Date: 8 August 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

SCEMBLIX

International non-proprietary name: asciminib as asciminib hydrochloride
Pharmaceutical form: film-coated tablet
Dosage strength(s): 20 mg, 40 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Novartis Pharma Schweiz AG
Marketing Authorisation No.: 68441
Decision and Decision date: approved on 9 June 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance asciminib as asciminib hydrochloride of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Status was granted on 9 November 2021.

Work-sharing procedure
The applicant requested a work-sharing procedure with Singapore, Australia, Canada and the United Kingdom.
The Access NAS (New Active Substance) work-sharing initiative is a collaboration between regulatory authorities, i.e. Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), Swissmedic, and the pharmaceutical industry.
The work-sharing initiative coordinates the assessment of an NAS application that has been filed in at least two jurisdictions.

2.2 Indication and Dosage

2.2.1 Requested Indication

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.

2.2.2 Approved Indication

Scemblix is indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP), in whom previous administration of two or more tyrosine kinase inhibitors has resulted in treatment failure or intolerance (see "Clinical efficacy").

2.2.3 Requested Dosage

Summary of the applied standard dosage:

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.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	30 July 2021
Formal control completed	27 August 2021
List of Questions (LoQ)	23 December 2021
Answers to LoQ	20 February 2022
Predecision	8 April 2022
Answers to Predecision	24 April 2022
Final Decision	9 June 2022
Decision	approval

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3 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

4 Nonclinical Aspects

4.1 Pharmacology

Asciminib targets the tyrosine kinase activity of the Abelson murine leukaemia viral oncogene homolog 1 (ABL1). Pharmacological models showed that the compound binds with a dissociation constant (K_D) of 0.5 nM to the myristate pocket of ABL1. Marketed tyrosine kinase inhibitors (TKIs) bind to the ATP binding site.

Asciminib efficiently inhibited the phosphorylation of downstream proteins (IC_{50} 0.4 to 2.6 nM). In addition, the compound selectively and efficiently inhibited the proliferation of BCR-ABL1-expressing human chronic myeloid leukaemia (CML)-derived cells (IC_{50} 1 to 24 nM) and was active on a broad range of BCR-ABL1 point mutations (IC_{50} 0.7 to 7.7 nM) that confer resistance to marketed TKIs. The drug was effective in murine subcutaneous xenograft models with CML-derived cells (oral doses ≥15 mg/kg/day) and in a murine disseminated Philadelphia chromosome positive (Ph+) acute lymphocytic leukaemia (ALL) patient-derived xenograft model (oral doses ≥7.5 mg/kg/day).

In a broad off-target screen involving G protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors and enzymes, asciminib showed significant effects (>50% inhibition at 10 µM) against 5-lipoxygenase (IC_{50} 3.3 µM), VMAT-2 vesicular monoamine transporter (IC_{50} 3.5 µM), and 5HT2b serotonin receptor (IC_{50} 5.1 µM). However, when taking the clinical exposure (C_{max}) at maximum recommended human dose (MRHD) into consideration, adverse reactions are unlikely with these targets (safety margins >60). Asciminib also did not induce relevant inhibition of trans-phosphorylation in a large panel of kinase constructs and lipid kinases. Therefore, preclinical pharmacology models confirmed the specificity and sensitivity of asciminib towards ABL1/BCR-ABL1.

In *in vitro* safety pharmacology studies, asciminib showed no relevant effects on the slowly activating delayed rectifier cardiac potassium channel (IKs), the human cardiac L-type calcium channel (hCav1.2) or the voltage-gated human cardiac sodium channel (Nav1.5). The human ether-à-go-go-related gene (hERG) potassium channel was slightly inhibited by asciminib (IC_{50}11.4 µM or 4498 ng/mL, safety margin to free C_{max} at MRHD >100-fold). Moderate cardiovascular effects (increased heart rate, decreased systolic and mean arterial pressure, and decreased arterial pulse pressure) were observed with asciminib in jacket telemetered (600 mg/kg) or telemetrised (60 mg/kg) dogs. QTc prolongation did not occur in the nonclinical safety pharmacology and toxicity studies up to the highest dose levels, associated with a safety margin ≥6.29. However, QTc prolongation was observed in the clinical trials and is considered an important risk.

4.2 Pharmacokinetics

The applicant characterised the pharmacokinetic (PK) behaviour of asciminib in mice, rats, dogs, monkeys and humans. The drug was highly absorbed after oral application (~50% in rats and monkeys and 33% to 57% in humans). Higher asciminib doses showed solubility-limited absorption. T_{max} was between 0.8 and 5.3 h after oral dosing in all species. Rats and monkeys showed a minimal or moderate first-pass effect. The applicant detected high and concentration-independent plasma protein binding in mice, rats, dogs, monkeys and human. The unbound fraction (fu) ranged from 0.02 to 0.055 (humans 0.027). Only dogs showed lower fu than humans.

Asciminib-related radioactivity distributed into all extravascular compartments (with the exception of the brain) in the oral rat quantitative whole body autoradiography (QWBA) study. Radioactivity was rapidly

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eliminated from most tissues. Highest exposures were in kidney, liver, adrenal glands, pancreas, salivary glands, heart, fat (brown), spleen, lungs, and digestive tract (colon, small intestine and stomach). The investigators detected moderate distribution in reproductive tissues (ovaries, uterus and testes) and in melanin-rich tissues such as the skin and uveal tract.

The applicant did not conduct studies on placental passage or milk transfer. However, asciminib increased dose-dependently in fetal plasma in the rat and rabbit embryo-fetal toxicity studies.

The compound was eliminated mainly via hepatic metabolism in rats, monkeys, and humans. In rats, the major metabolic pathways were oxidation phase I reactions, whereas in monkeys and humans, the major metabolic pathways were oxidative phase I and direct glucuronidation reactions. The investigators did not detect unique or disproportionate human metabolites. The major component in human plasma was asciminib (92.7%). After being secreted via the biliary/intestinal route, intestinal bacteria cleaved back asciminib-glucuronides to asciminib, resulting in high amounts of asciminib in the faeces. Urine constituted only a minor excretion pathway.

The applicant provided toxicokinetic measurements for mouse, rat, dog, rabbit, and monkey toxicity studies. No time-dependent accumulation and no gender difference in exposure occurred. Plasma exposure increased dose-dependently in mice, rats, rabbits and dogs. In monkeys, asciminib exposure increased more than dose-proportionally between 3 and 30 mg/kg and dose-proportionally between 30 and 100 mg/kg.

4.3 Toxicology

The applicant assessed asciminib in oral mouse, rat, dog, rabbit and monkey toxicity studies. The programme followed the ICH S9 guideline with consideration of other ICH guidance documents. The extensive toxicology programme included subchronic, chronic, reproductive, phototoxicity and genotoxicity studies. The applicant conducted repeated dose toxicity studies in rats (up to 26 weeks), dogs (up to 4 weeks), and monkeys (up to 39 weeks). The following target organs were identified: liver (rat, dog and monkey), haematopoietic system (rat, dog and monkey), adrenal glands (rat and monkey), pancreas (dog), gastro-intestinal tract (rat), and Harderian gland (rat). All changes demonstrated either reversibility or a tendency towards reversibility.

Rats, dogs and monkeys showed elevated liver enzymes and/or bilirubin values. In rats, centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia and increased individual hepatocyte necrosis occurred. Monkeys showed reversible diffuse hepatocellular hypertrophy. Liver changes occurred in the human exposure range (AUC) in rats. In dogs and monkeys, liver changes occurred at ≥12-fold higher MRHD AUC.

Haematopoietic system changes were minimal to mild regenerative reductions in red blood cell mass, with related mild increases in splenic and/or bone marrow pigment and an increased percentage of reticulocytes. This picture is consistent with mild and regenerative, extravascular, haemolytic anaemia. In rats, these changes occurred in the human exposure range (AUC). In monkeys and dogs, exposures (AUC) were ≥8-fold higher than at MRHD.

Adrenal gland findings were minimal or slight hypertrophy and mild or moderate decreased vacuolation in the *zona fasciculata*. These findings may be indicative of stress and increased production of corticosteroids, although an additional direct effect on the adrenal glands cannot be excluded. Exposure in monkeys was similar to the clinical exposure (AUC) and ≥13 -fold higher in rats.

The pancreas findings in dogs included increased serum amylase and lipase, which correlated with pancreatic acinar cell damage. Pancreatic toxicity occurred also in humans.

Reversible duodenal findings detected at high doses in rats (600 mg/kg/day) consisted of minimal mucosal hypertrophy/hyperplasia with increased mucosal thickness and frequent elongation of villi. These findings occurred at ≥ 22-fold higher exposure (AUC) at MRHD.

Changes to the Harderian gland observed in rats occurred in the human exposure (AUC) range. However, they are not relevant, as this gland does not exist in humans.

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Asciminib was not genotoxic *in vitro* and *in vivo.* The applicant did not conduct carcinogenicity studies, which is in line with ICH S9.

Asciminib showed no effect on reproductive function in rat fertility studies. Slight effects on sperm motility and/or sperm count in individual animals and embryo-lethality were observed at exposures >13-fold human MRHD exposure. Asciminib caused embryolethality and/or malformations in rats and rabbits at exposures (AUC) ≥3-fold higher than at MRHD. The paediatric development concerns the population from 3 to less than 18 years of age and does not foresee any nonclinical studies.

The compound was phototoxic *in vitro* and *in vivo* in mice. The C_{max} at the NOAEL was >6-fold higher than the MRHD exposure in patients.

The applicant adequately performed the impurity assessment according to ICH M7; impurities specified in the drug substance are qualified.

Based on the ERA, asciminib does not represent a risk for the environment at the prescribed dose and in the intended indication.

4.4 Nonclinical Conclusions

In conclusion, the pharmaco-toxicological profile of asciminib is considered sufficiently characterised. The submitted nonclinical data support the approval of asciminib in the proposed indication. The relevant information is included in the information for healthcare professionals.

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5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Scemblix was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This allows quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse effects. See “Adverse effects” for information on reporting adverse effects.

Scemblix

Composition

Active substances

Asciminib (as asciminib hydrochloride).

Excipients

20 mg film-coated tablets: 43 mg lactose monohydrate, microcrystalline cellulose (E460i), hydroxypropylcellulose (E463), croscarmellose sodium (E468), polyvinyl alcohol (E1203), titanium dioxide (E171), magnesium stearate (E470b), talc (E553b), colloidal anhydrous silica, iron oxide (E172, yellow and red), lecithin (E322), xanthan gum (E415).
One 20 mg film-coated tablet contains max. 0.47 mg sodium.
40 mg film-coated tablets: 86 mg lactose monohydrate, microcrystalline cellulose (E460i), hydroxypropylcellulose (E463), croscarmellose sodium (E468), polyvinyl alcohol (E1203), titanium dioxide (E171), magnesium stearate (E470b), talc (E553b), colloidal anhydrous silica, iron oxide (E172, black and red), lecithin (E322), xanthan gum (E415).
One 40 mg film-coated tablet contains max. 0.93 mg sodium.

Pharmaceutical form and quantity of active substance per unit

Scemblix 20 mg film-coated tablets:
The tablets are pale yellow, round and biconvex with bevelled edges and a diameter of approx. 6 mm, unscored, and imprinted with the Novartis logo on one side and “20” on the other side.
Each 20 mg film-coated tablet contains 21.62 mg asciminib hydrochloride equivalent to 20 mg asciminib.

Scemblix 40 mg film-coated tablets:
The tablets are violet-white, round and biconvex with bevelled edges and a diameter of approx. 8 mm, unscored, and imprinted with the Novartis logo on one side and “40” on the other side.
Each 40 mg film-coated tablet contains 43.24 mg asciminib hydrochloride equivalent to 40 mg asciminib.

Indications/Potential uses

Scemblix is indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP) in whom previous administration of two

or more tyrosine kinase inhibitors has resulted in treatment failure or intolerance (see “Clinical efficacy”).

Dosage/Administration

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

Usual dosage

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 who are switched 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 who are switched 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 (see “Clinical efficacy”).

Treatment duration

Scemblix treatment should be continued as long as a clinical benefit is observed or until unacceptable toxicity occurs.

Dose modification due to adverse effects/interactions

For the management of adverse effects of Scemblix the dose can be reduced based on individual safety and tolerability as described in Table 1. If adverse drug reactions are effectively managed, treatment with 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 dose 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 dose modification for the management of selected adverse effects is shown in Table 2.

Table 2 Scemblix dose modification for the management of selected adverse effects

Adverse effect	Dose modification
Thrombocytopenia and/or neutropenia	
ANC[1] <1 x 10^9/l and/or PLT[2] <50 x 10^9/l	Withhold Scemblix until ANC ≥1 x 10^9/l and/or PLT ≥50 x 10^9/l. If resolved: • Within 2 weeks: Resume treatment at the original Scemblix starting dose. • After more than 2 weeks: Resume treatment at a reduced Scemblix dose. For recurrent severe thrombocytopenia and/or neutropenia withhold Scemblix treatment until ANC ≥1 x 10^9/l and PLT ≥50 x 10^9/l, then resume at reduced dose.
Asymptomatic amylase and/or lipase elevation	
Elevation >2 x ULN[3]	Withhold Scemblix until value has decreased to <1.5 x ULN. • If resolved: Resume treatment at a reduced Scemblix dose. If events reoccur at reduced dose, permanently discontinue Scemblix. • If not resolved: Permanently discontinue Scemblix. Perform diagnostic tests to exclude pancreatitis.
Non-haematological adverse effects	
Grade 3 or higher[4]	Withhold Scemblix until resolved or improvement to grade 1 or lower. • If resolved: Resume treatment at a reduced Scemblix dose. • If not resolved: Permanently discontinue Scemblix.

[1]ANC: absolute neutrophil count; [2]PLT: platelets; [3]ULN: upper limit of normal; [4]Based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.03

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment receiving Scemblix (see “Pharmacokinetics”).

Patients with renal impairment

No dose adjustment is necessary in patients with mild, moderate or severe renal impairment receiving Scemblix (see “Pharmacokinetics”).

Elderly patients

No dose adjustment is required in patients 65 years of age and over.

Children and adolescents

Safety and efficacy in patients under 18 years of age have not been established.

Late administration

Once-daily dosage regimen: If a dose of Scemblix is more than approx. 12 hours late, it should be skipped and the next one taken as scheduled.
Twice-daily dosage regimen: If a dose of Scemblix is more than approx. 6 hours late, it should be skipped and the next one taken as scheduled.

Method of administration

Scemblix should be taken orally without food. Food should be avoided for at least 2 hours before and 1 hour after taking Scemblix (see “Interactions” and “Pharmacokinetics”).
Scemblix film-coated tablets must be swallowed whole with a glass of water and should not be broken, crushed or chewed.

Contraindications

Hypersensitivity to the active substance or any of the excipients listed under “Composition”.

Warnings and precautions

Myelosuppression
Thrombocytopenia, neutropenia and anaemia have occurred in patients receiving Scemblix. Severe (NCI CTCAE grade 3 or 4) thrombocytopenia and neutropenia have been reported during treatment with Scemblix (see “Adverse effects”). Myelosuppression was generally reversible and managed by temporarily withholding Scemblix. A complete blood count should be performed every 2 weeks in 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 Scemblix dose should be reduced, temporarily withheld or permanently discontinued as described in Table 2 (see “Dosage/Administration”).

Pancreatic toxicity

Pancreatitis occurred in 9 of 356 (2.5%) patients receiving Scemblix, with grade 3 events occurring in 4 (1.1%) patients. All these events occurred in the phase I study (X2101). Of the 9 patients with pancreatitis, Scemblix was permanently discontinued in 2 (0.6%), while Scemblix was temporarily withheld in 4 (1.1%) patients due to the adverse drug reaction. Asymptomatic elevation of serum lipase and amylase occurred in 76 of 356 (21.3%) patients receiving Scemblix treatment, with grade 3 and 4 events occurring in 36 (10.1%) and 8 (2.2%) patients, respectively. Of the 76 patients with elevation of pancreatic enzymes, Scemblix was permanently discontinued in 8 (2.2%) patients due to the adverse effect.

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. 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 “Dosage/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 “Dosage/Administration”).

QT prolongation

Electrocardiogram QT prolongation occurred in 3 of 356 (0.8%) patients receiving Scemblix treatment (see “Adverse effects”). In the ASCEMBL clinical study one patient had a prolonged QTcF greater than 500 ms together with a more than 60 ms QTcF increase from baseline and one patient had a prolonged QTcF with a more than 60 ms QTcF increase from baseline.

It is recommended that an electrocardiogram is performed prior to the start of treatment with Scemblix and that ECG monitoring is carried out during treatment as clinically indicated. Hypokalaemia and hypomagnesaemia should be corrected prior to Scemblix administration and monitored during treatment as clinically indicated.

Caution is required when co-administering Scemblix with medicinal products known to cause torsade de pointes (see “Interactions” and “Pharmacokinetics”).

Hypertension

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

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

Hypersensitivity
Hypersensitivity events occurred in 109 of 356 (30.6%) patients receiving Scemblix, with ≥ grade 3 events reported in 6 (1.7%) patients. Patients should be monitored for signs and symptoms of hypersensitivity and appropriate treatment should be initiated as clinically indicated.

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. 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.

Embryo-fetal toxicity
Based on findings from animal studies, Scemblix can cause fetal harm when administered to a pregnant woman. Pregnant women and women of child-bearing potential should be advised of the potential risk to the fetus if Scemblix is used during pregnancy or if the patient becomes pregnant while taking Scemblix. The pregnancy status of women of child-bearing potential should be verified prior to starting treatment with Scemblix. Sexually active women of childbearing potential should use effective contraception during treatment with Scemblix and for at least 3 days after the last dose (see “Pregnancy/Breast-feeding”).

Other components
The tablets contain lactose. Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.
This medicinal product contains less than 1 mmol (23 mg) of sodium per tablet, making it practically “sodium-free”.

Interactions

Agents that may affect asciminib plasma concentrations:
Strong CYP3A4 inhibitors:
The AUC_{inf} and C_{max} of asciminib increased by 36% and 19%, respectively, after co-administration of a single dose of 40 mg Scemblix with a strong CYP3A4 inhibitor (clarithromycin). No clinically significant differences in the pharmacokinetics of asciminib were observed after co-administration with itraconazole, which is also a strong CYP3A4 inhibitor.

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 Scemblix dose of 40 mg. Model calculations predict that co-administration of asciminib at 80 mg once daily with rifampicin decreases asciminib AUC_{tau} and C_{max} by 52% and 23%, respectively. Caution is required during co-administration of Scemblix with strong CYP3A4 inducers, including, but not limited to, carbamazepine, phenobarbital, phenytoin or St. John's wort (*Hypericum perforatum*). Scemblix dose adjustment is not required.

Imatinib

Asciminib AUC_{inf} and C_{max} increase by 108% and 59%, respectively, after co-administration of a single dose of 40 mg Scemblix with imatinib (an inhibitor of BCRP, CYP3A4, UGT2B17 and UGT1A3/4). The changes in exposure are not considered to be clinically significant.

Other agents

No clinically significant differences in the pharmacokinetics of asciminib were observed after co-administration with rabeprazole (acid-reducing agent) and quinidine (P-gp inhibitor).

Agents whose plasma concentrations may be altered by asciminib:

CYP3A4 substrates with a 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 40 mg Scemblix twice daily. Caution is required during co-administration of Scemblix with CYP3A4 substrates known to have a narrow therapeutic index, including, but not limited to, fentanyl, alfentanil, dihydroergotamine or ergotamine (see "Pharmacokinetics"). Scemblix dose adjustment is not required.

CYP2C8 substrates

The AUC_{inf} and C_{max} of repaglinide (substrate of CYP2C8, CYP3A4 and OATP1B) increased by 8% and 14%, respectively, after co-administration of repaglinide with 40 mg Scemblix twice daily. The AUC_{inf} and C_{max} of repaglinide increased by 12% and 8%, respectively, after co-administration with 80 mg Scemblix once daily. The AUC_{inf} and C_{max} of rosiglitazone (substrate of CYP2C8 and CYP2C9) increased by 20% and 3%, respectively, after co-administration of rosiglitazone with 40 mg Scemblix twice daily. The AUC_{inf} and C_{max} of rosiglitazone increased by 24% and 2%, respectively, after co-administration with Scemblix at a dosage of 80 mg once daily. The changes in exposure are not considered to be clinically significant.

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 40 mg Scemblix twice daily. Co-administration of asciminib at 80 mg once daily would be expected to increase S-warfarin AUC_{inf} and C_{max} by 52% and 4%, respectively.
Caution is required during co-administration of Scemblix with CYP2C9 substrates known to have a narrow therapeutic index, including, but not limited to, phenytoin or warfarin (see “Pharmacokinetics”). Scemblix dose adjustment is not required.

QT-prolonging agents

Caution is required during co-administration of Scemblix and medicinal products known to cause torsade de pointes, including, but not limited to, chloroquine, clarithromycin, haloperidol, methadone or moxifloxacin (see “Pharmacokinetics”).

Interactions with food

The bioavailability of asciminib decreases on consumption of food (see “Dosage/Administration” and “Pharmacokinetics”).

In vitro evaluation of drug interaction potential

CYP450 and UGT enzymes

In vitro, asciminib reversibly inhibits CYP3A4/5, CYP2C9 and UGT1A1 at plasma concentrations reached at a total daily dose of 80 mg.

Transporters

Asciminib is a substrate of BCRP and P-gp. Asciminib inhibits BCRP, P-gp, OATP1B1, OATP1B3 and OCT1 with Ki values of 24.3, 21.7, 2.46, 1.92 and 3.41 micromolar, respectively. Co-administration of Scemblix with a medicinal product that is a P-gp substrate may lead to a clinically relevant increase in plasma concentrations of P-gp substrates, with minimal concentration changes possibly leading to severe toxicities.

Multiple metabolic pathways

Asciminib is metabolised by several pathways, including the CYP3A4, UGT2B7 and UGT2B17 enzymes and biliary secretion by the transporter BCRP.
Medicinal products inhibiting or inducing multiple metabolic pathways may alter Scemblix exposure.

Pregnancy/Breast-feeding

Treatment of women of childbearing potential/contraception

The pregnancy status of women of child-bearing potential should be verified prior to starting treatment with Scemblix.
Sexually active women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with Scemblix and for at least 3 days after the last dose.

Pregnancy

There are no studies in pregnant women to inform a medicinal product-associated risk.
Animal reproduction studies in pregnant rats and rabbits demonstrated that oral administration of asciminib during organogenesis induced embryotoxicity, fetotoxicity and malformations (see “Preclinical data”). Asciminib is not recommended during pregnancy and in women of childbearing potential not using contraceptives. If Scemblix is used during pregnancy or if the patient becomes pregnant during treatment with Scemblix, the patient must be informed of the potential risk to the fetus (see “Warnings and precautions”).

Breast-feeding

It is unknown whether asciminib or its metabolites are excreted in human milk following administration of Scemblix. There are no data on the effects of asciminib on the breast-fed infant or milk production. Because of the potential for serious adverse effects in the breast-fed infant, breast-feeding is not recommended during treatment with Scemblix and for at least 3 days after the last dose.

Fertility

There are no data on the effects of Scemblix on human fertility.
In the rat fertility study asciminib did not affect reproductive function in male and female rats (see “Preclinical data/Fertility”).

Effects on ability to drive and use machines

Scemblix has no or negligible influence on the ability to drive or use machines. However, it is recommended that patients experiencing dizziness, fatigue or other adverse effects with a potential impact on the ability to drive or use machines should refrain from these activities as long as the adverse effects persist (see “Adverse effects”).

Adverse effects

Summary of the safety profile

The overall safety profile of asciminib was investigated in 356 patients with Ph+ CML. In the pooled data set of the pivotal phase III study A2301 (dosage of 40 mg twice daily) the median duration of exposure to asciminib was 116 weeks (range: 0.1 to 342 weeks).

The most common adverse reactions of any grade (incidence ≥20%) in patients receiving Scemblix were musculoskeletal pain (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 effects of ≥ grade 3 (incidence ≥5%) in patients receiving Scemblix were thrombocytopenia (18.5%), neutropenia (15.7%), increased pancreatic enzymes (12.4%), hypertension (8.7%) and anaemia (5.3%).
Serious adverse effects occurred in 12.4% of patients receiving Scemblix.
The most frequent serious adverse effects (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%).

List of adverse effects

Adverse effects are ordered by MedDRA system organ class and frequency according to 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 3 Adverse effects observed with Scemblix in clinical studies

Adverse effects	Frequency category[1] (N=356) (all grades)
Infections and infestations	
Upper respiratory tract infection[2]	Very common (28.1%)
Lower respiratory tract infection[3]	Common
Influenza	Common
Blood and lymphatic system disorders	
Thrombocytopenia[4]	Very common (27.5%)
Neutropenia[5]	Very common (19.4%)
Anaemia[6]	Very common (12.9%)
Febrile neutropenia	Uncommon
Metabolism and nutrition disorders	
Dyslipidaemia[7]	Very common (10.4%)
Decreased appetite	Common

Adverse effects	Frequency category[1] (N=356) (all grades)
Nervous system disorders	
Headache	Very common (24.2%)
Dizziness	Very common (11.2%)
Eye disorders	
Blurred vision	Common
Dry eye	Common
Cardiac disorders	
Palpitations	Common
Vascular disorders	
Hypertension[8]	Very common (18.5%)
Respiratory, thoracic and mediastinal disorders	
Cough	Very common (12.6%)
Pleural effusion	Common
Dyspnoea	Common
Non-cardiac chest pain	Common
Gastrointestinal disorders	
Increased pancreatic enzymes[9]	Very common (21.3%)
Vomiting	Very common (15.7%)
Diarrhoea	Very common (20.5%)
Nausea	Very common (20.2%)
Abdominal pain[10]	Very common (21.3%)
Pancreatitis[11]	Common
Hepatobiliary disorders	
Increased hepatic enzymes[12]	Very common (14.6%)
Increased blood bilirubin[13]	Common
Skin and subcutaneous tissue disorders	
Rash[14]	Very common (19.7%)
Urticaria	Common
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain[15]	Very common (37.1%)
Arthralgia	Very common (21.6%)
General disorders and administration site conditions	
Fatigue[16]	Very common (27.2%)
Pruritus	Very common (12.4%)
Fever[17]	Common
Oedema[18]	Common
Investigations	
Increased blood creatine phosphokinase	Common
Prolonged electrocardiogram QT	Uncommon
[1]Frequency based on the safety pool (A2301 and X2101) for Scemblix all-grade events (N=356).	

Adverse effects	Frequency category[1] (N=356) (all grades)
[2]Upper respiratory tract infections includes: upper respiratory tract infections, nasopharyngitis, pharyngitis and rhinitis; [3]Lower respiratory tract infections includes: pneumonia, bronchitis and tracheobronchitis; [4]Thrombocytopenia includes: thrombocytopenia and decreased platelet count; [5]Neutropenia includes: neutropenia and decreased neutrophil count; [6]Anaemia includes: anaemia, decreased haemoglobin, normocytic anaemia; *[7]Dyslipidaemia includes: hypertriglyceridaemia, increased blood cholesterol, hypercholesterolaemia, increased blood triglycerides, hyperlipidaemia and dyslipidaemia; [8]Hypertension includes: hypertension and increased blood pressure; [9] Increased pancreatic enzymes includes: increased lipase, increased amylase and hyperlipasaemia; [10]Abdominal pain includes: abdominal pain and upper abdominal pain; [11] Pancreatitis includes: pancreatitis and acute pancreatitis;* *[12]Increased hepatic enzymes includes: increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyltransferase and increased transaminases; [13] Increased blood bilirubin includes: increased blood bilirubin, increased conjugated bilirubin and hyperbilirubinaemia; [14]Rash includes: rash and maculopapular rash; [15]Musculoskeletal pain includes: pain in extremity, back pain, myalgia, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain, musculoskeletal discomfort; [16]Fatigue includes: fatigue and asthenia; [17]Pyrexia includes: pyrexia and increased body temperature; [18] Oedema includes: oedema and peripheral oedema.*	

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

Description of specific adverse effects and additional information

Myelosuppression

Thrombocytopenia occurred in 98 of 356 (27.5%) patients receiving Scemblix, with grade 3 and 4 events reported in 26 (7.3%) and 30 (8.4%) patients, respectively. Among the patients with ≥ grade 3 thrombocytopenia the median time to first occurrence of events was 6 weeks (range: 0.1 to 64 weeks) with a median duration of any occurring event of 1.71 weeks (95% CI, range: 1.43 to 2 weeks). Of the 98 patients with thrombocytopenia, 7 (2%) permanently discontinued Scemblix, while Scemblix was temporarily withheld in 45 (12.6%) patients due to the adverse effect.

Neutropenia occurred in 69 of 356 (19.4%) patients receiving Scemblix treatment, with grade 3 and 4 events reported in 26 (7.3%) and 30 (8.4%) patients, respectively. Among the patients with ≥ grade 3 neutropenia the median time to first occurrence of events was 6 weeks (range: 0.1 to 180 weeks) with a median duration of any occurring event of 1.7 weeks (95% CI, range: 1.29 to 2 weeks). Of the 69 patients with neutropenia, 4 (1.1%) permanently discontinued Scemblix, while Scemblix was temporarily withheld in 34 (9.6%) patients due to the adverse effect.

Anaemia occurred in 46 of 356 (12.9%) patients receiving Scemblix, with grade 3 events occurring in 19 (5.3%) patients. Among the patients with grade 3 anaemia the median time to first occurrence of events was 30 weeks (range: 0.4 to 207 weeks) with a median duration of any occurring event of 0.9 weeks (95% CI, range: 0.43 to 2.14 weeks). Of the 46 patients with anaemia, Scemblix was temporarily withheld in 2 (0.6%) patients due to the adverse effect.

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal ElViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

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

Properties/Actions

ATC code

L01EA06

Mechanism of action

Asciminib is an oral and 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-binding pocket.

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 harbouring 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 tumours harbouring the wild-type form of BCR-ABL1, with tumour 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 leukaemia (ALL) receiving Scemblix 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 Scemblix 40 mg twice-daily dose and 3.64 ms (upper bound of 90% CI: 4.68 ms) for the 80 mg once-daily dose.

Clinical efficacy

The clinical efficacy and safety of Scemblix 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 investigated in the multicentre, randomised, active-controlled and open-label phase III study ASCEMBL.
Resistance to the last TKI was defined as:

- Lack of haematological or cytogenetic response at 3 months
- BCR-ABL1 IS >10% at 6 months or thereafter
- >65% Philadelphia-positive (Ph+) metaphases at 6 months or >35% at 12 months or thereafter
- Loss of complete haematological response (CHR), of partial cytogenetic response (PCyR), of complete cytogenetic response (CCyR) or of major molecular response (MMR) at any time
- New BCR-ABL1 mutations which potentially cause resistance to the study medicinal product or clonal evolution in Ph+ metaphases at any time.

Intolerance to the 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 for treatment with either 40 mg Scemblix twice daily (N=157) or 500 mg bosutinib once daily (N=76). There are only limited clinical data on the 80 mg once-daily dosage. Pharmacological analyses indicate that both dosages have a comparable clinical profile. Patients continued treatment until unacceptable toxicity or treatment failure occurred. Patients with a known T315I and/or V299L mutation at any time prior to study entry were not included in ASCEMBL.

Patients with Ph+ CML-CP were 51.5% female and 48.5% male with a median age of 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 white (74.7%), Asian (14.2%) and black (4.3%). Of the 233 patients, 80.7% and 18% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, respectively. The proportion of 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 treatment was 103 weeks (range: 0.1 to 201 weeks) for patients receiving Scemblix and 31 weeks (range: 1 to 188 weeks) for patients receiving bosutinib.

The primary endpoint of the study was major molecular response rate (MMR) at 24 weeks and MMR at 96 weeks was the key secondary endpoint. MMR is defined as a BCR-ABL1 ratio ≤0.1% on the International Scale [IS]. A secondary endpoint was complete cytogenetic response rate (CCyR) at 24 and 96 weeks, defined as no Philadelphia-positive metaphases in bone marrow with a minimum of 20 metaphases examined.

The most important efficacy results from the ASCEMBL study are summarised in Table 4.

Table 4 Efficacy results in Ph+ CML-CP patients previously treated with two or more tyrosine kinase inhibitors (ASCEMBL)

	40 mg Scemblix twice daily	**500 mg bosutinib once daily**	**Difference (95% CI)**	**p-value**
MMR rate, % (95% CI) at 24 weeks	**N=157** 25.48 (18.87, 33.04)	**N=76** 13.16 (6.49, 22.87)	12.24[1] (2.19, 22.30)	0.029[2]
MMR rate, % (95% CI) at 96 weeks	**N=157** 37.58 (29.99, 45.65)	**N=76** 15.79 (8.43, 25.96)	21.74[1] (10.53, 32.95)	0.001[2]
CCyR rate, % (95% CI) at 24 weeks	**N=103**[3] 40.78 (31.20, 50.9)	**N=62**[3] 24.19 (14.22, 36.74)	17.3 (3.62, 30.99)	Not formally tested
CCyR rate, % (95% CI) at 96 weeks	**N=103**[3] 39.81 (30.29, 49.92)	**N=62**[3] 16.13 (8.02, 27.67)	23.87 (10.30, 37.43)	Not formally tested

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

[2]Cochrane-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

In the ASCEMBL study 12.7% of patients treated with Scemblix 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 Scemblix with or without any BCR-ABL1 mutation at baseline, respectively.

Elderly patients

In the ASCEMBL study 44 of the 233 (18.9%) patients were 65 years or older, while 6 (2.6%) were 75 years or older. No overall differences in the safety or efficacy of Scemblix were observed between patients aged 65 years or older and younger patients. There is an insufficient number of patients aged 75 years or older to assess whether there are differences in safety or efficacy.

Paediatric population

No studies on safety and efficacy have been performed in children and adolescents aged under 18 years.

Pharmacokinetics

Absorption

Asciminib is rapidly absorbed, with median maximum plasma levels (T_{max}) reached 2 to 3 hours after oral administration, independent of the dose. The geometric mean (geoCV%) of C_{max} at steady state is 1781 ng/ml (23%) and 793 ng/ml (49%) following administration of Scemblix at 80 mg once daily and 40 mg twice daily, respectively. The geometric mean (geoCV%) of AUC_{tau} is 5262 ng*h/ml (48%) following administration of Scemblix at the 40 mg twice-daily dose. According to model calculations asciminib absorption is estimated at 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 itraconazole 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 and C_{max} are decreased by 62.3% and 68.2%, respectively, with a high-fat meal and by 30% and 34.8%, respectively, with a low-fat meal compared to the fasted state (see “Dosage/Administration” and “Interactions”).

Distribution

Asciminib apparent volume of distribution at steady state is 151 l based on a population pharmacokinetic analysis. Asciminib is mainly distributed to plasma, with a mean blood-to-plasma ratio of 0.58, independent of the dose. Asciminib is 97.3% bound to human plasma proteins, independent of the dose.

Metabolism

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

Elimination

Asciminib is mainly eliminated faecally, with only a minor proportion eliminated renally. 80% and 11% of the asciminib dose were recovered in the faeces and 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 based on a population pharmacokinetic analysis. The accumulation half-life of asciminib is 5.2 hours at dosages of 40 mg twice daily and 80 mg once daily.

Linearity/non-linearity

Asciminib exhibits a slight 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, independent of the dose. Steady-state conditions are achieved within 3 days at the 40 mg twice-daily dose.

Pharmacokinetics in special populations

Asciminib systemic exposure is not affected by gender, age (20 to 88 years), ethnicity or body weight (42 to 84 kg) to any clinically relevant extent.

Hepatic impairment

A dedicated hepatic impairment study including 8 participants each with normal hepatic function, mild hepatic impairment (Child-Pugh A score 5 to 6), moderate hepatic impairment (Child -Pugh B score 7 to 9) or severe hepatic impairment (Child-Pugh C score 10 to 15) was conducted. Asciminib AUC_{inf} was increased by 22%, 3% and 33% in participants with mild, moderate and severe hepatic impairment, respectively, compared to participants with normal hepatic function following oral administration of a single 40 mg dose of Scemblix (see “Dosage/Administration”).

Renal impairment

A dedicated renal impairment study including 6 participants with normal renal function (absolute glomerular filtration rate [aGFR] ≥90 ml/min) and 8 participants with severe renal impairment not requiring dialysis (aGFR 15 to <30 ml/min) has been conducted. Asciminib AUC_{inf} and C_{max} are increased by 57% and 6%, respectively, in participants with severe renal impairment compared to participants with normal renal function following oral administration of a single 40 mg dose of Scemblix (see “Dosage/Administration”).
Population pharmacokinetic models show an increase in asciminib median steady-state $AUC_{0\text{-}24h}$ by 11.5% in participants with mild to moderate renal impairment compared to participants with normal renal function.

Preclinical data

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

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. No QTc prolongation was evident in dogs up to the highest asciminib free exposure of 6.3 micromolar.

Repeated-dose toxicity

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.
Minimal mucosal hypertrophy/hyperplasia (increase in thickness of the mucosa with frequent elongation of villi) occurred in the duodenum of rats at AUC exposures 30-fold or 22-fold higher than those achieved in patients on 40 mg twice daily or 80 mg once daily, respectively. This change was fully reversible.
Minimal or slight hypertrophy of the adrenal gland and mild to moderate decreased vacuolation in the zona fasciculata occurred at AUC exposures either equivalent to (monkeys) or 13- to 19-fold (rats) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily, respectively. These changes were fully reversible.

Carcinogenicity and mutagenicity

Asciminib did not show mutagenic, clastogenic or aneugenic potential *in vitro* or *in vivo*.
Carcinogenicity studies have not been conducted with asciminib.

Reproductive toxicity

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 organogenesis. In embryo-fetal development studies a slight increase in fetal malformations (anasarca and cardiac malformations) and an increase in visceral and skeletal variants were observed in rats. An increased incidence of resorptions indicative of embryo-fetal mortality and a low incidence of cardiac malformations indicative of teratogenicity were observed in rabbits. In rats, at the fetal NOAEL of 25 mg/kg/day, the AUC exposures were equal to or less than those achieved in patients at the 40 mg twice-daily or 80 mg once-daily doses. In rabbits, 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.

Fertility

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 or 13-fold higher than those achieved in patients at 40 mg twice daily and 80 mg once daily, respectively

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 or 6-fold higher than the exposure in patients on 40 mg twice daily or 80 mg once daily, respectively.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

Do not store above 25°C.
Store in the original pack to protect the contents from moisture.
Keep out of the reach of children.

Swissmedic number

68441

Pack sizes

Pack of 60 film-coated tablets each containing 20 or 40 mg asciminib [A]

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

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