Product Monograph

Including Patient Medication Information

PrSCEMBLIX®

asciminib tablets

For oral use

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

Antineoplastic Agent

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SCEMBLIX is a registered trademark

Recent Major Label Changes

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Part 1: Healthcare 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) who are newly diagnosed or who have previously received 1 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 x 10^9/L and/or PLT <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: • 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	Withhold SCEMBLIX until resolved to <1.5 x ULN. • 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. • If resolved: resume SCEMBLIX at a reduced dose.

Adverse reaction	Dosage modification
	• If not resolved: permanently discontinue SCEMBLIX.

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. Overdose

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 the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 3 Dosage Forms, Strengths, and Composition

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.

Description

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

Carcinogenesis and Genotoxicity

A 2-year preclinical carcinogenicity study conducted in rats demonstrated ovarian, mammary gland, thyroid, and testicular tumors (see 16 NON-CLINICAL TOXICOLOGY - Carcinogenicity). The relevance of these findings for humans is not known at this time.

Cardiovascular

Cardiovascular toxicity

Cardiovascular toxicity (including ischemic cardiac and CNS conditions, arterial thrombotic and embolic conditions) and cardiac failure occurred in 39 (7%) and in 14 (3%) of 556 patients receiving SCEMBLIX, respectively. Grade 3 cardiovascular toxicity was reported in 12 (2%) patients, while grade 3 cardiac failure was observed in 8 (1%) patients. Grade 4 cardiovascular

toxicity occurred in 3 (0.5%) patients, with fatalities occurring in 3 (0.5%) patients. Grade 4 cardiac failure was observed in 2 (0.4%) patients, with a fatality in 1 (0.2%) patient.

Permanent discontinuation of SCEMBLIX occurred in 3 (0.5%) patients due to cardiovascular toxicity and in 1 (0.2%) 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 36 of 556 (7%) patients receiving SCEMBLIX, with grade 3 or 4 arrhythmia reported in 11 (2%) and 2 (0.4%) patients, respectively. Electrocardiogram QTc prolongation occurred in 5 of 556 (0.9%) patients receiving SCEMBLIX, with grade 3 QTc prolongation reported in 2 out of 556 (0.4%) 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 a known risk of torsades de pointes (see 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY).

Hypertension

Hypertension occurred in 95 of 556 (17%) patients receiving SCEMBLIX, with grade 3 and 4 reactions reported in 50 (9%) and 1 (0.2%) patients, respectively. Among the patients with hypertension ≥ grade 3, the median time to first occurrence of reactions was 40 weeks (range: 0.1 to 365 weeks). SCEMBLIX was temporarily withheld in 5 (1%) patients due to hypertension.

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 156 of 556 (28%) patients receiving SCEMBLIX, with grade 3 and 4 reactions reported in 39 (7%) and 53 (10%) of patients, respectively. Among the patients with thrombocytopenia ≥ grade 3, the median time to first occurrence was 6 weeks (range: 0.1 to 64 weeks) with median duration of any occurring reaction of 2 weeks (95% CI, range: 1.1 to 2 weeks). SCEMBLIX was permanently discontinued in 11 (2%) patients, while it was temporarily withheld in 70 (13%) patients due to thrombocytopenia.

Neutropenia occurred in 121 of 556 (22%) patients receiving SCEMBLIX, with grade 3 and 4 reactions reported in 42 (8%) and 35 (6%) patients, respectively. Among the patients with neutropenia ≥ grade 3, the median time to first occurrence was 14 weeks (range: 0.1 to 180 weeks) with median duration of any occurring reaction of 2 weeks (95% CI, range: 1.2 to 2 weeks). SCEMBLIX was permanently discontinued in 7 (1%) patients, while it was temporarily withheld in 52 (9%) patients due to neutropenia.

Anemia occurred in 72 of 556 (13%) patients receiving SCEMBLIX, with grade 3 reactions occurring in 23 (4%) patients. Among the patients with anemia grade 3, the median time to first occurrence was 24 weeks (range: 0.1 to 207 weeks) with median duration of any occurring reaction of 0.9 weeks (95% CI, range: 0.3 to 1.7 weeks). SCEMBLIX was temporarily withheld in 3 (0.5%) patients due to anemia.

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 11 of 556 (2%) patients receiving SCEMBLIX, with grade 3 reactions occurring in 6 (1%) patients. SCEMBLIX was permanently discontinued in 3 (0.5%) patients, while it was temporarily withheld in 6 (1%) patients due to pancreatitis. Asymptomatic elevation of serum lipase and amylase occurred in 110 of 556 (20%) patients receiving SCEMBLIX, with grade 3 and 4 reactions occurring in 41 (7%) and 11 (2%) patients, respectively. SCEMBLIX was permanently discontinued in 11 (2%) patients due to the asymptomatic elevation of serum lipase and amylase (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 173 of 556 (31%) patients receiving SCEMBLIX, with ≥grade 3 events reported in 8 (1%) 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

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).

7.1. Special Populations

7.1.1 Pregnancy

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. There have been reports of spontaneous abortion and fetal or infant anomalies from women who have taken asciminib during pregnancy. The causal relationship to asciminib has not been yet established. 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) and 16 NON-CLINICAL TOXICOLOGY).

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with 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 Pregnancy and Monitoring and Laboratory Tests).

7.1.2 Breastfeeding

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):

Among the 556 patients receiving SCEMBLIX in the ASC4FIRST, ASCEMBL and X2101 studies, 130 (23%) were 65 years of age or older and 31 (6%) were 75 years of age 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.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The overall safety profile of SCEMBLIX has been evaluated in 556 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 J12301 (ASC4FIRST) (N=200 newly diagnosed Ph+ CML-CP patients), the pivotal phase III study A2301 (ASCEMBL) (N=156 Ph+ CML-CP patients previously treated with two or more TKIs) 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=556) 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 123 weeks (range: 0.1 to 439 weeks) with 79% of patients exposed for at least 48 weeks and 71% of patients exposed for at least 96 weeks, respectively.

The most common adverse reactions of any grade (incidence ≥20%) in patients receiving SCEMBLIX were musculoskeletal pain (34%), thrombocytopenia (28%), fatigue (25%), upper respiratory tract infections (25%), headache (23%), neutropenia (22%), arthralgia (21%), diarrhea (21%), abdominal pain (20%), pancreatic enzymes increased (20%) and rash (20%). The most common adverse reactions of ≥ grade 3 (incidence ≥5%) in patients receiving SCEMBLIX were thrombocytopenia (17%), neutropenia (14%), increased pancreatic enzymes (9%), and hypertension (9%).

Clinically relevant adverse reactions (incidence <20%) in patients receiving SCEMBLIX included hypersensitivity (0.2%).

Serious adverse reactions occurred in 10% of patients receiving SCEMBLIX. The most frequent serious adverse reactions (incidence ≥1%) were pleural effusion (2%), lower respiratory tract infections (2%), thrombocytopenia (1%), pancreatitis (1%) and pyrexia (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.

Adverse Reactions in Patients with Newly Diagnosed Ph+ CML-CP

The ASC4FIRST clinical trial randomized 405 patients with newly diagnosed Ph+ CML-CP to receive SCEMBLIX 80 mg once daily or investigator selected tyrosine kinase inhibitors (IS-TKIs). IS-TKIs included imatinib (400 mg once daily), nilotinib (300 mg twice daily), dasatinib (100 mg once daily), or bosutinib (400 mg once daily) (see 14 Clinical Trials). The safety population included 200 patients with newly diagnosed Ph+ CML-CP who received at least 1 dose of SCEMBLIX. Among patients who received SCEMBLIX, 90% were exposed for 48 weeks or longer.

The most common (≥ 20%) adverse reactions in patients who received SCEMBLIX were musculoskeletal pain, thrombocytopenia and neutropenia.

Serious adverse events occurred in 15% of patients who received SCEMBLIX. Serious adverse reactions in ≥ 1% included pancreatitis (1%).

Permanent discontinuation due to an adverse reaction occurred in 3% of patients receiving SCEMBLIX. Adverse reactions which resulted in permanent discontinuation of SCEMBLIX in > 1% of patients included pancreatic enzymes increased (2%) and thrombocytopenia (1%).

Dosage interruptions of SCEMBLIX due to an adverse reaction occurred in 28% of patients. Adverse reactions which required dosage interruption in > 5% of patients included thrombocytopenia (13%) and neutropenia (10%).

Dose reductions of SCEMBLIX due to an adverse reaction occurred in 6% of patients. Adverse reactions which required dose reductions in > 1% of patients included thrombocytopenia (3%) and neutropenia (2%).

Table 4 Summary of adverse reactions (≥ 10%) observed with SCEMBLIX in ASC4FIRST

System organ class/adverse reaction	Scemblix 80 mg QD N = 200		IS-TKIs[1] 100-400 mg QD or BID N = 201	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
Blood and lymphatic system disorders				
Thrombocytopenia[2]	28	13	31	10
Neutropenia[3]	26	11	33	18
Gastrointestinal disorders				
Abdominal pain[4]	16	0.5	10	0.5

Diarrhea	18	0	28	1
Constipation	10	0	9	0.5
Nausea	10	0	20	0
General disorders				
Fatigue[5]	19	1	22	1
Infections and infestations				
Upper respiratory tract infection[6]	17	0	19	0.5
Metabolism and nutrition disorders				
Dyslipidemia[7]	19	1	11	0.5
Musculoskeletal and connective tissue disorders				
Arthralgia	13	2	10	0.5
Musculoskeletal pain[8]	27	1	33	0.5
Nervous system disorders				
Headache	17	0.5	16	0
Skin and subcutaneous tissue disorders				
Rash[9]	16	0	20	2
Pruritus	10	0	5	0
Vascular disorders				
Hypertension[10]	11	6	5	4

[1]Investigator-selected TKIs (IS-TKIs) include imatinib (400 mg once daily) or second generation (2G) TKIs, i.e. nilotinib (300 mg twice daily), dasatinib (100 mg once daily) or bosutinib (400 mg once daily). IS-TKIs median duration of exposure: 109 weeks (range: 1 to 150 weeks). 2G TKIs median duration of exposure: 116 weeks (range: 1 to 150 weeks) Imatinib median duration of exposure: 100 weeks (range:3 to 146 weeks);

[2]Thrombocytopenia includes: thrombocytopenia and platelet count decreased;

[3]Neutropenia includes: neutropenia and neutrophil count decreased;

[4]Abdominal pain includes abdominal pain and abdominal pain upper;

[5]Fatigue includes fatigue and asthenia;

[6]Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis;

[7]Dyslipidemia includes hypertriglyceridemia, blood cholesterol increased, hypercholesterolemia, blood triglycerides increased, hyperlipidemia and dyslipidemia;

[8]Musculoskeletal pain includes pain in extremity, back pain, myalgia, non-cardiac chest pain, bone pain; musculoskeletal pain, neck pain, musculoskeletal chest pain, and musculoskeletal discomfort;

[9]Rash includes: rash, rash maculopapular and rash pruritic;

[10] Hypertension includes: hypertension and blood pressure increased.

The cause-specific hazard ratio of time to discontinuation of study treatment due to adverse events (TTDAE) for patients receiving asciminib versus 2G TKIs and asciminib versus imatinib is 0.46 (95% CI: 0.215, 0.997) and 0.38 (95% CI: 0.178, 0.818), respectively. The probability of discontinuation due to AEs during the first 24 months of treatment was 5.5% (95% CI: 2.9, 9.3), 13.1% (95% CI: 7.4, 20.6) and 12.7% (95% CI: 7.1, 20) for patients receiving asciminib, imatinib and 2G TKIs, respectively.

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

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 (≥ 20%) adverse reactions in patients who received SCEMBLIX were upper respiratory tract infections (27%), fatigue (21%) and musculoskeletal pain (22%).

Serious adverse events occurred in 22% of patients who received SCEMBLIX. Serious adverse events in ≥ 1% included urinary tract infection (2%), pyrexia (1%), cardiac failure (2%) and thrombocytopenia (1%).

Five patients (3%) receiving asciminib died during the on-treatment period with cause of death in one each: cardiac disorder, cardiac failure, embolism arterial, ischemic stroke and unknown cause of death.

Permanent discontinuation of SCEMBLIX due to an adverse reaction occurred in 8% of patients. Adverse reactions which resulted in permanent discontinuation of SCEMBLIX in ≥ 2% of patients included thrombocytopenia (3%) and neutropenia (3%).

Dosage interruptions of SCEMBLIX due to an adverse reaction occurred in 35% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients included thrombocytopenia (19%) and neutropenia (18%).

Dose reductions of SCEMBLIX due to an adverse reaction occurred in 5% of patients. Adverse reactions which required dose reductions in ≥ 1% of patients included thrombocytopenia (5%) and neutropenia (1%).
Adverse reactions from the phase III clinical study A2301 (ASCEMBL) (Table 5) are listed by MedDRA system organ class and ranked by frequency within each system organ class.

Table 5 Summary of adverse reactions (≥ 10%) observed with SCEMBLIX in ASCEMBL

System organ class/adverse reaction	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	13	0	72	11

System organ class/adverse reaction	SCEMBLIX 40 mg BID[1] N=156 %		Bosutinib 500 mg QD[2] N=76 %	
	All grades	Grade 3/4	All grades	Grade 3/4
Nausea	12	0.6	46	0
Abdominal pain[3]	13	0.6	22	3
General disorders and administration site conditions				
Fatigue[4]	21	2	12	1
Infections and infestations				
Upper respiratory tract infection[5]	27	0.6	9	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[6]	22	3	18	1
Arthralgia	15	0.6	3	0
Nervous system disorders				
Headache	19	2	16	0
Skin and subcutaneous tissue disorders				
Rash[7]	15	0	25	5
Vascular disorders				
Hypertension[8]	15	8	5	4

[1]SCEMBLIX median duration of exposure: 156 weeks (range: 0.1 to 256 weeks).

[2]Bosutinib median duration of exposure: 31 weeks (range: 1 to 239 weeks).

[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;

System organ class/adverse reaction	SCEMBLIX 40 mg BID[1] N=156 %		Bosutinib 500 mg QD[2] N=76 %	
	All grades	Grade 3/4	All grades	Grade 3/4
[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;				
[7]Rash includes: rash, rash maculopapular and rash pruritic;				
[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.

Adverse Reactions in Patients with Newly Diagnosed Ph+ CML-CP

Blood and lymphatic system disorders: Febrile neutropenia (0.5%)

Cardiac disorders: Palpitations (1%)

Endocrine disorders: Hypothyroidism (3%)

Eye disorders: Dry eye (7%) and vision blurred (1%)

Gastrointestinal disorders: Vomiting (7%) and pancreatitis (1%)

General disorders and administration site conditions: Pyrexia (6%) and edema (3%)

Infections and infestations: Lower respiratory tract infection (6%) and influenza (3%)

Investigations: Gamma glutamyl transferase increased (2%) and electrocardiogram QT prolonged (0.5%)

Metabolism and nutrition disorders: Decreased appetite (3%)

Nervous system disorders: Dizziness (5%)

Respiratory, thoracic and mediastinal disorders: Cough (6%) and dyspnea (1%)

Skin and subcutaneous tissue disorders: Urticaria (3%)

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

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

Cardiac disorders: Palpitations (3%)

Endocrine disorders: Hypothyroidism (1%)

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

Gastrointestinal disorders: Vomiting (8%), constipation (5%)

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

Immune system disorders: Hypersensitivity (0.3%)

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

Investigations: Electrocardiogram QT prolonged (1%)

Metabolism and nutrition disorders: Dyslipidemia (6%), decreased appetite (5%)

Nervous system disorders: Dizziness (9%)

Respiratory, thoracic and mediastinal disorders: Cough (9%), dyspnea (5%), pleural effusion (1%)

Skin and subcutaneous tissue disorders: Pruritus (5%), urticaria (1%)

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

Table 6 Clinically relevant or ≥ 10% new or worsened laboratory abnormalities in adult patients with newly diagnosed Ph+ CML in CP in ASC4FIRST

Laboratory abnormality	SCEMBLIX[1]		IS-TKIs[1]	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Hematologic parameters				
Lymphocyte count decreased	72	4	84	11
Leukocyte count decreased	55	5	68	13
Platelet count decreased	48	13	56	11
Neutrophil count decreased	47	12	63	21
Hemoglobin decreased	25	3	51	5
Biochemical parameters				
Uric acid increased	37	-	22	-
Calcium corrected decreased	46	0.5	76	2
Creatine kinase increased	21	-	39	-

Lipase increased	39	12	50	12
Cholesterol increased	40	0	34	0
Creatinine increased	14	0	32	0
Alanine aminotransferase (ALT) increased	33	3	45	6
Alkaline phosphatase (ALP) increase	26	0.5	36	0
Triglycerides increased	25	1	20	2
Amylase increased	20	1	27	4
Aspartate aminotransferase (AST) increased	20	2	34	2
Bilirubin increased	17	0.5	19	0.5
Phosphate decreased[2]	20	-	42	-
Potassium increased	11	0.5	5	0

[1]The denominator used to calculate the rate for SCEMBLIX, IS TKIs, imatinib and 2G TKI strata varied from 198 to 200, 201, 99 and 102 respectively, based on the number of patients with a baseline value and at least one post-treatment value.

[2]Worst post-baseline laboratory abnormalities based on normal ranges.

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Table 7 Clinically relevant or ≥ 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	43	22	33	15

Hemoglobin decreased	37	2	54	5
Lymphocyte count decreased	21	3	36	3
Biochemical parameters				
Triglycerides increased	45	5	32	3
Creatine kinase increased	33	3	25	5
Alanine aminotransferase (ALT) increased	30	1	50	16
Aspartate aminotransferase (AST) increased	23	3	46	7
Uric acid increased	21	6	18	3
Phosphate decreased	18	7	20	7
Lipase increased	17	5	20	7
Corrected calcium decreased	18	1	22	0
Creatinine increased	17	0	26	0
Amylase increased	13	1	13	0
Alkaline phosphatase (ALP) increased	13	0	12	0
Bilirubin increased	12	0	4	0
Cholesterol increased	16	0	8	0
Potassium decreased	12	0	9	0

[1] The denominator used to calculate the rate for SCEMBLIX and bosutinib varied from 152 to 156 and 75 to 76, respectively, based on the number of patients with a baseline value and at least one post-treatment value.

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 may result in increased risk of adverse reactions related to these agents.

BCRP substrates: Concomitant administration of SCEMBLIX with substrates of BCRP may increase plasma concentrations of these substrates and may result in increased risk of adverse reactions related to these substrates.

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 8 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 AUCinf by 14.9%, while increasing asciminib Cmax by 9% in healthy subjects receiving a single SCEMBLIX dose of 40 mg. Co-administration of a strong CYP3A4 inducer (phenytoin) decreased asciminib AUCinf and Cmax by 34% and 22%, respectively, in healthy subjects receiving a single Scemblix dose of 200 mg.	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 AUCinf by 40% and Cmax 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.
CYP3A4 substrates (e.g., fentanyl, alfentanil, dihydroergotamine, or ergotamine)	CT, T	Co-administration of asciminib with a CYP3A4 substrate (midazolam) increased midazolam AUCinf and Cmax by 28% and 11%, respectively, in healthy subjects receiving SCEMBLIX 40 mg twice daily. PBPK models predict that co-administration of asciminib at 80 mg once daily would increase midazolam AUCinf and Cmax by 24% and 17%, respectively.	Caution should be exercised during concomitant administration of SCEMBLIX with CYP3A4 substrates known to have a narrow therapeutic index.
CYP2C9 substrates (e.g., phenytoin or warfarin)	CT, T	Co-administration of asciminib with a CYP2C9 substrate (warfarin) increased S-warfarin AUCinf and Cmax by 41% and 8%, respectively, in healthy subjects receiving SCEMBLIX 40 mg twice daily. PBPK models predict that co-administration of asciminib at 80 mg once daily would increase S-warfarin AUCinf and Cmax by 52% and 4%, respectively.	Caution should be exercised during concomitant administration of SCEMBLIX with CYP2C9 substrates known to have a narrow therapeutic index. Consider dose adjustment of CYP2C9 substrates as per their Product Monographs.

Agents/medicinal products with known risk of torsades de pointes (e.g., bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozide)	CT	Events of arrhythmia, including QTc prolongation, were observed in patients receiving SCEMBLIX in clinical studies (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).	Caution should be exercised during concomitant administration of SCEMBLIX and medicinal products known to cause torsades de pointes.
P-gp substrates (e.g., digoxin, dabigatran and colchicine)	T	PBPK models predict that co-administration of asciminib 80 mg total daily dose with a P-gp substrate (digoxin) would increase digoxin AUCinf by 4%-34% and Cmax by 6%-38%.	Caution should be exercised during concomitant administration of SCEMBLIX with P-gp substrates known to have a narrow therapeutic index.
BCRP substrates (e.g., sulfasalazine, methotrexate, rosuvastatin)	T	Based upon a mechanistic understanding of the elimination of asciminib and its in vitro inhibitory potential, concomitant use of SCEMBLIX with BCRP substrates may increase Cmax and AUC of the substrates, increasing the risk of adverse reactions.	Caution should be exercised during concomitant administration of SCEMBLIX with BCRP substrates and the dosage of the substrates should be reduced as recommended in their product monographs. Avoid coadministration of SCEMBLIX with rosuvastatin.

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.

Effect of asciminib on OATP1B substrates (e.g. atorvastatin): Co-administration of asciminib at 80 mg once daily with an OATP1B, CYP3A4 and P-gp substrate (atorvastatin) increased atorvastatin AUCinf and Cmax by 14% and 24%, respectively, in healthy subjects. Clinically relevant interactions between SCEMBLIX and OATP1B substrates are unlikely to occur.

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 CYP3A4, CYP2C9, 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: Asciminib is a substrate of BCRP and P-gp. Asciminib is an inhibitor of BCRP, P-gp, OATP1B1, and OATP1B3 (see Table 8).

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_{50} values below 3 nanomolar. In patient-derived cancer cells, asciminib specifically inhibits the proliferation of cells harboring BCR::ABL1 with IC_{50} values between 1 and 25 nanomolar. In cells expressing the wild-type form of BCR::ABL1, asciminib inhibits cell growth with mean IC_{50} 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 (ΔQTcF) 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 Cmax) 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 9 summarizes the steady state asciminib exposures and accumulation ratios in patients at the recommended dosages under fasting condition.

Table 9 Steady State Asciminib Exposure (Geometric Mean (CV%)) and Accumulation Ratios at Recommended Dosages

Asciminib Dose	Cmax (ng/mL)	AUCtau (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

Cmax = maximum (peak) concentration; AUC_{tau} = $AUC_{0\text{-}12h}$ for twice daily dosing and $AUC_{0\text{-}24h}$ for once daily dosing

Absorption

Asciminib is rapidly absorbed, with median maximum plasma levels (Tmax) 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 [^{14}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 ($T_{1/2}$) of asciminib is between 7 and 15 hours. The accumulation half-life ($T_{1/2}$) of asciminib is 5.2 hours at 80 mg total daily dose, derived from population pharmacokinetic analysis.

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 Insufficiency:** 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 AUCinf 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 Insufficiency:** 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 AUCinf and Cmax 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 2: Scientific Information

13. Pharmaceutical Information

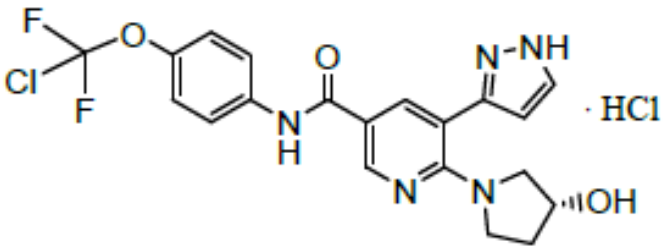
Drug Substance

Non-proprietary name of the drug substance: 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: $C_{20}H_{18}ClF_2N_5O_3.HCl$

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

14.1. Clinical Trials by Indication

Newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP)

Table 10 Summary of patient demographics for clinical trials in newly diagnosed Ph+ CML-CP

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study: CABL001J12301 (ASC4FIRST)	Multi-center, randomized, active-controlled and open-label phase III study to demonstrate efficacy and safety of SCEMBLIX in the treatment of patients with newly diagnosed Ph+ CML-CP.	Tablets, Oral. Either SCEMBLIX 80 mg once daily or investigator selected tyrosine kinase inhibitors (IS-TKIs) at clinically recommended doses (doses are detailed in Table 11). The median duration of treatment was 27 months (range: 0.2 to 36 months) for patients receiving SCEMBLIX and 25 months (range: 0.3 to 35 months) for patients receiving IS-TKIs.	405 patients	51 years (range: 18 to 86 years)	37% female and 63% male.

The clinical efficacy of SCEMBLIX in the treatment of patients with newly diagnosed Ph+ CML-CP was evaluated in the multi-center, randomized, active-controlled and open-label phase III study ASC4FIRST.

In this study, a total of 405 patients were randomized in a 1:1 ratio to receive either SCEMBLIX or investigator selected tyrosine kinase inhibitors (IS-TKIs). Prior to randomization, the investigator selected the TKI (imatinib, nilotinib, dasatinib, or bosutinib) to be used in the event of randomization to the comparator arm, based on patient characteristics and comorbidities. Patients were stratified according to EUTOS long-term survival (ELTS) risk group (low, intermediate, high), and pre-randomization selection of TKI (imatinib or second generation [2G] TKI [nilotinib, dasatinib, or bosutinib]). Patients received either SCEMBLIX or IS-TKIs, and continued treatment until unacceptable toxicity or treatment failure.

Of the 405 patients, 23.5% were 65 years or older, while 6.2% were 75 years or older. Patients were Caucasian (53.8%), Asian (44.4%), Black (1%) and 0.7% unknown. The demographic characteristics within the imatinib (N=203) and the 2G TKIs (N=202) strata were:

- Median age: 55 years and 43 years, respectively;

- ELTS high risk group: 8.4% and 13.9%, respectively;
- Framingham cardiovascular disease high risk group: 35.5% and 17.8%, respectively.

The demographic characteristics were balanced across SCEMBLIX and IS-TKIs, as well as across the two arms within the imatinib and 2G TKIs strata.

Of the 405 patients, 200 received SCEMBLIX, while 201 received IS-TKIs (99 received imatinib, 49 received nilotinib, 42 received dasatinib, and 11 received bosutinib). Four patients did not receive any treatment.

The median duration of treatment was 27 months (range: 0.2 to 36 months) for patients receiving SCEMBLIX and 25 months (range: 0.3 to 35 months) for patients receiving IS-TKIs. By 96 weeks, 82% of patients on SCEMBLIX and 60% of patients on IS-TKIs were still receiving treatment.

The study had two primary objectives, both assessing major molecular response rate (MMR) at 48 weeks. One primary objective evaluated MMR in patients receiving SCEMBLIX compared to IS-TKIs. The other primary objective evaluated MMR in the subset of patients within the imatinib stratum, comparing SCEMBLIX to imatinib. The key secondary objective evaluated MMR at 96 weeks for SCEMBLIX compared both to IS-TKIs and to IS-TKIs within the imatinib stratum.

The main efficacy outcomes from ASC4FIRST are summarized in Table 11.

Table 11 Results of study CABL001J12301 (ASC4FIRST) in patients with newly diagnosed Ph+ CML-CP

SCEMBLIX vs IS-TKIs (All patients)				
Response	**SCEMBLIX 80 mg once daily** (N=201)	**IS-TKIs[1] at clinically recommended doses** (N=204)	**Difference (95% CI)[2]**	**p-value[3]**
MMR rate at 48 weeks MMR (%) (95% CI)	68 (61, 74)	49 (42, 56)	19 (10, 28)	<0.001
MMR rate at 96 weeks MMR (%) (95% CI)	74 (68, 80)	52 (42, 59)	22 (14, 31)	<0.001
SCEMBLIX vs IS-TKIs (imatinib stratum)				
Response	**SCEMBLIX 80 mg once daily** (N=101)	**IS-TKI at clinically recommended doses** (N=102)	**Difference (95% CI)**	**p-value[4]**
MMR rate at 48 weeks MMR (%) (95% CI)	69 (59, 78)	40 (31, 50)	30 (17, 42)	<0.001
MMR rate at 96 weeks MMR (%) (95% CI)	76 (67, 84)	47 (37, 57)	30 (18, 42)	<0.001

Abbreviations: MMR, major molecular response (BCR::ABL1^{IS} ≤ 0.1%); IS-TKIs, investigator-selected tyrosine kinase inhibitors; PRS-TKI, pre-randomization selection of TKI.

[1]IS-TKIs include imatinib (400 mg once daily), nilotinib (300 mg twice daily), dasatinib (100 mg once daily) or bosutinib (400 mg once daily).

[2] Estimated using a common risk difference stratified by PRS-TKI and baseline ELTS risk groups.
[3] Adjusted p-value using a Cochran-Mantel-Haenszel 1-sided test stratified by PRS-TKI and baseline ELTS risk groups.
[4] Adjusted p-value using a Cochran-Mantel-Haenszel 1-sided test stratified by baseline ELTS risk groups.

MMR rates at 96 weeks in patients receiving SCEMBLIX and IS-TKIs within the 2G TKIs stratum were: 72% (95% CI: 62% to 81%) and 57% (95% CI: 47% to 67%), respectively. The common treatment difference in the MMR rate was 15.14% (95% CI: 2.32, 27.95) estimated using the Cochran–Mantel–Haenszel method after stratifying by baseline ELTS risk groups.

Median time to MMR in patients receiving SCEMBLIX, IS-TKIs, IS-TKIs within the imatinib stratum, and IS-TKIs within the 2G TKIs stratum were: 24 weeks (95% CI: 24 to 25 weeks), 36 weeks (95% CI: 36 to 49 weeks), 49 weeks (95% CI: 36 to 60 weeks), and 36 weeks (95% CI: 24 to 48 weeks), respectively.

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

Table 12 Summary of patient demographics for clinical trials in Ph+ CML- CP previously treated with two or more tyrosine kinase inhibitors (ASCEMBL)

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). The median duration of treatment was 156 weeks (range: 0.1 to 256 weeks) for patients receiving SCEMBLIX and 31 weeks (range: 1 to 239 weeks) for patients receiving bosutinib.	233 patients	52 years (range: 19 to 83 years)	52% female and 49% male

The clinical efficacy of SCEMBLIX in the treatment of patients with 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 (has not been authorized in Canada) 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 MMR rate at 24 weeks. MMR is defined as a BCR::ABL1 ratio ≤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 13.

Table 13 Results of study CABL001A2301 in Ph+ CML-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]
Key Secondary Endpoint MMR rate, % (95% CI) at 96 weeks	38 (30, 46)	16 (8, 26)	22 (11, 33)	0.001[2]
Other Secondary Endpoint CCyR rate, % (95% CI) at 24 weeks	**N=103**[3] 41 (31, 51)	**N=62**[3] 24 (14, 37)	17 (4, 31)	Not formally tested
CCyR rate, % (95% CI) at 96 weeks	40 (30, 50)	16 (8, 28)	24[1] (10, 37)	Not formally tested

[1]On adjustment for the baseline major cytogenetic response status

[2]Cochran-Mantel-Haenszel two-sided test stratified by baseline major cytogenetic response status

[3]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:

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 19- to 13-fold (rats) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily, respectively. These changes were fully reversible.

Genotoxicity

Asciminib did not have mutagenic, clastogenic or aneugenic potential neither *in vitro* nor *in vivo*.

Carcinogenicity

In a 2-year rat carcinogenicity study, asciminib was administered at doses of 20, 66 and 200 mg/kg/day to male rats and 10, 30 and 66 mg/kg/day to female rats. Male rats at 200 mg/kg/day and female rats at ≥30 mg/kg/day showed reduced longevity.

A dose-dependent increase in the incidence of Sertoli cells hyperplasia in the ovaries was noted in female rats at all doses, with benign Sertoli cell tumors observed at 66 mg/kg/day. Mammary gland fibroadenoma was noted at all doses in female rats. AUC exposures to asciminib in female rats at 10 mg/kg/day were generally 0.7-fold or 0.5-fold human exposure at the dose of 40 mg twice daily or 80 mg once daily, respectively.

Increased thyroid follicular cell adenoma was noted at 200 mg/kg/day in male rats. A dose-dependent increase in Leydig cell adenoma of the testis was noted at all doses in male rats. AUC exposures to asciminib in male rats at 20 mg/kg/day were generally 2-fold or 1.4-fold human exposure at the dose of 40 mg twice daily or 80 mg once daily, respectively.

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.

Special Toxicology

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 Cmax 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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrSCEMBLIX®

Asciminib tablets

This Patient Medication Information is written for the person who will be taking **SCEMBLIX®**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **SCEMBLIX**, talk to a healthcare professional.

What SCEMBLIX is used for:

SCEMBLIX is used in adults to treat Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase. The Ph+ CML is newly detected or previously treated with other similar medicines called tyrosine kinase inhibitors.

How SCEMBLIX works:

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

The ingredients in SCEMBLIX are:

Medicinal ingredient: 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 form:

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.
- Medicines used to treat severe inflammation of the bowel or severe rheumatic or painful joint inflammation, such as sulfasalazine and colchicine.
- Medicines used to treat cancer, severe rheumatic joint inflammation, or psoriasis, such as methotrexate.
- A medicine used to reduce blood cholesterol levels called rosuvastatin.

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, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or 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.

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.

- Nose and throat infections (upper respiratory tract infection)
- Headache
- Dizziness
- Cough
- Vomiting
- Diarrhea
- Nausea
- Abdominal pain

- Constipation
- Itching
- Pain in muscles, bones, joints or chest (musculoskeletal pain)
- Joint pain
- Tiredness (fatigue)
- 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
- Generalized swelling
- Fever

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 fats/lipids (dyslipidemia)
- 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 creatine phosphokinase (muscles function)

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

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this 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,		√	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
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			
Hypothyroidism (underactive/low thyroid): Weight gain, tiredness, hair loss, muscle weakness, feeling cold, dry skin, constipation, puffy face, heavier than normal or irregular menstrual periods, enlarged thyroid gland		√	
Pleural effusion (fluid around the lungs): chest pain, difficult or painful breathing, cough			√
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heartbeat, nausea, vomiting, tenderness when touching the abdomen			√
Uncommon			
Heart failure (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		√	
Febrile neutropenia: fever above 38°C associated with a low level of white blood cells			√
Hypersensitivity (allergic reaction): fever, skin rash, hives, itching, swelling, shortness of breath, wheezing, runny nose, itchy, watery eyes		√	
Prolongation of the QT interval: irregular heartbeat,			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
change in the electrical activity of the heart			

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare 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.

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