---------------------------------|-----------------------|
| 80 mg once daily  | 1781 (23%)                  | 15112 (28%)                     | 1.3                   |
| 40 mg twice daily | 793 (49%)                   | 5262 (48%)                      | 1.7                   |

C<sub>max</sub> = maximum (peak) concentration; AUC<sub>tau</sub> = AUC<sub>0-12h</sub> for twice daily dosing and AUC<sub>0-24h</sub> for once daily dosing

### Absorption

Asciminib is rapidly absorbed, with median maximum plasma levels (T<sub>max</sub>) reached 2 to 3 hours after oral administration.

### **Food effect**

Food consumption decreases asciminib bioavailability, with a high-fat meal having a higher impact on asciminib pharmacokinetics than a low-fat meal. Asciminib AUC is decreased by 62.3% with a high-fat meal and by 30% with a low-fat meal compared to the fasted state, independent of the dose (see [4 DOSAGE AND ADMINISTRATION](#) and [9 DRUG INTERACTIONS](#)).

### **Distribution**

Asciminib apparent volume of distribution at steady state is 111 L, based on population pharmacokinetic analysis. Asciminib is the main circulating component in plasma (92.7% of the administered dose). Asciminib is mainly distributed to plasma, with a mean blood-to-plasma ratio of 0.58. Based on in vitro data, asciminib is 97.3% bound to human plasma proteins.

### **Metabolism**

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

### **Elimination**

Asciminib is mainly eliminated via fecal excretion, with a minor contribution of the renal route. 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 [<sup>14</sup>C]-labelled asciminib. The biliary excretion of asciminib is mediated by breast cancer resistant protein (BCRP).

The oral total apparent clearance (CL/F) of asciminib is 6.31 L/hour, based on population pharmacokinetic analysis. The terminal elimination half-life (T<sub>1/2</sub>) of asciminib is between 7 and 15 hours.

### **Special Populations and Conditions**

- **Pediatrics (<18 years):** No studies have been conducted to investigate the pharmacokinetics in pediatric patients below the age of 18 years.
- **Geriatrics (≥ 65 years):** Based on population pharmacokinetic analyses, age (20 to 88 years of age) has no clinically significant effect on asciminib pharmacokinetics.
- **Sex/Ethnic Origin/Obesity:** Based on population pharmacokinetic analyses, gender, race (White 71%, Asian 20%, Black/American African 4%) or body weight (42 kg to 184 kg) have no clinically significant effect on asciminib pharmacokinetics. The effect of obesity based on BMI (body mass index) on the pharmacokinetics of asciminib is unclear.
- **Hepatic impairment:** A dedicated hepatic impairment study including 8 subjects each with normal hepatic function, mild hepatic impairment (Child-Pugh A), moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) was conducted.

Asciminib AUC<sub>inf</sub> is increased by 22%, 3% and 66% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic function, following oral administration of a single 40 mg dose of SCEMBLIX.

- **Renal impairment:** A dedicated renal impairment study including 6 subjects with normal renal function (aGFR  $\geq$ 90 mL/min) and 8 subjects with severe renal impairment not requiring dialysis (aGFR 15 to  $<$ 30 mL/min) has been conducted. Asciminib AUC<sub>inf</sub> and C<sub>max</sub> are increased by 56% and 8%, respectively, in subjects with severe renal impairment compared to subjects with normal renal function, following oral administration of a single 40 mg dose of SCEMBLIX.

Population pharmacokinetics analyses indicate that mild to moderate renal impairment (aGFR 30 to  $<$ 90 mL/min) has no clinically significant effect on the systemic exposure of asciminib.

## 11 STORAGE, STABILITY AND DISPOSAL

Do not store above 25 °C.

Store in the original package in order to protect from moisture.

SCEMBLIX must be kept out of the reach and sight of children.

## 12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

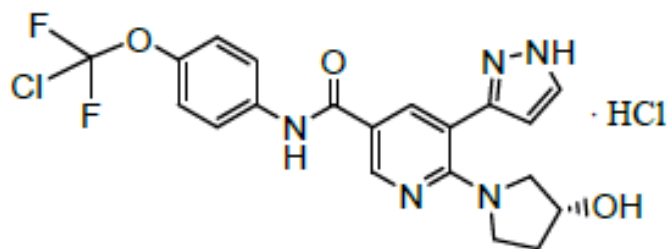
#### Drug Substance

Proper/Common name: Asciminib hydrochloride

Chemical name:

*N*-[4-(Chlorodifluoromethoxy) phenyl]-6-[(3*R*)-3-hydroxypyrrolidin-1-yl]-5-(1*H*-pyrazol-3-yl) pyridine-3-carboxamide-hydrogen chloride (1/1)

Molecular formula



Molecular mass:

Free base: 449.84

Salt form: 486.30

Structural formula:

Free base:  $C_{20}H_{18}ClF_2N_5O_3$

Salt form:  $C_{20}H_{18}ClF_2N_5O_3 \cdot HCl$

Physicochemical properties:

Physical description: White to slightly yellow powder.

Solubility: The drug substance is slightly soluble in water, soluble in methanol and practically insoluble in acetone.

| Solvent            | Solubility (g/100 mL) |
|--------------------|-----------------------|
| Water              | 0.072                 |
| pH 1.0 (HCl 0.1N)  | 0.191                 |
| pH 2.0 (HCl 0.01N) | ≥ 0.320               |

|                           |        |
|---------------------------|--------|
| pH 3.0 (citrate buffer)   | 0.017  |
| pH 4.0 (acetate buffer)   | 0.009  |
| pH 5.0 (acetate buffer)   | 0.001  |
| pH 6.8 (phosphate buffer) | <0.001 |

pH: The pH of a 1.0% (m/V) solution of asciminib hydrochloride in water/ethanol (50:50) is in the range of 2.37 – 2.47 (~25°C).

pKa: The pKa value of the free base component of the drug substance is 3.93 ± 0.02.

Partition Coefficient: The distribution coefficient (log D) of asciminib hydrochloride at 37°C for *n*-octanol/0.1 N HCl is 1.26.

Melting Point: There is no clear identified melting point for asciminib hydrochloride.



## 14 CLINICAL TRIALS

### Clinical Trials by Indication

**Table 8 - Summary of patient demographics for clinical trials in Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP)**

| Study #                       | Study design   | Dosage, route of administration and duration  | Study subjects (n) | Mean age (Range)                 | Sex                         |
|-------------------------------|--|---|--------------------|----------------------------------|-----------------------------|
| Study: CABL001A2301 (ASCEMBL) | Multi-center, randomized, active-controlled and open-label phase III study to demonstrate efficacy and safety of SCEMBLIX in the treatment of patients with Ph+ CML-CP previously treated with two or more tyrosine kinase inhibitors. | Tablets, Oral.<br>Either SCEMBLIX 40 mg twice daily (N=157) or bosutinib 500 mg once daily (N=76).<br>Patients continued treatment until unacceptable toxicity or treatment failure occurred. 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. | 233 patients       | 52 years (range: 19 to 83 years) | 51.5% female and 48.5% male |

#### Ph+ CML-CP, previously treated with two or more TKIs

The clinical efficacy of SCEMBLIX in the treatment of patients with Philadelphia chromosome-positive myeloid leukemia 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 phase III study ASCEMBL.

In this study, a total of 233 patients were randomized in a 2:1 ratio and stratified according to major cytogenetic response (MCyR) status at baseline. Patients in the treatment arm received SCEMBLIX (40 mg) twice daily while patients in the control arm received bosutinib (500 mg) once daily. Patients randomized to either arm were to continue treatment until treatment failure (i.e. lack of efficacy), unacceptable toxicity or withdrawal.

Eligible patients had to be at least 18 years of age with a diagnosis of Ph+ CML-CP, have an ECOG 0 or 1, have adequate organ function, have evidence of BCR::ABL1 transcripts at screening, have received prior treatment with two or more ATP binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib\* or ponatinib) and had either a treatment failure or were intolerant to the most recent TKI. Patients with known presence of T315I and/or V299L mutations at any time prior to study entry were not included in ASCEMBL.

The primary endpoint of the study was the major molecular response (MMR) rate at 24 weeks. MMR is defined as a BCR::ABL1 ratio  $\leq 0.1\%$  by International Scale [IS]. The key secondary

endpoint was the MMR rate at 96 weeks. Other secondary endpoints were complete cytogenetic response (CCyR) rate at 24 and 96 weeks. CCyR is defined as no Philadelphia-positive metaphases in bone marrow with a minimum of 20 metaphases examined. BCR::ABL1 levels for the primary and key secondary endpoints were determined by a central laboratory blinded to treatment assignment.

Of the 233 patients, 19% were 65 years or older, while 3% were 75 years or older. Patients were Caucasian (75%), Asian (14%) and Black (4%). 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, 5 or more prior lines of TKIs were 48%, 31%, 15% and 6%, respectively.

The main efficacy outcomes from ASCEMBL are summarized in Table 9.

**Table 9 Results of study CABL001A2301 in Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) previously treated with two or more tyrosine kinase inhibitors.**

|   | <b>SCEMBLIX<br/>40 mg BID</b>              | <b>Bosutinib<br/>500 mg QD</b>            | <b>Difference (95%<br/>CI)</b> | <b>p-value</b>         |
|---|--|---|--------------------------------|------------------------|
| Primary Endpoint<br>MMR rate, % (95% CI) at<br>24 weeks             | <b>N=157</b><br>25<br>(19, 33)             | <b>N=76</b><br>13<br>(6, 23)              | 12 <sup>1</sup><br>(2, 22)     | 0.03 <sup>2</sup>      |
| Key Secondary Endpoint<br>MMR rate, % (95% CI) at<br>96 weeks       | 38<br>(30, 46)                             | 16<br>(8, 26)                             | 22<br>(11, 33)                 | 0.001 <sup>2</sup>     |
| Other Secondary<br>Endpoint<br>CCyR rate, % (95% CI) at<br>24 weeks | <b>N=103<sup>3</sup></b><br>41<br>(31, 51) | <b>N=62<sup>3</sup></b><br>24<br>(14, 37) | 17<br>(4, 31)                  | Not formally<br>tested |
| CCyR rate, % (95% CI) at<br>96 weeks                                | 40<br>(30, 50)                             | 16<br>(8, 28)                             | 24 <sup>1</sup><br>(10, 37)    | Not formally<br>tested |

<sup>1</sup>On adjustment for the baseline major cytogenetic response status

<sup>2</sup>Cochran-Mantel-Haenszel two-sided test stratified by baseline major cytogenetic response status

<sup>3</sup>CCyR analysis based on patients who were not in CCyR at baseline

A pre-planned subgroup analysis showed that the MMR rates were higher with asciminib than with bosutinib in all analyzed demographic and prognostic factors of response including across all lines of TKI therapy (third, fourth, fifth or more lines) and irrespective of the detection of BCR::ABL1 mutations 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 who achieved MMR had not yet been reached.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology:

Asciminib was evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity and phototoxicity studies.

### Repeat dose toxicity

Repeat dose toxicity studies identified the pancreas, liver, hematopoietic system, adrenal gland and gastro-intestinal tract as target organs of asciminib.

Pancreatic effects (serum amylase and lipase increases, acinar cell lesions) occurred in dogs at Area Under the Curve (AUC) exposures below those achieved in patients on 40 mg twice daily or 80 mg once daily. A trend towards recovery was observed. Additional studies were conducted in order to investigate the pancreas toxicity mechanism, however the mechanism of pancreas toxicity in dogs could not be elucidated.

Elevations in liver enzymes and/or bilirubin were observed in rats, dogs and monkeys. Histopathological hepatic changes (centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia, increased individual hepatocyte necrosis and diffuse hepatocellular hypertrophy) were seen in rats and monkeys. These changes occurred at AUC exposures either equivalent to (rats) or 8- to 18-fold (dogs and monkeys) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily. These changes were fully reversible.

Effects on the hematopoietic system (reduction in red blood cells mass, increased splenic or bone marrow pigment and increased reticulocytes) were consistent with a mild and regenerative, extravascular, hemolytic anemia in all species. These changes occurred at AUC exposures either equivalent to (rats) or 10- to 14- fold (dogs and monkeys) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily. These changes were fully reversible.

Minimal mucosal hypertrophy/hyperplasia (increase in thickness of the mucosa with frequent elongation of villi) was present in the duodenum of rats, at AUC exposures 30-fold or 22-fold higher than those achieved in patients on 40 mg twice daily or 80 mg once daily, respectively. This change was fully reversible.

Minimal or slight hypertrophy of the adrenal gland and mild to moderate decreased vacuolation in the zona fasciculata occurred at AUC exposures either equivalent to (monkeys) or 13- to 19-fold (rats) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily, respectively. These changes were fully reversible.

### Phototoxicity

In mice, asciminib showed dose-dependent phototoxic effects indicated by clinical signs (erythema) and local lymph-node inflammatory reactions starting at 200 mg/kg/day. At the No-Observed-Adverse-Effect Level (NOAEL) of 60 mg/kg/day, exposure based on C<sub>max</sub> in plasma was 15-fold or 6-fold higher than the exposure in patients on 40 mg twice daily or 80 mg once daily respectively.

**Carcinogenicity/Genotoxicity:** Asciminib did not have mutagenic, clastogenic or aneugenic potential neither *in vitro* nor *in vivo*. Carcinogenicity studies have not been conducted with asciminib.

## **Reproductive and Developmental Toxicology:**

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, asciminib was not tolerated in maternal animals at 600 mg/kg/day and resulted in the early termination of the dose group. There was no evidence of asciminib-related embryo-fetal death at doses below or equal to 150 mg/kg/day. A dose-related increase in fetal weights at 25 and 150 mg/kg/day was observed. Fetal variations in the urinary tract and skeleton (skull, vertebral column and ribs), indicative of changes in the rate of development, were observed primarily at 150 mg/kg/day. An increase in the malformation rate (anasarca and cardiac malformations) and some visceral variants indicative of adverse effects on embryo-fetal development were also observed at 150 mg/kg/day. The maternal no-observed-adverse-effect level (NOAEL) was 150 mg/kg/day and the fetal NOAEL was 25 mg/kg/day. At the fetal NOAEL of 25 mg/kg/day, the AUC exposures were equivalent to or below those achieved in patients at the 40 mg twice-daily or 80 mg once-daily doses, respectively.

In rabbits, 300 mg/kg/day caused morbidity in the maternal animals and resulted in the early termination of the dose group. An increased incidence of resorptions, indicative of embryo-fetal mortality, and a low incidence of cardiac malformations, indicative of teratogenicity, were observed at 50 mg/kg/day. There was no effect on fetal growth. The NOAEL for maternal toxicity was 50 mg/kg/day and the fetal NOAEL was 15 mg/kg/day. At the fetal NOAEL of 15 mg/kg/day, the AUC exposures were equivalent to or below those achieved in patients at the 40 mg twice-daily or 80 mg once-daily doses, respectively.

In the rat fertility study, asciminib did not affect reproductive function in male and female rats. A slight effect on male sperm motility and sperm count was observed at doses of 200 mg/kg/day, likely at AUC exposures 19-fold, 13-fold higher than those achieved in patients at the 40 mg twice-daily, or 80 mg once-daily twice-daily doses, respectively. 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.

## **PATIENT MEDICATION INFORMATION**

### **READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PrSCEMBLIX™**

#### **Asciminib tablets**

Read this carefully before you start taking **SCEMBLIX™** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SCEMBLIX**.

#### **What is SCEMBLIX used for?**

SCEMBLIX is used to treat Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Ph+ CML is a type of blood cancer (leukemia) in which the body produces too many abnormal white blood cells. Chronic phase is the first phase of this blood cancer. It is used in adults with Ph+ CML who were previously treated with other similar medicines called tyrosine kinase inhibitors.

#### **How does SCEMBLIX work?**

SCEMBLIX blocks the action of a protein (called BCR::ABL1) of the abnormal white blood cells and stops their division and growth.

#### **What are the ingredients in SCEMBLIX?**

Medicinal ingredients: asciminib (as asciminib hydrochloride)

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, iron oxide (yellow and red for 20 mg film-coated tablets; black and red for 40 mg film-coated tablets), lactose monohydrate, lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide, xanthan gum.

#### **SCEMBLIX comes in the following dosage forms:**

Tablets: 20 mg and 40 mg

#### **Do not use SCEMBLIX if:**

- you are allergic to asciminib or any other ingredients in SCEMBLIX

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SCEMBLIX. Talk about any health conditions or problems you may have, including if you:**

- have or have ever had severe upper stomach pain (inflamed pancreas, pancreatitis).
- have or have ever had a hepatitis B infection. This is because during treatment with SCEMBLIX, hepatitis B may become active again. You will be carefully checked by your healthcare professional for signs of this infection before starting treatment.

- have a heart problem, such as heart failure (heart does not pump blood as well as it should)
- have a heart rhythm problem, such as an irregular heartbeat or an abnormal electrical signal called prolongation of the QT interval.
- are taking medicines that may have an unwanted effect on the function of the heart (torsades de pointes). See **The following may interact with SCEMBLIX** section below for information on these medicines.

## **Other warnings you should know about:**

### **Female patients**

#### Pregnancy and birth control

- If you are pregnant, think you might be pregnant or are planning to have a baby ask your healthcare professional for advice before taking this medicine. They will discuss with you the potential risks of taking SCEMBLIX during pregnancy or breast-feeding.
- Avoid becoming pregnant while taking SCEMBLIX. It can harm your unborn baby.
- Use effective birth control during treatment with SCEMBLIX and for at least 1 week after the last dose. Ask your healthcare professional about effective birth control options.
- **For women who can get pregnant:** A pregnancy test should be done before you start treatment with SCEMBLIX.
- Tell your healthcare professional right away if you become pregnant or think you are pregnant after starting treatment with SCEMBLIX.

#### Breast-feeding

- Do NOT breast-feed during treatment with SCEMBLIX and for at least 1 week after the last dose. It is not known if SCEMBLIX passes into your breast milk.
- Talk to your healthcare professional about the best way to feed your baby during treatment with SCEMBLIX.

### **Male patients**

#### Birth control

- Use effective method of birth control (including a barrier method) during treatment with SCEMBLIX. Continue using effective method of birth control for at least 1 week after the last dose.
- Tell your healthcare professional right away if your partner becomes pregnant.

### **Fertility**

Treatment with SCEMBLIX may affect your ability to have children. Talk to your healthcare professional if you have concerns about this.

### **Check-ups and testing**

Your healthcare professional will regularly monitor your condition to check that the treatment is working for you.

You will have regular tests including blood tests during treatment. These tests will monitor:

- The amount of blood cells (white blood cells, red blood cells and platelets), every 2 weeks for the first 3 months of treatment, then monthly as needed.

- The levels of pancreas enzymes (amylase and lipase), every month or as needed to check for problems with your pancreas.
- The levels of electrolytes (potassium, magnesium).
- Your heart rate and your blood pressure.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with SCEMBLIX:**

- Medicines used to treat seizures such as carbamazepine, phenobarbital or phenytoin.
- Medicines used to treat tuberculosis, such as rifampicin.
- Itraconazole as oral solution, a medicine used to treat fungal infections.
- Medicines used to treat pain or used as sedatives before or during medical or surgical procedures, such as alfentanil or fentanyl.
- Medicines used to treat migraine or dementia, such as dihydroergotamine or ergotamine.
- Medicines that may have an unwanted effect on the electrical activities of the heart (torsades de pointes), such as bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozide.
- Medicines used to reduce the blood's ability to clot, such as warfarin or dabigatran.
- Medicines used to treat high blood pressure or heart problems, such as digoxin.
- St. John's wort (also known as Hypericum perforatum), an herbal medicine used to treat depression and other conditions.

If you are already taking SCEMBLIX and you are prescribed any new medicine, tell your healthcare professional you are taking SCEMBLIX.

**How to take SCEMBLIX:**

- Take SCEMBLIX exactly as your healthcare professional tells you. They will tell you exactly how many SCEMBLIX tablets to take and how to take them. Check with your healthcare professional if you are not sure.
- Swallow SCEMBLIX tablets whole. Do NOT break, crush or chew SCEMBLIX tablets.
- Do NOT take SCEMBLIX with food. Take SCEMBLIX:
  - At least 2 hours after any food
  - Then wait at least 1 hour before eating again
- Try to take SCEMBLIX at the same time each day. This will help you remember when to take it.
- Continue taking SCEMBLIX for as long as your healthcare professional tells you. If you have questions about how long to take SCEMBLIX, talk to your healthcare professional .
- This is a long-term treatment, possibly lasting for months or years. Your healthcare professional will regularly monitor your condition to check that the treatment is working for you.



**Usual dose:**

The usual total daily dose of SCEMBLIX is 80 mg. You may take your daily dose either:

- Once daily: 80 mg at approximately the same time each day.
- OR**
- Twice daily: 40 mg, every 12 hours.

Do NOT take more than the recommended dose prescribed by your healthcare professional.

Depending on how you respond to treatment with SCEMBLIX, your healthcare professional may reduce your dose, temporarily stop or permanently stop the treatment. You should not change the SCEMBLIX dose or schedule without first talking to your healthcare professional.

**Overdose:**

If you think you, or a person you are caring for, have taken too much SCEMBLIX, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:****If you take SCEMBLIX once daily**

If you forget to take SCEMBLIX by more than 12 hours, skip the missed dose. Take the next dose at the usual time.

**If you take SCEMBLIX twice daily**

If you forget to take SCEMBLIX by more than 6 hours, skip the missed dose. Take the next dose at the usual time.

**What are possible side effects from using SCEMBLIX?**

These are not all the possible side effects you may have when taking SCEMBLIX. If you experience any side effects not listed here, tell your healthcare professional.

**Side effects may include:**

- Nose and throat infections (upper respiratory tract infection)
- Headache
- Dizziness
- Cough
- Vomiting
- Diarrhea
- Nausea
- Abdominal pain
- Pain in muscles, bones, joints or chest (musculoskeletal pain)
- Joint pain (arthralgia)
- Tiredness (fatigue)
- Itching (pruritus)



- Fever, coughing, difficulty breathing, wheezing (signs of lower respiratory tract infections)
- Influenza
- Loss of appetite
- Blurred vision
- Dry eyes
- Palpitations
- Shortness of breath, laboured breathing (signs of dyspnoea)
- Fever (pyrexia)
- Generalized swelling (oedema)

**Abnormal blood test results:**

During SCEMBLIX treatment, the results of blood tests may be abnormal. This can give your healthcare professional information on the function of your organs. For example:

- High level of the enzymes lipase and amylase (pancreas function)
- High level of the enzymes transaminases (liver function)
- High level of bilirubin (liver function)
- High level of fats/lipids
- High level of creatine phosphokinase (muscles function)

Your healthcare professional will decide when to perform blood tests and will interpret the results. Inform your healthcare professional if the side effects become bad enough.

| <b>Serious side effects and what to do about them</b>   |   |                     |  |
|---|---|---------------------|--|
| <b>Symptom / effect</b>   | <b>Talk to your healthcare professional</b> |                     | <b>Stop taking drug and get immediate medical help</b> |
|   | <b>Only if severe</b>                       | <b>In all cases</b> |  |
| <b>VERY COMMON</b>  |   |                     |  |
| <b>Hypertension</b> (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations         |   |                     | √  |
| <b>Myelosuppression</b> (a large decrease in the production of blood cells and platelets by the bone marrow): bleeding, bruising, chills, fatigue, fever, infections, weakness, shortness of breath or other signs of frequent infections |   | √                   |  |
| <b>Rash from allergic origin, including urticaria:</b> Itchy skin with or without rash, hives   |   | √                   |  |

| Serious side effects and what to do about them   |                                      |              |   |
|--|--------------------------------------|--------------|---|
| Symptom / effect   | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|  | Only if severe                       | In all cases |   |
| <b>COMMON</b>  |                                      |              |   |
| <b>Pleural effusion</b> (fluid around the lungs): chest pain, difficult or painful breathing, cough  |                                      |              | √   |
| <b>Pancreatitis</b> (inflammation of the pancreas): upper abdominal pain, fever, rapid heartbeat, nausea, vomiting, tenderness when touching the abdomen   |                                      |              | √   |
| <b>UNCOMMON</b>  |                                      |              |   |
| <b>Heart failure</b> (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise |                                      | √            |   |
| <b>Prolongation of the QT interval:</b> irregular heartbeat, change in the electrical activity of the heart  |                                      |              | √   |
| <b>Febrile neutropenia:</b> fever above 38°C associated with a low level of white blood cells  |                                      |              | √   |
| <b>Hypersensitivity</b> (allergic reaction): fever, skin rash, hives, itching, swelling, shortness of breath, wheezing, runny nose, itchy, watery eyes   |                                      | √            |   |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

## Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

## Storage:

- Do not store above 25°C
- Keep in the original package. Protect from moisture.
- Do not take this medicine after the expiry date, which is stated on the box.
- Keep out of reach and sight of children. Do not take this medicine if you notice any damage to the packaging or if there are any signs of tampering.

Ask your pharmacist how to dispose of medicines you no longer use.

## If you want more information about SCEMBLIX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website ([www.novartis.ca](http://www.novartis.ca)), or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc

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