Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist physicians in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for the healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Asciminib 20 mg film-coated tablets
Asciminib 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Asciminib 20 mg film-coated tablets

Each film-coated tablet contains 20 mg asciminib (as hydrochloride).

Excipients with known effect
Each film-coated tablet contains 43.11 mg lactose monohydrate.

Asciminib 40 mg film-coated tablets

Each film-coated tablet contains 40 mg asciminib (as hydrochloride)

Excipients with known effect
Each film-coated tablet contains 86.22 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Asciminib 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.

Asciminib 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 EAMS Therapeutic indications

Asciminib is indicated for the treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) without T315I mutation previously treated with two or more tyrosine kinase inhibitors.

4.2 Posology and method of administration

Treatment with asciminib should be initiated by a physician experienced in the diagnosis and treatment of patients with chronic myeloid leukaemia (CML).

Posology

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

Patients for whom a dose of 40 mg twice daily is not considered appropriate a dose of 80 mg once daily at approximately the same time each day may be prescribed.

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

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

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

Delayed or missed dose
80 mg once -daily dosage regimen: If a dose is missed by more than approximately 12 hours, it should be skipped and the next dose should be taken as scheduled.

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

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

Dose adjustments for adverse reactions
For the management of adverse reactions, the dose can be reduced based on individual safety and tolerability, as described in Table 1.

If adverse reactions are effectively managed, asciminib may be resumed as described in Table 1. It should be permanently discontinued in patients unable to tolerate a total daily dose of 40 mg.

Table 1 Asciminib 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 dosage modification for the management of selected adverse reactions is shown in Table 2.

Table 2 Asciminib dose modification schedule for the management of adverse reactions

Adverse reaction	Dosage 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	Withhold asciminib until resolved (Grade ≤1). • If resolved: resume at a reduced dose. • If not resolved: permanently discontinue.
Pancreatitis	
Grade 2 (radiologic findings for pancreatitis)	Asymptomatic radiologic pancreatitis, withhold asciminib until recovery of the radiologic findings If resolved: resume at reduced dose. If events reoccur at reduced dose, permanently discontinue
Grade ≥ 3	Permanently discontinue
Based on Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. ANC: absolute neutrophil count; PLT: platelets; ULN: upper limit of normal	

Special populations

Elderly (≥65 years)
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. Since there are no data available in patients with moderate or severe hepatic impairment, caution should be exercised in these patients (see section 4.8 and 5.2).

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

Method of administration

Asciminib should be taken orally without food. Food consumption should be avoided for at least 2 hours before and 1 hour after taking asciminib (see sections 4.5 and 5.2).

The film-coated tablets should be swallowed whole and should not be broken, crushed or chewed.

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 events 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 weekly for the first month, every two weeks for the second and third 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 reduced, temporarily withheld or permanently discontinued (see section 4.2).

Pancreatic toxicity

Pancreatitis occurred in 9 of 356 (2.5%) patients receiving asciminib, with grade 3 events occurring in 4 (1.1%) patients. (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 elevation 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 elevation, the dose should be reduced, temporarily withheld or permanently discontinued (see section 4.2).

QT prolongation

Electrocardiogram QT prolongation occurred in 3 of 356 (0.8%) patients receiving asciminib (see section 4.8). In the ASCEMBL clinical study, one patient had a prolonged QTcF greater than 500 ms together with more than 60 ms QTcF increase from baseline.

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.
Asciminib should be administered with caution to patients who have a history of or predisposition for QTc prolongation, who have uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia
(see sections 4.5 and 5.1).

Hypertension

Hypertension occurred in 64 of 356 (18%) patients receiving asciminib, with grade 3 and 4 events reported in 29 (8.1%) and 1 (0.3%) patients, respectively. Among the patients with hypertension ≥ grade 3, the median time to first occurrence of events was 14 weeks (range: 0.1 to 156 weeks). Of the 64 patients with hypertension, asciminib was temporarily withheld in 3 (0.8%) patients due to the adverse reaction.

Hypertension should be monitored and managed using standard antihypertensive therapy during treatment with asciminib 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-ABL 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 medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that may decrease asciminib plasma concentrations

Strong CYP3A4 inducers
Coadministration of a strong CYP3A4 inducer in healthy subjects decreased asciminib AUC_{inf} by 14.9% and increased C_{max} by 9% in healthy subjects receiving a single asciminib dose of 40 mg. Physiologically based pharmacokinetic (PBPK) models predict that coadministration of asciminib at 80 mg once daily with rifampicin would decrease asciminib AUC_{tau} and C_{max} by 52% and 23%.

Caution should be exercised during concomitant administration of asciminib with strong CYP3A inducers, including, but not limited to, carbamazepine, phenobarbital, phenytoin or St. John's wort (*Hypericum perforatum*). Dose adjustment of asciminib is not required.

Medicinal products that may have their plasma concentrations altered by asciminib

CYP3A4 substrates with narrow therapeutic index
Coadministration 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. PBPK models predict that coadministration of asciminib at 80 mg once daily would increase midazolam AUC_{inf} and C_{max} by 24% and 17%, respectively.

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
Coadministration of asciminib with a CYP2C9 substrate (warfarin) increased Swarfarin AUC_{inf} and C_{max} by 41% and 8%, respectively, in healthy subjects receiving asciminib 40 mg twice daily. PBPK models predict that coadministration of asciminib at 80 mg once daily would increase Swarfarin AUC_{inf} and C_{max} by 52% and 4%, respectively.

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.

P-gp substrates
Caution should be exercised during concomitant use of asciminib and P-gp substrates with narrow therapeutic index (e.g dabigatran). Asciminib is expected to be a weak to moderate inhibitor of P-gp mediated transport at 40 mg twice daily and 80 mg once daily.

PBPK models predict that co-administration of asciminib at 40 mg twice daily or 80 mg once daily would increase dabigatran AUC_{inf} by 117% and 139%, respectively.

QT prolongation
Caution should be exercised during concomitant administration of asciminib and medicinal products known to cause torsades de pointes, including, but not limited to, bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozide (see section 5.2).

Drug -food interactions
The bioavailability of asciminib decreases on consumption of food (see sections 4.2 and 5.2).
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4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Women of childbearing potential should be advised to use effective contraception during treatment with asciminib and for at least 3 days after stopping treatment and to avoid becoming pregnant while receiving asciminib. In addition, the patient should be advised that vomiting or diarrhoea may reduce the efficacy of oral contraceptives by preventing full absorption.

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 for use during pregnancy, or 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 is 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 is not recommended 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 (see section 5.3).

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 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 (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of asciminib has been evaluated in 356 patients with Ph+ CML -in chronic (CP) and accelerated (AP) phases receiving asciminib as monotherapy. It is based on the safety pool of the pivotal phase III study A2301 (ASCEMBL) (N=156 Ph+ CML--CP patients) and the phase I study X2101 (N=115 Ph+ CML--CP, N=70 Ph+ CML--CP harbouring the T315I mutation and N=15 Ph+ CML--AP patients).

The safety pool (N=356) includes patients receiving asciminib at doses ranging from 10 to 200 mg twice daily and 80 to 200 mg once daily with 187 patients receiving asciminib at dose of 40 mg twice daily and 18 patients receiving asciminib at dose of 80 mg once daily In the pooled dataset, median duration of exposure to asciminib was 89 weeks (range: 0.1 to 342 weeks).

At least 1 adverse reaction of any toxicity grade was reported for 327 (91.90%) patients. The most common adverse reactions of any grade (incidence ≥20%) in patients receiving asciminib were musculoskeletal pain (36.2%), upper respiratory tract infections (28.1%), thrombocytopenia (27.5%), fatigue (25.8%), headache (23.6%), increased pancreatic enzymes (21.3%), arthralgia (21.3%) and nausea (20.2%). The most common adverse reactions of ≥ grade 3 (incidence ≥5%) in patients receiving asciminib were thrombocytopenia (18.5%), neutropenia (15.7%), increased pancreatic enzymes (12.4%), hypertension (8.4%) 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%).

The predicted safety profile of asciminib at the 80 mg once--daily dose is similar to the 40 mg twice--daily dose, based on exposure--safety analysis.

Tabulated list of adverse reactions

Adverse reactions from clinical studies (Table 3) 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 categories are defined as: 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 reactions observed with asciminib in clinical studies

System organ class	Frequency category[1]	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infection[2]
	Common	Lower respiratory tract infection[3], influenza
Blood and lymphatic system disorders	Very common	Thrombocytopenia[4], neutropenia[5], anaemia[6]
	Uncommon	Febrile neutropenia
Metabolism and nutrition disorders	Very common	Dyslipidaemia[7]
	Common	Decreased appetite
Nervous system disorders	Very common	Headache, dizziness
Eye disorders	Very common	Dry eye, vision blurred
Cardiac disorders	Very common	Palpitations
Vascular disorders	Very common	Hypertension[8]
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Pleural effusion, dyspnoea, non-cardiac chest pain
Gastrointestinal disorders	Very common	Pancreatic enzymes increased[9], vomiting, diarrhoea, nausea, abdominal pain[10]
	Common	Pancreatitis[11]
Hepatobiliary disorders	Very common	Hepatic enzyme increased[12]
	Common	Blood bilirubin increased[13]
Skin and subcutaneous tissue disorders	Very common	Rash[14]
	Common	Urticaria
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[15], arthralgia
General disorders and administration site conditions	Very common	Fatigue[16], pruritus
	Common	Pyrexia[17], oedema[18]
Investigations	Common	Blood creatine phosphokinase increased
	Uncommon	Electrocardiogram QT prolonged

[1] Frequency based on the safety pool (A2301 + X2101) asciminib all grade events (N=356).
[2] Upper respiratory tract infection includes: upper respiratory tract infection, nasopharyingitis, pharyngitis and rhinitis.
[3] Lower respiratory tract infections includes: pneumonia, bronchitis and tracheobronchitis.
[4] Thrombocytopenia includes: thrombocytopenia and platelet count decreased.
[5] Neutropenia includes: neutropenia and neutrophil count decreased.
[6] Anaemia includes: anaemia, haemoglobin decreased, normocytic anaemia.
[7] Dyslipidaemia includes: hypertriglyceridaemia, blood cholesterol increased, hypercholesterolaemia, blood triglycerides increased, hyperlipidaemia and dyslipidaemia.
[8] Hypertension includes: hypertension and blood pressure increased.
[9] Pancreatic enzymes increased includes: lipase increased, amylase increased and hyperlipasaemia.
[10] Abdominal pain includes: abdominal pain and abdominal pain upper.
[11] Pancreatitis includes: pancreatitis and pancreatitis acute.
[12] Hepatic enzymes increased includes: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased and transaminases increased.
[13] Blood bilirubin increased includes: blood bilirubin increased, bilirubin conjugated increased and hyperbilirubinaemia.
[14] Rash includes: rash and rash maculopapular.
[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 body temperature increased.
[18] Oedema includes: oedema and oedema peripheral.

Description of selected adverse reactions

Myelosuppression
Thrombocytopenia occurred in 98 of 356 (27.5%) patients receiving asciminib, with grade 3 and 4 events reported in 24 (6.7%) and 42 (11.8%) of patients, respectively. Among the patients with thrombocytopenia ≥ grade 3, the median time to first occurrence of events was 6 weeks (range: 0.14 to 64 weeks) with median duration of any occurring event of 1.71 weeks (95% CI, range: 1.43 to 2 weeks). Of the 97 patients with thrombocytopenia, 7 (2%) permanently discontinued asciminib, while asciminib was temporarily withheld in 45 (12.6%) patients due to the adverse reaction.

Neutropenia occurred in 69 of 356 (19.4%) patients receiving asciminib, with grade 3 and 4 events reported in 27 (7.6%) and 29 (8.1%) patients, respectively. Among the patients with neutropenia ≥ grade 3, the median time to first occurrence of events was 6 weeks (range: 0.14 to 180 weeks) with 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%) patients permanently discontinued asciminib, while asciminib was temporarily withheld in 34 (9.6%) patients due to the adverse reaction.

Anaemia occurred in 45 of 356 (12.6%) patients receiving asciminib, with grade 3 events occurring in 19 (5.3%) patients. Among the patients with anaemia ≥grade 3, the median time to first occurrence of events was 30 weeks (range: 0.4 to 207 weeks) with median duration of any occurring event of 0.9 weeks (95% CI, range: 0.4 to 2.1 weeks). Of the 45 patients with anaemia, asciminib was temporarily withheld in 2 (0.6%) patient due to the adverse reaction.
(see section 4.4)

Biochemistry abnormalities

Decrease in phosphate levels occurred as a laboratory abnormality in 16.7% (all grades) and 6.4% (grade 3/4) of 156 patients receiving asciminib at 40 mg twice daily.

Pancreatic disorders

Pancreatitis occurred in 9 of 356 (2.5%) patients receiving asciminib, 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, 2 (0.6%) permanently discontinued asciminib, while asciminib was temporarily withheld in 4 (1.1%) patients due to the adverse reaction. Asymptomatic elevation of serum lipase and amylase occurred in 76 of 356 (21.3%) patients receiving asciminib, 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, asciminib was permanently discontinued in 7 (2%) patients due to the adverse drug reaction. (see section 4.4)

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 Yellow Card and to Novartis by completing the AE form provided in the physician pack.

4.9 Overdose

There is limited experience of asciminib overdoseIn clinical studies, asciminib has been administered with a wide dose range from 10 mg .up to 280 mg twice daily.with no evidence of increasing toxicity.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, 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.

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

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

Pharmacodynamic effects

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 and 3.64 ms (upper bound of 90% CI: 4.68 ms) for the asciminib 80 mg once daily dose.

To the most recent data cut-off in the Phase III A2301 ASCEMBL study, two patients (1.3%) reported Electrocardiogram QTc prolongation. One was a grade 3 event. No clinical symptoms were associated to these events

Clinical efficacy and safety

Clinical study in previously treated 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) previously treated with two or

more tyrosine kinase inhibitors were evaluated in the multicentre, randomised, active--controlled and open--label phase III study ASCEMBL.

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 continued treatment until unacceptable toxicity or treatment failure occurred. Patients with the T315I and/or V299L mutation were excluded from study entry due to the expected limited activity of the comparator in patients with these mutations

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 treatment was 67 weeks (range: 0.1 to 162 weeks) for patients receiving asciminib and 30 weeks (range: 1 to 149 weeks) for patients receiving bosutinib.

The primary endpoint of the study was major molecular response rate (MMR) at 24 weeks, defined as BCR--ABL1 ratio ≤0.1% on International Scale. The key secondary endpoint of the study was MMR at 96 weeks (not yet reached). Other efficacy endpoints included MMR at 48 weeks, MMR by scheduled time points (24, 48 and 96 weeks), complete cytogenetic response (CCyR) (defined as no Philadelphia-positive metaphases in bone marrow with a minimum of 20 metaphases examined) by selected time points (24, 48, and 96 weeks), time to and duration of MMR, time to and duration of CCyR, time to treatment failure, progression free survival and overall survival.,

Results

The main efficacy outcomes are summarised in Table 4.

Table 4 MMR and CCyR at 24 and 48 Weeks in patients treated with two or more tyrosine kinase inhibitors (ASCEMBL)

	Asciminib 40 mg twice daily	**Bosutinib 500 mg once daily**	**Difference (95% CI)**	**p -value**
	N=157	**N=76**		
MMR rate, % (95% CI) at 24 weeks	25.48	13.16	12.241	0.0292
	(18.87, 33.04)	(6.49, 22.87)	(2.19, 22.30)	
MMR rate, % (95% CI) at 48 weeks	29.3	13.16		
	(22.32, 37.08)	(6.49, 22.87)		
	N=103[3]	**N=62[3]**		
CCyR rate, % (95% CI) at 24 weeks	40.78	24.19	17.3	0.019[2,4]
	(31.20, 50.90)	(14.22, 36.74)	(3.62, 30.99)	
CCyR rate, % (95% CI) at 48 weeks	39.81	20.97		
	(30.29, 49.92)	(11.66, 33.18)		

[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

[4] Nominal p -value

The Kaplan Meier estimated proportion of patients receiving asciminib and maintaining MMR for at least 48 weeks was 96.1% (95% CI: 85.4, 99.0).

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.

Table 5 MMR rate at 24 weeks from selected subgroup analysis

Subgroup	Asciminib n/N (%)	Bosutinib n/N (%)	Risk difference (95% CI)
Line of therapy of randomised treatment			
3	24/82 (29.30)	6/30 (20.0)	9.3 (-8.1 to 26.6)
4	11/44 (25.0)	4/29 (13.8)	11.2 (-6.7 to 29.1)
≥ 5	5/31 (16.1)	0/17 (0.0)	16.1 (3.2 to 29.1)
BCR-ABL 1 mutation at day 1 of week 1			
Unmutated	31/125 (24.8)	7/63 (11.1)	13.7 (2.8 to 24.5)
Mutated	6/17 (35.3)	2/8 (25)	10.3 (27.3 to 47.9)

n: The number of patients with response
N: The total number of patients in the subgroup and treatment group with response variable defined
95% Wald CI for risk difference. Risk difference is asciminib vs. bosutinib.
Patients with T315I and V299L BCR-ABL1 mutations or non-evaluable mutation assessment were excluded from subgroup analysis

Results from the X2101 phase I study for patients with Ph+ CML- CP receiving asciminib 80 mg once daily

In the first-in-human multicentre and open label Phase 1 study X2101, dose escalation of single agent asciminib at a wide range of doses (10 mg – 200 mg twice daily, and 80 mg – 200 mg once daily.) was evaluated. Maximum tolerated dose for single agent asciminib was not reached. No dose limiting toxicities were reported at 80 mg once daily dose.

A total of 18 patients in this study received asciminib at a dose of 80 mg once daily (n=18). The MMR rate by week 24 was reported in 4 patients (28.6%).The predicted MMR rate at 24 weeks for the asciminib 80 mg once daily dose is comparable to the MMR rate at 24 weeks observed in ASCEMBL with the asciminib 40 mg twice daily dose, based on exposure response analysis.

Elderly patients (65 years of age or above)
In ASCEMBL, 44 of the 233 (18.9%) patients were 65 years or older, while 6 (2.6%) were 75 years or older. In study X2101, 16 of the 48 (33.3%) patients were 65 years or older, while 4 (8.3%) were 75 years or older.

No overall differences in the safety or efficacy of Asciminib were observed between patients of 65 years of age or above and younger patients. There is an insufficient number of patients of 75 years of age or above to assess whether there are differences in safety or efficacy. (see section 4.2)

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} at steady state is 1781 ng/ml (23%) and 793 ng/ml (49%) following administration of asciminib at 80 mg once--daily and 40 mg

twice--daily doses, respectively. The geometric mean (geoCV%) of AUC_{tau} is 5262 ng*h/ml (48%) 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 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 is decreased by 62.3% with a high--fat meal and by 30% with a low-fat meal compared to the fasted state, independent of the dose (see sections 4.2 and 4.5).

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. Asciminib is 97.3% bound to human plasma proteins, independent of the dose.

Biotransformation

Asciminib is primarily metabolised via CYP3A4-mediated oxidation (36%), UGT2B7--mediated glucuronidation and UGT2B17--mediated glucuronidation (13.3% and 7.8%, respectively). PBPK models predict that asciminib biliary secretion via BCRP accounts for 31.1% of its total systemic clearance. 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 [14C]--labelled asciminib. Faecal elimination of unchanged asciminib accounts for 56.7% of the administered dose.

The oral total clearance (CL/F) of asciminib is 6.31 l/hour, based on population pharmacokinetic analysis. The terminal elimination half--life ($T_{½}$) of asciminib is between 7 and 15 hours.

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 average 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.

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 and P-gp with Ki values of 24.3 and 21.7 micromolar, respectively. Based on PBPK models, no clinically relevant interaction is expected for substrates of these transporters.

Inhibition of multiple pathways
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 multiple pathways may increase asciminib exposure.

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} are increased by 56% and 8%, respectively, in subjects with severe renal impairment compared to subjects with normal renal function, following oral administration of a single 40 mg dose of asciminib (see section 4.2). Population pharmacokinetics models indicate an increase in asciminib median steady-state AUC_{0-24h} 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} is increased by 22%, 3% and 66% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic function, following oral administration of a single 40 mg dose of asciminib (see section 4.2).

5.3 Preclinical safety data

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

Safety pharmacology

In safety pharmacology studies, asciminib did not have any effect on the central nervous and respiratory systems in rats at doses up to 600 mg/kg/day.

In an *in vitro* study, asciminib inhibited the human ether-à-go-go-related gene (hERG) channels with an IC_{50} of 11.4 micromolar. This value translates into a clinical safety margin at least 200fold or 100fold higher when compared to asciminib free C_{max} in patients at the 40 mg twicedaily or 80 mg oncedaily dose, respectively.

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.

Repeat dose toxicity

Repeat dose toxicity studies identified the pancreas, liver, haematopoietic system, adrenal gland and gastrointestinal tract as target organs of asciminib.

Pancreatic effects (serum amylase and lipase increases, acinar cell lesions) occurred in dogs at AUC exposures below those achieved in patients on 40 mg twice daily or 80 mg once 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 8- to 18--fold (dogs and monkeys) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily. These changes were fully reversible.

Effects on the 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 10- to 14--fold (dogs and monkeys) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily. These changes were fully reversible.

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

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

Carcinogenicity and mutagenicity

Asciminib did not have mutagenic, clastogenic or aneugenic potential either *in vitro* nor *in vivo*. Carcinogenicity studies have not been conducted with asciminib.

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, pregnant animals received oral doses of asciminib at 25, 150 and 600 mg/kg/day in rats and at 15, 50 and 300 mg/kg/day in rabbits during the period of organogenesis.

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

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

In the rat fertility study, asciminib did not affect reproductive function in male and female rats. A slight effect on male sperm motility and sperm count was observed at doses of 200 mg/kg/day, likely at AUC exposures 19-fold or 13-fold higher than those achieved in patients at the 40 mg twice-daily and 80 mg once-daily doses, 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 Cmax in plasma was 15-fold or 6-fold higher than the exposure in patients on 40 mg twice daily or 80 mg once daily, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Asciminib 20 mg film-coated tablets

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

Asciminib 40 mg film-coated tablets
Lactose monohydrate
Microcrystalline cellulose
Hydroxypropylcellulose
Croscarmellose sodium
Polyvinyl alcohol
Titanium dioxide (E171)
Magnesium stearate
Talc (E553b)
Colloidal silicon dioxide
Iron oxide (E172, black and red)
Lecithin (E322)
Xanthan gum (E415)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months
After first opening of the HDPE bottle: 3 months. Do not store above 25°C.

6.4 Special precautions for storage

Do not store above 25°C.

. For storage conditions after first opening of the medicinal product, see section 6.3

6.5 Nature and contents of container

Screw cap HDPE Bottle containing 30 film-coated tablets.

6.6 Special precautions for disposal

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

7. Scientific Opinion Holder

Novartis Pharmaceuticals UK Limited
2nd Floor, The WestWorks Building
White City Place
195 Wood Lane
London
W12 7FQ
UNITED KINGDOM

8. EAMS NUMBER

00101/0006

9. DATE OF SCIENTIFIC OPINION
To be completed by the MHRA

Additional information

The prescribing physician should carefully read the information provided in the rest of this document. Each prescribing physician interested in enrolling a patient in the programme should submit an initial request via the Novartis Grants, External Studies and Managed Access System (GEMS) via https://www.novartis.com/our-focus/healthcare-professionals/managed-access-programs. The prescribing physician will be required to register with Novartis Managed Access Programme Portal and patient details will need to be entered into the portal for each individual application. A unique initial request ID will be assigned to each eligible patient enrolled onto EAMS. This unique initial request ID will be used for future drug re-supply requests and adverse event reporting.

Novartis will request the baseline demographics data at the time of initial application and additional information at the time of re-supply request. The purpose of this data collection (registry) is to ensure the safe and effective use of the product in line with the EAMS Treatment protocols and EAMS scientific opinion.

The prescribing physician will be requested to provide the following information by completing an Initial Application and Drug Supply Request for each patient to be enrolled on to the programme for eligibility assessment:

- Month and year of birth
- Gender
- Disease/condition to be treated
- Additional information e.g. previous treatment history, concomitant medication and response data.

Novartis will review the application for eligibility. If a patient is deemed eligible for EAMS, Novartis will assign a unique EAMS number and communicate it to the requesting physician.

An EAMS Agreement Letter with Novartis will be required to be signed by the prescribing Physician, the Trust and Novartis. The EAMS Agreement Letter will be signed either on a per patient basis or on a Trust basis. Drug supply will only be shipped once a fully executed EAMS Agreement Letter and attestation has been completed.

For patients approved under this scheme and requiring ongoing drug supply, the HCPs will be required to complete the Re-supply Form on GEMS to request further cycles of treatment. The HCPs will also be asked for confirmation that they understand and agree to comply with their obligations to report all Adverse Events (AEs) and Special Situations (SSs) to Novartis and that they are complying with this requirement. They will be also asked to confirm that all AEs and SSs experienced since the last re-supply request have been reported or there are no new AEs to report. HCPs will also be requested to confirm at the time of first re-supply request if the patient alert card has been given to the patient and the patient understands the purpose of the Patient

Alert Card. HCPs will also be requested to confirm that patient agrees to carry the Patient Alert Card with them at all times.

HCPs should also report all known and suspected adverse drug reactions (ADRs) (i.e. those AEs which are related to the use of asciminib) to the MHRA via the Yellow Card scheme, www.mhra.gov.uk/yellowcard. In addition to this, the EAMS patient ID number should be provided in the report narrative to help the MHRA identify that the AE is related to EAMS product and to help Novartis link the AE report to the correct EAMS patient.

A 3-monthly periodic safety report will be submitted to the MHRA to summarise data on safety and usage of asciminib under the scheme.

For NHS England only - additional requirement for registering a patient:

Following notification from Novartis of eligibility approval, the physician must complete a Blueteq form online and register their patient with NHS England, which is located at https://www.blueteq-secure.co.uk/Trust/default.aspx. Once the Blueteq form has been completed, an approval email will be received by the user and pharmacy stating the request has been approved, also stating an EAMS number. This EAMS number must be communicated back to Novartis.

Contact information: obu.medical@novartis.com

AE reporting: uk.patientsafety@novartis.com