

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr**SCSEMBLIX**TM

asciminib tablets

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

Antineoplastic Agent

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Quebec
H9S 1A9

Date of Initial Approval:
JUN 21, 2022

Submission Control No: 255700

SCSEMBLIX is a trademark

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics.....	4
1.2 Geriatrics.....	4
2 CONTRAINDICATIONS	4
4 DOSAGE AND ADMINISTRATION	4
4.1 Dosing Considerations	4
4.2 Recommended Dose and Dosage Adjustment	4
4.4 Administration	6
4.5 Missed Dose	6
5 OVERDOSAGE	6
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	7
7 WARNINGS AND PRECAUTIONS	7
7.1 Special Populations	10
7.1.1 Pregnant Women	10
7.1.2 Breast-feeding.....	10
7.1.3 Pediatrics.....	11
7.1.4 Geriatrics	11
8 ADVERSE REACTIONS	11
8.1 Adverse Reaction Overview	11
8.2 Clinical Trial Adverse Reactions	11
8.3 Less Common Clinical Trial Adverse Reactions.....	14
8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.....	14
9 DRUG INTERACTIONS	16
9.2 Drug Interactions Overview	16
9.4 Drug-Drug Interactions	16

	9.5 Drug-Food Interactions	19
	9.6 Drug-Herb Interactions	19
10	CLINICAL PHARMACOLOGY.....	19
	10.1 Mechanism of Action	19
	10.2 Pharmacodynamics.....	19
	10.3 Pharmacokinetics.....	20
11	STORAGE, STABILITY AND DISPOSAL.....	21
12	SPECIAL HANDLING INSTRUCTIONS.....	22
	PART II: SCIENTIFIC INFORMATION	23
13	PHARMACEUTICAL INFORMATION	23
14	CLINICAL TRIALS	24
	Clinical Trials by Indication	24
	Ph+ CML-CP, previously treated with two or more TKIs	25
15	MICROBIOLOGY.....	26
16	NON-CLINICAL TOXICOLOGY.....	26
	PATIENT MEDICATION INFORMATION.....	29

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

Adverse reaction	Dosage modification
Abbreviations: ANC, absolute neutrophil count; PLT, platelets; ULN, upper limit of normal ¹ 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 20 mg and 40 mg asciminib (as asciminib 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 (including ischemic cardiac and CNS conditions, arterial thrombotic and embolic conditions) and cardiac failure occurred in 28 (8%) and in 10 (2.8%) 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 7 (2.0%) patients. Grade 4 cardiovascular toxicity occurred in 1 (0.3%) patient, with fatalities occurring in 2 (0.6%) 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](#)).

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 64 of 356 (18%) patients receiving SCEMBLIX, with grade 3 and 4 reactions reported in 29 (8.1%) 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 64 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 27 (7.6%) and 29 (8.1%) patients, respectively. Among the patients with neutropenia \geq grade 3, the median time to first occurrence of reactions was 6 weeks (range: 0.1 to 180 weeks) with median duration of any occurring reaction of 1.7 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 45 of 356 (12.6%) 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: 0.4 to 2.1 weeks). Of the 45 patients with anemia, SCEMBLIX was temporarily withheld in 2 (0.6%) due to 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 7 (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](#) below).

Hypersensitivity

Hypersensitivity events occurred in 109 of 356 (30.6%) patients receiving SCEMBLIX, with \geq 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 [7 WARNINGS AND PRECAUTIONS](#) and [Monitoring and Laboratory Tests](#) below).

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 [7 WARNINGS AND PRECAUTIONS](#) 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 89 weeks (range: 0.1 to 342 weeks).

The most common adverse reactions of any grade (incidence ≥20%) in patients receiving SCEMBLIX were musculoskeletal pain (37.9%), upper respiratory tract infections (28.1%), thrombocytopenia (27.5%), fatigue (25.8%), headache (23.6%), increased pancreatic enzymes (21.3%), arthralgia (21.3%) 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 (8.4%) and anemia (5.3%).

Serious adverse reactions occurred in 12.4% of patients receiving SCEMBLIX. The most frequent serious adverse reactions (incidence ≥1%) were pleural effusion (2.5%), lower respiratory tract infections (2.2%), thrombocytopenia (1.7%), pyrexia (1.4%), pancreatitis (1.1%), musculoskeletal pain (1.1%) 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 (cross-reference to 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%).

Serious adverse events occurred in 15% of patients who received SCEMBLIX. Serious adverse events in $\geq 1\%$ included pyrexia (1.3%), urinary tract infection (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 5.1% 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 35.3% of patients. Adverse reactions which required dosage interruption in $\geq 5\%$ of patients included thrombocytopenia (18.6%) and neutropenia (17.9%).

Dose reductions of SCEMBLIX due to an adverse reaction occurred in 5.1% 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 (ASCSEMBL) (Table 4) are listed by MedDRA system organ class and ranked by frequency within each system organ class.

Table 4 Summary of adverse reactions ($\geq 10\%$) observed with SCEMBLIX in ASCSEMBL

Adverse reactions	SCEMBLIX 40 mg BID ¹ N=156 (%)		Bosutinib 500 mg QD ² N=76 (%)	
	All grades	Grade 3/4	All grades	Grade 3/4
Gastrointestinal disorders				
Diarrhea	18 (12)	0 (0)	54 (71)	8 (11)
Nausea	18 (12)	1 (0.6)	35 (46)	0 (0)
Abdominal pain ³	15 (10)	0 (0)	17 (22)	2 (3)

Adverse reactions	SCEMBLIX 40 mg BID ¹ N=156 (%)		Bosutinib 500 mg QD ² N=76 (%)	
	All grades	Grade 3/4	All grades	Grade 3/4
General disorders and administration site conditions				
Fatigue ⁴	26 (17)	1 (0.6)	8 (11)	1 (1)
Infections and infestations				
Upper respiratory tract infection ⁵	38 (24)	1 (0.6)	7 (9)	0 (0)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ⁶	31 (20)	4 (3)	12 (16)	1 (1)
Arthralgia	19 (12)	0 (0)	3 (4)	0 (0)
Nervous system disorders				
Headache	29 (19)	3 (2)	11 (15)	0 (0)
Skin and subcutaneous tissue disorders				
Rash ⁷	20 (13)	0 (0)	19 (25)	4 (5)
Vascular disorders				
Hypertension ⁸	19 (12)	9 (6)	4 (5)	3 (4)
¹ SCEMBLIX median duration of exposure: 67 weeks (range: 0.1 to 162 weeks) with 56.7% of patients ongoing treatment. ² Bosutinib median duration of exposure: 30 weeks (range: 1 to 149 weeks) with 22.4% of patients ongoing treatment. ³ Abdominal pain includes: abdominal pain and abdominal pain upper; ⁴ Fatigue includes: fatigue and asthenia; ⁵ Upper respiratory tract infection includes: upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis; ⁶ Musculoskeletal pain includes: pain in extremity, back pain, myalgia, non-cardiac chest pain, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain, musculoskeletal discomfort;				

Adverse reactions	SCEMBLIX 40 mg BID ¹ N=156 (%)		Bosutinib 500 mg QD ² N=76 (%)	
	All grades	Grade 3/4	All grades	Grade 3/4
⁷ Rash includes: rash and rash maculopapular;				
⁸ 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 (7%)

General disorders and administration site conditions: Edema (6%), pruritus (5%), pyrexia (4%)

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

Investigations: Electrocardiogram QT prolonged (1.3%)

Metabolism and nutrition disorders: 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

	SCEMBLIX ¹ 40 mg BID N = 156	Bosutinib ¹ 500 mg QD N = 76

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	39	17	33	13
Hemoglobin decreased	35	2	54	5
Lymphocyte count decreased	18	2	34	2.6
Biochemical parameters				
Triglycerides increased	44	5	29	2.6
Creatine kinase increased	27	2.6	22	5
Alanine aminotransferase (ALT) increased	23	0.6	50	16
Aspartate aminotransferase (AST) increased	19	1.9	46	7
Uric acid increased	19	6	17	2.6
Phosphate decreased	17	6	18	7
Lipase increased	14	3.9	18	7
Calcium corrected decreased	14	0.6	20	0
Creatinine increased	14	0	26	0
Amylase increased	12	1.3	13	0
Alkaline phosphatase (ALP) increased	13	0	12	0
Bilirubin increased	12	0	4.2	0
Cholesterol increased	11	0	8	0
Potassium decreased	10	0	9	0

¹ The denominator used to calculate the rate for SCEMBLIX and bosutinib varied from 145 to 156 and 71 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
----------------------	--------------------	--------	------------------

<p>Strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin or St. John's wort).</p>	<p>CT</p>	<p>Co-administration of a strong CYP3A4 inducer (rifampicin) decreased asciminib AUC_{inf} by 14.9%, while increasing asciminib C_{max} by 9% in healthy subjects receiving a single SCEMBLIX dose of 40 mg.</p> <p>The effect of strong CYP3A4 inducers on a SCEMBLIX dose of 80 mg has not been characterized.</p>	<p>Caution should be exercised during concomitant administration of SCEMBLIX with strong CYP3A4 inducers.</p>
<p>Itraconazole oral solution containing hydroxypropyl-β-cyclodextrin</p>	<p>CT</p>	<p>Co-administration of the strong CYP3A4 inhibitor itraconazole as an oral solution containing hydroxypropyl-β-cyclodextrin decreased asciminib AUC_{inf} by 40% and C_{max} by 50% in healthy subjects receiving a single SCEMBLIX dose of 40 mg.</p>	<p>Avoid concomitant administration of SCEMBLIX with itraconazole oral solution containing hydroxypropyl-β-cyclodextrin.</p>
<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_{inf} and C_{max} 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_{inf} and C_{max} 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>

CYP2C9 substrates (e.g., phenytoin or warfarin)	CT, T	<p>Co-administration of asciminib with a CYP2C9 substrate (warfarin) increased S-warfarin AUC_{inf} and C_{max} 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_{inf} and C_{max} 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-gp substrates (e.g., digoxin, dabigatran)	T	<p>PBPK models predict that co-administration of asciminib with a P-gp substrate (digoxin) would increase digoxin AUC_{inf} and C_{max}.</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 pimozide)	CT	<p>Events of arrhythmia, including QTc prolongation, were observed in patients receiving SCEMBLIX in clinical studies (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).</p>	<p>Caution should be exercised during concomitant administration of SCEMBLIX and medicinal products known to cause torsades de pointes.</p>

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 C_{max} 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 C_{max} of asciminib.

Effect of P-gp inhibitors on asciminib: Co-administration of a P-gp inhibitor, quinidine, had no effect on the AUC and C_{max} 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 IC₅₀ values below 3 nanomolar. In patient-derived cancer cells, asciminib specifically inhibits the proliferation of cells harboring BCR::ABL1 with IC₅₀ values between 1 and 25 nanomolar. In cells expressing the wild-type form of BCR::ABL1, asciminib inhibits cell growth with mean IC₅₀ 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_{max}) 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 _{max} (ng/mL)	AUC _{tau} (ng*h/mL)	Accumulation Ratio
80 mg once daily	1781 (23%)	15112 (28%)	1.3
40 mg twice daily	793 (49%)	5262 (48%)	1.7

C_{max} = maximum (peak) concentration; AUC_{tau} = AUC_{0-12h} for twice daily dosing and AUC_{0-24h} for once daily dosing

Absorption

Asciminib is rapidly absorbed, with median maximum plasma levels (T_{max}) 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 [¹⁴C]-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_{1/2}) 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_{inf} 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 ≥90 mL/min) and 8 subjects with severe renal impairment not requiring dialysis (aGFR 15 to <30 mL/min) has been conducted. Asciminib AUC_{inf} and C_{max} 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

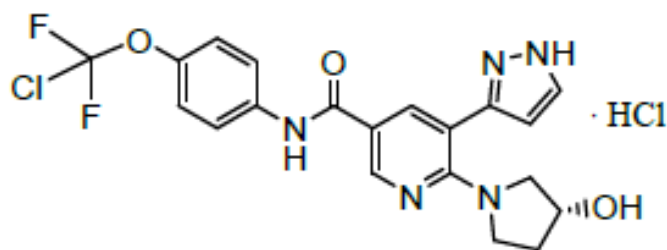
Drug Substance

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: C₂₀H₁₈ClF₂N₅O₃

Salt form: C₂₀H₁₈ClF₂N₅O₃.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. 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. The median duration of treatment was 67 weeks (range: 0.1 to 162 weeks) for patients receiving SCEMBLIX and 30 weeks (range: 1 to 149 weeks) for patients receiving bosutinib.	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 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 MMR rate at 96 weeks. Another secondary endpoint was complete cytogenetic response (CCyR) rate at 24 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.

	SCEMBLIX 40 mg BID	Bosutinib 500 mg QD	Difference (95% CI)	p-value
Primary Endpoint MMR rate, % (95% CI) at 24 weeks	N=157 25 (19, 33)	N=76 13 (6, 23)	12 ¹ (2, 22)	0.03 ²
Other Secondary Endpoint CCyR rate, % (95% CI) at 24 weeks	N=103³ 41 (31, 51)	N=62³ 24 (14, 37)	17 (4, 31)	Not formally tested

¹On adjustment for the baseline major cytogenetic response status

²Cochrane-Mantel-Haenszel two-sided test stratified by baseline major cytogenetic response status

³CCyR analysis based on patients who were not in CCyR at baseline

A pre-planned subgroup analysis showed that the MMR rates at 24 weeks 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.

The MMR rate at 48 weeks was 29% (95% CI: 22, 37) in patients receiving SCEMBLIX and 13% (95% CI: 6, 23) in patients receiving bosutinib. The MMR rate at 96 weeks was not achieved in patients receiving SCEMBLIX or bosutinib. By the data cut-off date, the timepoint of assessment of MMR rate at 96 weeks had not been reached.

With a median duration of follow-up of 20 months (range: 1 day to 36 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_{max} 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 disorder or a heart rhythm disorder, 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.

Monitoring during your treatment with SCEMBLIX

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 pimozone.
- 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 one 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 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.

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	
VERY COMMON			
Hypertension (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			√
Myelosuppression (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		√	
Rash from allergic origin, including urticaria: Itchy skin with or without rash, hives		√	
COMMON			
Pleural effusion (fluid around the lungs): chest pain, difficult or painful breathing, cough			√

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	
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			√
UNCOMMON			
Prolongation of the QT interval: irregular heart-beat, change in the electrical activity of the heart			√
Febrile neutropenia: fever above 38°C associated with a low level of white blood cells			√

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), or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc

Last Revised: [JUN 21, 2022]