ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Scemblix 20 mg film-coated tablets
Scemblix 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Scemblix 20 mg film-coated tablets

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

Excipient with known effect
Each film-coated tablet contains 43 mg lactose monohydrate.

Scemblix 40 mg film-coated tablets

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

Excipient with known effect
Each film-coated tablet contains 86 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Scemblix 20 mg film-coated tablets

Pale yellow, round, biconvex film-coated tablets with bevelled edges of approximately 6 mm diameter, debossed with company logo on one side and “20” on the other side.

Scemblix 40 mg film-coated tablets

Violet white, round, biconvex film-coated tablets with bevelled edges of approximately 8 mm diameter, debossed with company logo on one side and “40” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Scemblix is indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia.

Posology

The recommended dose is 40 mg twice daily at approximately 12-hour intervals.

Missed dose
If a dose is missed by less than 6 hours, it should be taken and the next dose should be taken as scheduled.

If a dose is missed by more than approximately 6 hours, it should be skipped and the next dose should be taken as scheduled.

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

Dose adjustments for adverse reactions
The starting dose is 40 mg twice daily, while the reduced dose is 20 mg twice daily. The dose can be modified based on individual safety and tolerability as shown in Table 1. Asciminib should be permanently discontinued in patients unable to tolerate a dose of 20 mg twice daily.

Table 1 Asciminib dose modification schedule for the management of adverse reactions

Adverse reaction	**Dose modification**
Thrombocytopenia and/or neutropenia	
ANC <1.0 x 10^9/l and/or PLT <50 x 10^9/l	Withhold asciminib until resolved to ANC ≥1 x 10^9/l and/or PLT ≥50 x 10^9/l. If resolved: • Within 2 weeks: resume at starting dose. • After more than 2 weeks: resume at reduced dose. For recurrent severe thrombocytopenia and/or neutropenia, withhold asciminib 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 >2.0 x ULN	Withhold asciminib until resolved to <1.5 x ULN. • If resolved: resume at reduced dose. If events reoccur at reduced dose, permanently discontinue. • If not resolved: permanently discontinue. Perform diagnostic tests to exclude pancreatitis.
Non-haematological adverse reactions	
Grade 3 or higher[1] adverse reactions	Withhold asciminib until resolved to grade 1 or lower. • If resolved: resume at a reduced dose. • If not resolved: permanently discontinue.

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
Elderly
No dose adjustment is required in patients aged 65 years or above.

Renal impairment
No dose adjustment is required in patients with mild, moderate or severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild, moderate or severe hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Scemblix in paediatric patients aged below 18 years have not been established. No data are available.

Method of administration

Scemblix is for oral use. The film-coated tablets should be swallowed whole with a glass of water and should not be broken, crushed or chewed.

The tablets should be taken orally without food. Food consumption should be avoided for at least 2 hours before and 1 hour after taking asciminib (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Myelosuppression

Thrombocytopenia, neutropenia and anaemia occurred in patients receiving asciminib. Severe (NCI CTCAE grade 3 or 4) thrombocytopenia and neutropenia were reported during treatment with asciminib (see section 4.8). Myelosuppression was generally reversible and managed by temporarily withholding treatment. Complete blood counts should be performed every two weeks for the first 3 months of treatment and then monthly thereafter, or as clinically indicated. Patients should be monitored for signs and symptoms of myelosuppression.

Based on the severity of thrombocytopenia and/or neutropenia, the dose should be temporarily withheld, reduced or permanently discontinued as described in Table 1 (see section 4.2).

Pancreatic toxicity

Pancreatitis and asymptomatic elevations of serum lipase and amylase, including severe reactions, occurred in patients receiving asciminib (see section 4.8).

Serum lipase and amylase levels should be assessed monthly during treatment with asciminib, 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. If serum lipase and amylase elevations are accompanied by abdominal symptoms, treatment should be temporarily withheld and appropriate diagnostic tests should be considered to exclude pancreatitis (see section 4.2).

Based on the severity of serum lipase and amylase elevations, the dose should be temporarily withheld, reduced or permanently discontinued as described in Table 1 (see section 4.2).

QT prolongation

QT prolongation occurred in patients receiving asciminib (see section 4.8).

It is recommended that an electrocardiogram is performed prior to the start of treatment with asciminib, and monitored during treatment as clinically indicated. Hypokalaemia and hypomagnesaemia should be corrected prior to asciminib administration and monitored during treatment as clinically indicated.

Caution should be exercised when administering asciminib concomitantly with medicinal products with known risk of *torsades de pointes* (see sections 4.5 and 5.1).

Hypertension

Hypertension, including severe hypertension, occurred in patients receiving asciminib (see section 4.8).

Hypertension and other cardiovascular risk factors should be monitored regularly and managed using the standard therapies during treatment with asciminib.

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 asciminib. HBV carriers who require treatment with asciminib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Lactose

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

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products with known risk of *torsades de pointes*

Caution should be exercised during concomitant administration of asciminib and medicinal products with known risk of *torsades de pointes*, including, but not limited to, bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozide (see section 5.1).

Medicinal products that may decrease asciminib plasma concentrations

Strong CYP3A4 inducers
Co-administration of a strong CYP3A4 inducer (rifampicin) decreased asciminib AUC_{inf} by 15% and increased C_{max} by 9% in healthy subjects receiving a single asciminib dose of 40 mg.

Caution should be exercised during concomitant administration of asciminib with strong CYP3A4 inducers, including, but not limited to, carbamazepine, phenobarbital, phenytoin or St. John's wort (*Hypericum perforatum*), which may result in lower efficacy of asciminib.

Medicinal products that may have their plasma concentrations altered by asciminib

CYP3A4 substrates with narrow therapeutic index
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 asciminib 40 mg twice daily.

Caution should be exercised during concomitant administration of asciminib with CYP3A4 substrates known to have a narrow therapeutic index, including, but not limited to, the CYP3A4 substrates fentanyl, alfentanil, dihydroergotamine or ergotamine (see section 5.2). Dose adjustment of asciminib is not required.

CYP2C9 substrates
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 asciminib 40 mg twice daily.

Caution should be exercised during concomitant administration of asciminib with CYP2C9 substrates known to have a narrow therapeutic index, including, but not limited to, phenytoin or warfarin (see section 5.2). Dose adjustment of asciminib is not required.

OATP1B, BCRP substrates or substrates of both transporters
Based on PBPK modelling, caution should be exercised during concomitant administration of asciminib with substrates of OATP1B, BCRP or both transporters, including, but not limited to sulfasalazine, methotrexate, pravastatin, atorvastatin, pitavastatin, rosuvastatin and simvastatin. No clinical drug interaction study was performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status of women of childbearing potential should be verified prior to starting treatment with asciminib.

Sexually-active women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with asciminib and for at least 3 days after stopping treatment.

Pregnancy

There are no or limited amount of data from the use of asciminib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Asciminib is not recommended during pregnancy and in women of childbearing potential not using contraception. The patient should be advised of a potential risk to the foetus if asciminib is used during pregnancy or if the patient becomes pregnant while taking asciminib.

Breast-feeding

It is unknown whether asciminib/metabolites are excreted in human milk. There are no data on the effects of asciminib on the breast-fed newborn/infant or on milk production. Because of the potential for serious adverse reactions in the breast-fed newborn/infant, breast-feeding should be discontinued during treatment and for at least 3 days after stopping treatment with asciminib.

Fertility

There are no data on the effect of asciminib on human fertility. In rat fertility studies, asciminib did not affect reproductive function in male and female rats. However, adverse effects on sperm motility and count were observed in rats at doses of 200 mg/kg/day (see section 5.3). The relevance for humans is not known.

4.7 Effects on ability to drive and use machines

Asciminib has no or negligible influence on the ability to drive and use machines. However, it is recommended that patients experiencing dizziness, fatigue or other undesirable effects (see section 4.8) with a potential impact on the ability to drive or use machines safely should refrain from these activities as long as the undesirable effects persist.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions of any grade (incidence ≥20%) in patients receiving asciminib were musculoskeletal pain (37.1%), upper respiratory tract infections (28.1%), thrombocytopenia (27.5%), fatigue (27.2%), headache (24.2%), arthralgia (21.6%), increased pancreatic enzymes (21.3%), abdominal pain (21.3%), diarrhoea (20.5%) and nausea (20.2%).

The most common adverse reactions of ≥ grade 3 (incidence ≥5%) in patients receiving asciminib were thrombocytopenia (18.5%), neutropenia (15.7%), increased pancreatic enzymes (12.4%), hypertension (8.7%) and anaemia (5.3%).

Serious adverse reactions occurred in 12.4% of patients receiving asciminib. 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%), non-cardiac chest pain (1.1%) and vomiting (1.1%).

Tabulated list of adverse reactions

The overall safety profile of asciminib has been evaluated in 356 patients with Ph+ CML in chronic (CP) and accelerated (AP) phases in the pivotal phase III study A2301 (ASCEMBL) and the phase I study X2101. In ASCEMBL, patients received asciminib as monotherapy at a dose of 40 mg twice daily. In X2101, patients received asciminib as monotherapy 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 asciminib was 116 weeks (range: 0.1 to 342 weeks).

Adverse reactions from clinical studies (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000).

Table 2 Adverse reactions observed with asciminib in clinical studies

System organ class	Frequency category	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infection[1]
	Common	Lower respiratory tract infection[2], influenza
Blood and lymphatic system disorders	Very common	Thrombocytopenia[3], neutropenia[4], anaemia[5]
	Uncommon	Febrile neutropenia
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Very common	Dyslipidaemia[6]
	Common	Decreased appetite, hyperglycaemia
Nervous system disorders	Very common	Headache, dizziness
Eye disorders	Common	Dry eye, vision blurred
Cardiac disorders	Common	Palpitations
Vascular disorders	Very common	Hypertension[7]
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Pleural effusion, dyspnoea, non-cardiac chest pain
Gastrointestinal disorders	Very common	Pancreatic enzymes increased[8], vomiting, diarrhoea, nausea, abdominal pain[9]
	Common	Pancreatitis[10]
Hepatobiliary disorders	Very common	Hepatic enzyme increased[11]
	Common	Blood bilirubin increased[12]
Skin and subcutaneous tissue disorders	Very common	Rash[13]
	Common	Urticaria
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[14], arthralgia
General disorders and administration site conditions	Very common	Fatigue[15], pruritus
	Common	Pyrexia[16], oedema[17]
Investigations	Common	Blood creatine phosphokinase increased
	Uncommon	Electrocardiogram QT prolonged

[1] Upper respiratory tract infection includes: upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis.
[2] Lower respiratory tract infections include: pneumonia, bronchitis and tracheobronchitis.
[3] Thrombocytopenia includes: thrombocytopenia and platelet count decreased.
[4] Neutropenia includes: neutropenia and neutrophil count decreased.
[5] Anaemia includes: anaemia, haemoglobin decreased and normocytic anaemia.
[6] Dyslipidaemia includes: hypertriglyceridaemia, blood cholesterol increased, hypercholesterolaemia, blood triglycerides increased, hyperlipidaemia and dyslipidaemia.
[7] Hypertension includes: hypertension and blood pressure increased.
[8] Pancreatic enzymes increased includes: lipase increased, amylase increased and hyperlipasaemia.
[9] Abdominal pain includes: abdominal pain and abdominal pain upper.
[10] Pancreatitis includes: pancreatitis and pancreatitis acute.
[11] Hepatic enzymes increased includes: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased and transaminases increased.
[12] Blood bilirubin increased includes: blood bilirubin increased, bilirubin conjugated increased and hyperbilirubinaemia.
[13] Rash includes: rash and rash maculopapular.
[14] Musculoskeletal pain includes: pain in extremity, back pain, myalgia, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain and musculoskeletal discomfort.
[15] Fatigue includes: fatigue and asthenia.
[16] Pyrexia includes: pyrexia and body temperature increased.
[17] Oedema includes: oedema and oedema peripheral.

Description of selected adverse reactions

Myelosuppression
Thrombocytopenia occurred in 27.5% of patients receiving asciminib, with grade 3 and 4 reactions reported in 6.7% and 11.8% of patients, respectively. Among the patients with thrombocytopenia ≥ grade 3, the median time to first occurrence of reactions was 6 weeks (range: 0.14 to 64 weeks), with median duration of any occurring reaction of 1.71 weeks (95% CI, range: 1.43 to 2 weeks). 2% of patients receiving asciminib permanently discontinued due to thrombocytopenia, while asciminib was temporarily withheld in 12.6% of patients due to the adverse reaction.

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

Anaemia occurred in 12.9% of patients receiving asciminib, with grade 3 reactions occurring in 5.3% of patients. Among the patients with anaemia ≥ grade 3, the median time to first occurrence of reactions was 30 weeks (range: 0.4 to 207 weeks), with median duration of any occurring reaction of 0.9 weeks (95% CI, range: 0.43 to 2.14 weeks). Asciminib was temporarily withheld in 0.6% of patients due to the adverse reaction.

Pancreatic toxicity
Pancreatitis occurred in 2.5% of patients receiving asciminib, with grade 3 reactions occurring in 1.1% of patients. All these reactions occurred in the phase I study (X2101). 0.6% of patients receiving asciminib permanently discontinued due to pancreatitis, while asciminib was temporarily withheld in 1.1% of patients due to the adverse reaction. Asymptomatic elevations of serum lipase and amylase occurred in 21.3% of patients receiving asciminib, with grade 3 and 4 reactions occurring in 10.1% and 2.2% of patients, respectively. Of the patients with elevation of pancreatic enzymes, asciminib was permanently discontinued in 2.2% of patients due to the adverse reaction.

QT prolongation
Electrocardiogram QT prolongation occurred in 0.8% of patients receiving asciminib. In the ASCEMBL clinical study, one patient had a prolonged QTcF greater than 500 milliseconds (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.

Hypertension
Hypertension occurred in 18.5% of patients receiving asciminib, with grade 3 and 4 reactions reported in 8.4% and 0.3% of patients, respectively. Among the patients with hypertension ≥ grade 3, the median time to first occurrence of reactions was 14 weeks (range: 0.1 to 156 weeks). Asciminib was temporarily withheld in 0.8% of patients due to the adverse reaction.

Laboratory abnormalities
Decrease in phosphate levels occurred as a laboratory abnormality in 17.9% (all grades) and 6.4% (grade 3/4) of 156 patients receiving asciminib at 40 mg twice daily.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical studies, asciminib 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Asciminib is a potent 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.

Pharmacodynamic effects

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 harbouring BCR::ABL1 with IC_{50} values between 1 and 25 nanomolar. In cells engineered to express either the wild-type or the T315I mutant form of BCR::ABL1, asciminib inhibits cell growth with mean IC_{50} values of 0.61 ± 0.21 and 7.64 ± 3.22 nanomolar, respectively.

In mouse xenograft models of CML, asciminib dose-dependently inhibited the growth of tumours harbouring either the wild-type or the T315I mutant form of BCR::ABL1, with tumour regression being observed at doses above 7.5 mg/kg or 30 mg/kg twice daily, respectively.

Cardiac electrophysiology
Asciminib treatment is associated with an exposure-related prolongation of the QT interval.

The correlation between asciminib concentration and the estimated 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 leukaemia (ALL) receiving asciminib at doses ranging from 10 to 280 mg twice daily and 80 to 200 mg once daily. The estimated mean ΔQTcF was 3.35 ms (upper bound of 90% CI: 4.43 ms) for the asciminib 40 mg twice-daily dose. See section 4.4.

Clinical efficacy and safety

Ph+ CML-CP
The clinical efficacy and safety of asciminib in the treatment of patients with Philadelphia chromosome-positive myeloid leukaemia in chronic phase (Ph+ CML-CP) with treatment failure or intolerance to two or more tyrosine kinase inhibitors were evaluated in the multicentre, randomised, active-controlled and open-label phase III study ASCEMBL. Resistance to last TKI was defined as any of the following: failure to achieve either haematological or cytogenetic response at 3 months; BCR::ABL1 (on the International Scale, IS) >10% at 6 months or thereafter; >65% Ph+ metaphases at 6 months or >35% at 12 months or thereafter; loss of complete haematological response (CHR), partial cytogenetic response (PCyR), complete cytogenetic response (CCyR) or major molecular response (MMR) at any time; new BCR::ABL1 mutations which potentially cause resistance to study medicinal product or clonal evolution in Ph+ metaphases at any time. Intolerance to last TKI was defined as non-haematological toxicities unresponsive to optimal management, or as haematological toxicities recurring after dose reduction to the lowest recommended dose.

In this study, a total of 233 patients were randomised in a 2:1 ratio and stratified according to major cytogenetic response (MCyR) status at baseline to receive either asciminib 40 mg twice daily (N=157) or bosutinib 500 mg once daily (N=76). Patients with known presence of T315I and/or V299L mutations at any time prior to study entry were not included in ASCEMBL. Patients continued treatment until unacceptable toxicity or treatment failure occurred.

Patients with Ph+ CML-CP were 51.5% female and 48.5% male, with median age 52 years (range: 19 to 83 years). Of the 233 patients, 18.9% were 65 years or older, while 2.6% were 75 years or older. Patients were Caucasian (74.7%), Asian (14.2%) and Black (4.3%). Of the 233 patients, 80.7% 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 48.1%, 31.3%, 14.6% and 6%, respectively.

The median duration of the randomised treatment was 103 weeks (range: 0.1 to 201 weeks) for patients receiving asciminib and 31 weeks (range: 1 to 188 weeks) for patients receiving bosutinib.

Results
The primary endpoint of the study was MMR rate at 24 weeks and the key secondary endpoint was MMR rate at 96 weeks. MMR is defined as BCR::ABL1 IS ratio ≤0.1%. Other secondary endpoints were CCyR rate at 24 and 96 weeks, defined as no Philadelphia-positive metaphases in bone marrow with a minimum of 20 metaphases examined.

The main efficacy outcomes from the ASCEMBL study are summarised in Table 3.

Table 3 Efficacy results in patients treated with two or more tyrosine kinase inhibitors (ASCEMBL)

	Asciminib 40 mg twice daily	**Bosutinib 500 mg once daily**	**Difference (95% CI)[1]**	**p-value**
	N=157	**N=76**		
MMR rate, % (95% CI) at 24 weeks	25.48 (18.87, 33.04)	13.16 (6.49, 22.87)	12.24 (2.19, 22.30)	0.029[2]
MMR rate, % (95% CI) at 96 weeks	37.58 (29.99, 45.65)	15.79 (8.43, 25.96)	21.74 (10.53, 32.95)	0.001[2]
	N=103[3]	**N=62[3]**		
CCyR rate, % (95% CI) at 24 weeks	40.78 (31.20, 50.90)	24.19 (14.22, 36.74)	17.30 (3.62, 30.99)	Not formally tested
CCyR rate, % (95% CI) at 96 weeks	39.81 (30.29, 49.92)	16.13 (8.02, 27.67)	23.87 (10.3, 37.43)	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

The primary and key secondary endpoints were the only ones formally tested for statistical significance according to protocol.

In ASCEMBL, 12.7% of patients treated with asciminib and 13.2% of patients receiving bosutinib had one or more BCR::ABL1 mutations detected at baseline. MMR at 24 weeks was observed in 35.3% and 24.8% of patients receiving asciminib with or without any BCR::ABL1 mutation at baseline, respectively. MMR at 24 weeks was observed in 25% and 11.1% of patients receiving bosutinib with or without any mutation at baseline, respectively. The MMR rate at 24 weeks in patients in whom the randomised treatment represented the third, fourth, or fifth or more line of TKI was 29.3%, 25%, and 16.1% in patients treated with asciminib and 20%, 13.8%, and 0% in patients receiving bosutinib, respectively.

The Kaplan-Meier estimated proportion of patients receiving asciminib and maintaining MMR for at least 72 weeks was 96.7% (95% CI: 87.4, 99.2).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Scemblix in one or more subsets of the paediatric population in CML (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Asciminib is rapidly absorbed, with median maximum plasma level (T_{max}) reached 2 to 3 hours after oral administration, independent of the dose. The geometric mean (geoCV%) of C_{max} and AUC_{tau} at steady state is 793 ng/ml (49%) and 5262 ng*h/ml (48%), respectively, following administration of asciminib at the 40 mg twice-daily dose. PBPK models predict that asciminib absorption is approximately 100%, while bioavailability is approximately 73%.

Asciminib bioavailability may be reduced by co-administration of oral medicinal products containing hydroxypropyl-β-cyclodextrin as an excipient. Co-administration of multiple doses of an itraconazole oral solution containing hydroxypropyl-β-cyclodextrin at a total of 8 g per dose with a 40 mg dose of asciminib decreased asciminib AUC_{inf} by 40.2% in healthy subjects.

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 (see section 4.2).

Distribution

Asciminib apparent volume of distribution at steady state is 111 litres based on population pharmacokinetic analysis. Asciminib is mainly distributed to plasma, with a mean blood-to-plasma ratio of 0.58, independent of the dose based on *in vitro* data. Asciminib is 97.3% bound to human plasma proteins, independent of the dose.

Biotransformation

Asciminib is primarily metabolised via CYP3A4-mediated oxidation, and UGT2B7- and UGT2B17-mediated glucuronidation. Asciminib is the main circulating component in plasma (92.7% of the administered dose).

Elimination

Asciminib is mainly eliminated via faecal excretion, with a minor contribution of the renal route. Eighty and 11% of the asciminib dose were recovered in the faeces and in the urine of healthy subjects, respectively, following oral administration of a single 80 mg dose of [^{14}C]-labelled asciminib. Faecal elimination of unchanged asciminib accounts for 56.7% of the administered dose.

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

The oral total clearance (CL/F) of asciminib is 6.31 l/hour after 40 mg twice daily, based on population pharmacokinetic analysis. The elimination half-life of asciminib is between 7 and 15 hours at 40 mg twice daily.

Linearity/non-linearity

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 administered once or twice daily.

The geometric mean accumulation ratio is approximately 2-fold. Steady-state conditions are achieved within 3 days at the 40 mg twice-daily dose.

In vitro evaluation of drug interaction potential

Asciminib is metabolised by several pathways, including the CYP3A4, UGT2B7 and UGT2B17 enzymes, and biliary secreted by the transporter BCRP. Medicinal products inhibiting or inducing the CYP3A4, UGT and/or BCRP pathways may alter asciminib exposure.

CYP450 and UGT enzymes
In vitro, asciminib reversibly inhibits CYP3A4/5, CYP2C9 and UGT1A1 at plasma concentrations reached at a 40 mg twice-daily dose. Asciminib may increase the exposure of medicinal products which are substrates of CYP3A4/5 and CYP2C9 (see section 4.5).

Transporters
Asciminib is a substrate of BCRP and P-gp.

Asciminib inhibits BCRP, P-gp and OATP1B with Ki values of 24, 22 and 2 micromolar, respectively. Based on PBPK models, asciminib may increase the exposure of medicinal products which are substrates of these transporters.

Special populations

Gender, race, body weight
Asciminib systemic exposure is not affected by gender, race or body weight to any clinically relevant extent.

Renal impairment
A dedicated renal impairment study including 6 subjects with normal renal function (absolute glomerular filtration rate [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} were 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 asciminib (see section 4.2). Population pharmacokinetic models indicate an increase in asciminib median steady-state $AUC_{0\text{-}24h}$ by 11.5% in subjects with mild to moderate renal impairment, compared to subjects with normal renal function.

Hepatic impairment
A dedicated hepatic impairment study including 8 subjects each with normal hepatic function, mild hepatic impairment (Child-Pugh A score 5-6), moderate hepatic impairment (Child-Pugh B score 7-9) or severe hepatic impairment (Child-Pugh C score 10-15) was conducted. Asciminib AUC_{inf} was 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 asciminib (see section 4.2).

5.3 Preclinical safety data

Safety pharmacology

Moderate cardiovascular effects (increased heart rate, decreased systolic pressure, decreased mean arterial pressure, and decreased arterial pulse pressure) were observed in *in vivo* cardiac safety studies in dogs, likely at AUC exposures 12-fold higher than those achieved in patients at the recommended dose (RD) of 40 mg twice daily.

Repeat dose toxicity

Pancreatic effects (serum amylase and lipase increases, acinar cell lesions) occurred in dogs at AUC exposures below those achieved in patients at the RD of 40 mg twice daily. A trend towards recovery was observed.

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 12- to 18-fold (dogs and monkeys, respectively) higher than those achieved in patients at the RD of 40 mg twice daily. These changes were fully reversible.

Effects on the haematopoietic system (reduction in red blood cell mass, increased splenic or bone marrow pigment and increased reticulocytes) were consistent with a mild and regenerative, extravascular, haemolytic anaemia in all species. These changes occurred at AUC exposures either equivalent to (rats) or 12- to 14-fold (dogs and monkeys, respectively) higher than those achieved in patients at the RD of 40 mg twice 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 higher than those achieved in patients at the RD of 40 mg twice daily. 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-fold (rats) higher than those achieved in patients at the RD of 40 mg twice daily. These changes were fully reversible.

Carcinogenicity and mutagenicity

Asciminib did not have mutagenic, clastogenic or aneugenic potential either *in vitro* nor *in vivo*.

In a 2-year rat carcinogenicity study, non-neoplastic proliferative changes consisting of ovarian Sertoli cell hyperplasia were observed in female animals at doses equal to or above 30 mg/kg/day. Benign Sertoli cell tumours in the ovaries were observed in female rats at the highest dose of 66 mg/kg/day. AUC exposures to asciminib in female rats at 66 mg/kg/day were generally 8-fold higher than those achieved in patients at the dose of 40 mg twice daily.

The clinical relevance of these findings is currently unknown.

Reproductive toxicity

Animal reproduction studies in pregnant rats and rabbits demonstrated that oral administration of asciminib during organogenesis induced embryotoxicity, foetotoxicity and teratogenicity.

In embryo-foetal development studies, a slight increase in foetal malformations (anasarca and cardiac malformations) and increased visceral and skeletal variants were observed in rats. Increased incidence of resorptions indicative of embryo-foetal mortality and a low incidence of cardiac malformations indicative of teratogenicity were observed in rabbits. In rats, at the foetal no observed adverse effect level (NOAEL) of 25 mg/kg/day, the AUC exposures were equivalent to those achieved in patients at the RD of 40 mg twice daily. In rabbits, at the foetal NOAEL of 15 mg/kg/day, the AUC exposures were equivalent to those achieved in patients at the RD of 40 mg twice daily.

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 higher than those achieved in patients at the RD of 40 mg twice daily.

A pre- and postnatal developmental toxicity study was not performed.

Phototoxicity

In mice, asciminib showed dose-dependent phototoxic effects starting at 200 mg/kg/day. At the NOAEL of 60 mg/kg/day, exposure based on C_{max} in plasma was 15-fold higher than the exposure in patients at the RD of 40 mg twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Scemblix 20 mg and 40 mg film-coated tablets

Lactose monohydrate
Microcrystalline cellulose (E460i)
Hydroxypropylcellulose (E463)
Croscarmellose sodium (E468)
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Magnesium stearate
Talc (E553b)
Colloidal silicon dioxide
Lecithin (E322)
Xanthan gum (E415)
Iron oxide red (E172)

Scemblix 20 mg film-coated tablets only

Iron oxide yellow (E172)

Scemblix 40 mg film-coated tablets only

Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Scemblix is supplied in PCTFE/PVC/Alu blisters containing 10 film-coated tablets.

The following pack sizes are available:
Packs containing 20 or 60 film-coated tablets.

Scemblix 40 mg film-coated tablets are also available in multipacks containing 180 (3 packs of 60) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1670/001-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 August 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Scemblix 20 mg film-coated tablets
asciminib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains asciminib hydrochloride, equivalent to 20 mg asciminib.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

20 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1670/001	20 film-coated tablets of 20 mg
EU/1/22/1670/002	60 film-coated tablets of 20 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Scemblix 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Scemblix 20 mg tablets
asciminib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Scemblix 40 mg film-coated tablets
asciminib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains asciminib hydrochloride, equivalent to 40 mg asciminib.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

20 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1670/003	20 film-coated tablets of 40 mg
EU/1/22/1670/004	60 film-coated tablets of 40 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Scemblix 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Scemblix 40 mg film-coated tablets
asciminib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains asciminib hydrochloride, equivalent to 40 mg asciminib.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 180 (3 x 60) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1670/005 180 (3 x 60) film-coated tablets of 40 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Scemblix 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Scemblix 40 mg film-coated tablets
asciminib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains asciminib hydrochloride, equivalent to 40 mg asciminib.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

60 film-coated tablets
Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1670/005 180 (3 x 60) film-coated tablets of 40 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Scemblix 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Scemblix 40 mg tablets
asciminib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Scemblix 20 mg film-coated tablets
Scemblix 40 mg film-coated tablets
asciminib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Scemblix is and what it is used for

What Scemblix is
Scemblix contains the active substance asciminib, which belongs to a group of medicines called protein kinase inhibitors.

What Scemblix is used for
Scemblix is a cancer medicine used to treat adults with a type of blood cancer (leukaemia) called Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP). It is given to patients who were previously treated with two or more cancer medicines called tyrosine kinase inhibitors.

How Scemblix works
In Ph+ CML, the body produces large numbers of abnormal white blood cells. Scemblix blocks the action of a protein (BCR::ABL1) that is produced by these abnormal white blood cells and stops their division and growth.

If you have any questions about how this medicine works or why this medicine has been prescribed for you, ask your doctor or pharmacist.

2. What you need to know before you take Scemblix

Do not take Scemblix
- if you are allergic to asciminib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Scemblix if any of the following applies to you:
- if you have or have ever had severe upper stomach pain that could be due to problems with your pancreas (inflamed pancreas, pancreatitis).
- if you have ever had or might now have a hepatitis B infection. This is because Scemblix could cause hepatitis B to become active again. You will be carefully checked by your doctor for signs of this infection before treatment is started.

Tell your doctor or pharmacist immediately if you get any of the following during treatment with Scemblix:
- if you experience weakness, spontaneous bleeding or bruising and frequent infections with signs such as fever, chills, sore throat or mouth ulcers. These can be signs of decreased bone marrow activity, resulting in myelosuppression (a reduction in the number of white blood cells, red blood cells and platelets).
- if blood tests show that you have high levels of enzymes called lipase and amylase (signs of damage to the pancreas, also known as pancreatic toxicity).
- if you have a heart disorder or a heart rhythm disorder, such as an irregular heartbeat or an abnormal electrical activity of the heart called QT interval prolongation that can be seen on an electrocardiogram (ECG).
- if blood tests show that you have a low level of potassium or magnesium (hypokalaemia or hypomagnesaemia).
- if you are being treated with medicines that may have an unwanted effect on the function of the heart (*torsades de pointes*) (see "Other medicines and Scemblix").
- if you experience headache, dizziness, chest pain or shortness of breath (possible signs of high blood pressure, also known as hypertension).

Monitoring during your treatment with Scemblix
Your doctor will regularly monitor your condition to check that the treatment is having the desired effect. 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).
- the levels of pancreas enzymes (amylase and lipase).
- the levels of electrolytes (potassium, magnesium).
- your heart rate and blood pressure.

Children and adolescents
Do not give this medicine to children or adolescents aged under 18 years.

Other medicines and Scemblix
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular, tell your doctor or pharmacist if you are using:
- medicines usually used to treat seizures (fits), such as carbamazepine, phenobarbital or phenytoin.
- medicines used to treat pain and/or 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 activity 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.
- medicines used to treat severe inflammation of the bowel or severe rheumatic joint inflammation, such as sulfasalazine.
- medicines used to treat cancer, severe rheumatic joint inflammation or psoriasis, such as methotrexate.
- medicines used to reduce blood cholesterol levels, such as pravastatin, atorvastatin, pitavastatin, rosuvastatin and simvastatin.
- St. John's wort (also known as *Hypericum perforatum*), a herbal medicine used to treat depression.

If you are already taking Scemblix, you should tell your doctor if you are prescribed any new medicine.

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

Scemblix with food and drink
Do not take this medicine with food. Take it at least 2 hours after and 1 hour before any food. For more information, see "When to take Scemblix" in section 3.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
Scemblix may harm your unborn baby. If you are a woman who could become pregnant, your doctor will discuss with you the potential risks of taking it during pregnancy or breast-feeding.

If you are a woman who could become pregnant, your doctor may perform a pregnancy test before starting treatment with Scemblix.

If you do become pregnant, or think you may be pregnant, after starting treatment with Scemblix, tell your doctor straight away.

Contraceptive advice for women
If you are a woman who could become pregnant, you should use an effective method of contraception during treatment with Scemblix and for at least 3 days after you stop taking it to avoid becoming pregnant. Ask your doctor about effective methods of contraception.

Breast-feeding
It is not known if Scemblix passes into breast milk. Therefore, you should discontinue breast-feeding while you are taking it and for at least 3 days after you stop taking it.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines. If you experience side effects (such as dizziness or visual disorders) with a potential impact on the ability to safely drive or use any tools or machines after taking this medicine, you should refrain from these activities until the effect has disappeared.

Scemblix contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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

3. How to take Scemblix

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much Scemblix to take
Your doctor will tell you exactly how many tablets you should take per day, and how to take them.

The recommended dose is 1 tablet of Scemblix 40 mg twice per day. Take 1 tablet, then take another one approximately 12 hours later.

Depending on how you respond to treatment and on possible side effects, your doctor may ask you to change to a lower dose or to temporarily or permanently stop the treatment.

When to take Scemblix
Take Scemblix:
- at least 2 hours after any food
- then wait at least 1 hour before eating again.

Taking this medicine at the same time each day will help you to remember when to take it.

How to take Scemblix
Swallow the tablets whole with a glass of water. Do not break, crush or chew them to ensure proper dosing.

How long to take Scemblix
Continue taking this medicine for as long as your doctor tells you. This is a long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.
If you have questions about how long to take this medicine, talk to your doctor or pharmacist.

If you take more Scemblix than you should
If you have taken more tablets than you should have, or if someone else accidentally takes your medicine, contact a doctor for advice straight away. Show them the pack. Medical treatment may be necessary.

If you forget to take Scemblix
If there are less than 6 hours until your next dose, skip the missed dose and then take the next one as planned.
If there are more than 6 hours until your next dose, take the missed dose and then take the next one as planned.

If you stop taking Scemblix
Do not stop taking this medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious
If you experience any serious side effects, stop taking this medicine and tell your doctor immediately.

Very common (may affect more than 1 in 10 people)
- spontaneous bleeding or bruising (signs of low level of platelets, thrombocytopenia)
- fever, sore throat, frequent infections (signs of low level of white blood cells, neutropenia)

Uncommon (may affect up to 1 in every 100 people)
- irregular heart-beat, change in the electrical activity of the heart (prolongation of the QT interval)
- fever above 38°C associated with a low level of white blood cells (febrile neutropenia)

Other possible side effects
Other side effects include the following listed below. If these side effects become severe, please tell your doctor or pharmacist.

Very common (may affect more than 1 in 10 people)
- nose and throat infections (upper respiratory tract infection)
- tiredness, fatigue, pale skin (signs of low level of red blood cells, anaemia)
- headache, dizziness, chest pain, shortness of breath (signs of high blood pressure, hypertension)
- headache
- dizziness
- cough
- vomiting
- diarrhoea
- nausea
- abdominal (belly) pain
- rash
- pain in muscles, bones or joints (musculoskeletal pain)
- joint pain (arthralgia)
- tiredness (fatigue)
- itching (pruritus)

Common (may affect up to 1 in every 10 people)
- fever, coughing, difficulty breathing, wheezing (signs of lower respiratory tract infections)
- influenza
- loss of appetite
- blurred vision
- dry eyes
- palpitations
- chest pain, cough, hiccups, rapid breathing, fluid collection between the lungs and chest cavity which, if severe, could make you breathless (pleural effusion)
- shortness of breath, laboured breathing (signs of dyspnoea)
- chest pain (non-cardiac chest pain)
- severe upper stomach pain (sign of inflamed pancreas, pancreatitis)
- itchy rash (urticaria)
- fever (pyrexia)
- generalised swelling (oedema)

Uncommon (may affect up to 1 in every 100 people)
- allergic reaction which may include rash, hives, difficulty breathing or low blood pressure (hypersensitivity)

Abnormal blood test results
During treatment, the results of blood tests may be abnormal, which can give your doctor information on the function of your organs. For example:

Very common (may affect more than 1 in 10 people)
- high level of the enzymes lipase and amylase (pancreas function)
- high level of the enzymes transaminases, which include alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) (liver function)
- high level of fats/lipids

Common (may affect up to 1 in every 10 people)
- high level of the substance bilirubin (liver function)
- high level of the enzyme creatine phosphokinase (muscle function)
- high level of blood sugar

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Scemblix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

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

Do not use this medicine if you notice any damage to the packaging or if there are any signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Scemblix contains
- The active substance is asciminib.
  Each 20 mg film-coated tablet contains asciminib hydrochloride, equivalent to 20 mg asciminib.
  Each 40 mg film-coated tablet contains asciminib hydrochloride, equivalent to 40 mg asciminib.
- The other ingredients are:
  20 mg and 40 mg film-coated tablets: lactose monohydrate, microcrystalline cellulose (E460i), hydroxypropylcellulose (E463), croscarmellose sodium (E468), polyvinyl alcohol (E1203), titanium dioxide (E171), magnesium stearate, talc (E553b), colloidal silicon dioxide, lecithin (E322), xanthan gum (E415), iron oxide red (E172).
  20 mg film-coated tablets only: iron oxide yellow (E172)
  40 mg film-coated tablets only: iron oxide black (E172).
  See “Scemblix contains lactose and sodium” in section 2.

What Scemblix looks like and contents of the pack
Scemblix 20 mg film-coated tablets (tablets): pale yellow, round, biconvex tablet with bevelled edges of approximately 6 mm diameter, debossed with company logo on one side and “20” on the other side.

Scemblix 40 mg film-coated tablets (tablets): violet white, round, biconvex tablet with bevelled edges of approximately 8 mm diameter, debossed with company logo on one side and “40” on the other side.

Scemblix is supplied in blisters containing 10 film-coated tablets.

The following pack sizes are available:
Packs containing 20 or 60 film-coated tablets.

Scemblix 40 mg film-coated tablets are also available in multipacks containing 180 (3 packs of 60) film-coated tablets.

Not all pack sizes may be marketed.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.