NOVARTIS

BACRELBA

(asciminib hydrochloride)

20 and 40 mg film-coated tablets

Professional Information

Document status: Final

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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

BACRELBA™ 20 mg film-coated tablets

BACRELBA™ 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Contains sugar: lactose

BACRELBA 20 mg, contains 43.11 mg of lactose per film-coated tablet.

BACRELBA 40 mg, contains 86.22 mg of lactose per film-coated tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

20 mg film-coated tablets:

Pale yellow, round, biconvex, film-coated tablets with bevelled edges, approximately 6.2 mm diameter, unscored, debossed with “Novartis” logo on one side and “20” on the other side.

40 mg film-coated tablets:

Violet white, round, biconvex, film-coated tablets with bevelled edges, approximately 8.2 mm diameter, unscored, debossed with “Novartis” logo on one side and “40” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

BACRELBA is indicated for the treatment of adult patients with:

- Newly diagnosed or previously treated Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP).
- Ph+ CML in CP harbouring the T315I mutation.

4.2 Posology and method of administration

Posology

Treatment with BACRELBA should be initiated by a medical practitioner experienced in the use of anticancer therapies.

General target population

Ph+ CML-CP

The recommended total daily dose of BACRELBA is 80 mg. BACRELBA can be taken orally either as 80 mg once daily at approximately the same time each day, or as 40 mg twice daily at approximately 12-hour intervals.

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

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

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

Ph+ CML-CP harbouring the T315I mutation

The recommended dose of BACRELBA is 200 mg taken orally twice daily at approximately 12-hour intervals.

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

Missed dose

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

Twice-daily dosage regimens: If a BACRELBA dose is missed by more than approximately 6 hours, it should be skipped and the next dose should be taken as scheduled.

Dose modifications

Ph+ CML-CP

For the management of adverse drug reactions, BACRELBA dose can be reduced based on individual safety and tolerability, as described in Table 1. If adverse drug reactions are effectively managed, BACRELBA may be resumed as described in Table 1.

BACRELBA should be permanently discontinued in patients unable to tolerate a total daily dose of 40 mg.

Ph+ CML-CP harbouring the T315I mutation

For the management of adverse drug reactions, BACRELBA dose can be reduced based on individual safety and tolerability, as described in Table 1. If adverse drug reactions are effectively managed, BACRELBA may be resumed as described in Table 1.

BACRELBA should be permanently discontinued in patients unable to tolerate a dose of 160 mg twice daily.

Table-1 BACRELBA dosage modification

Starting dose	**Reduced dose**	**Resumed dose**
80 mg once daily	40 mg once daily	80 mg once daily
40 mg twice daily	20 mg twice daily	40 mg twice daily
200 mg twice daily	160 mg twice daily	200 mg twice daily

The recommended dosage modification for the management of selected adverse drug reactions is shown in Table 2.

Table-2 BACRELBA dosage modification for the management of selected adverse drug reactions

Adverse drug reaction	**Dosage modification**
Thrombocytopenia and/or neutropenia	
ANC[1] < 1 x 10^9/L and/or PLT[2] < 50 x 10^9/L	Withhold BACRELBA until resolved to ANC ≥ 1 x 10^9/L and/or PLT ≥ 50 x 10^9/L. If resolved: • Within 2 weeks: resume BACRELBA at starting dose. • After more than 2 weeks: resume BACRELBA at reduced dose. For recurrent severe thrombocytopenia and/or neutropenia, withhold BACRELBA until resolved to ANC ≥ 1 x 10^9/L and PLT ≥ 50 x 10^9/L, then resume at reduced dose.
Asymptomatic amylase and/or lipase elevation	
Elevation > 2 x ULN[3]	Withhold BACRELBA until resolved to < 1.5 x ULN. • If resolved: resume BACRELBA at reduced dose. If reactions reoccur at reduced dose, permanently discontinue BACRELBA. • If not resolved: permanently discontinue BACRELBA. Perform diagnostic tests to exclude pancreatitis.

Non-hematologic adverse drug reactions	
Grade 3 or higher[4] adverse reactions	Withhold BACRELBA until resolved to Grade 1 or lower[4]. • If resolved: resume BACRELBA at a reduced dose. • If not resolved: permanently discontinue BACRELBA.

[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.

Special populations

Renal impairment

No dose adjustment is required in patients with mild, moderate or severe renal impairment receiving BACRELBA. Caution should be exercised in patients with severe renal impairment receiving BACRELBA 200 mg twice daily dose (see section 5).

Hepatic impairment

No dose adjustment is required in patients with mild, moderate or severe hepatic impairment receiving BACRELBA. Caution should be exercised in patients with severe hepatic impairment receiving BACRELBA 200 mg twice daily dose (see section 5).

Paediatric patients (below 18 years)

The safety and efficacy of BACRELBA in paediatric patients (below 18 years) has not been established.

Elderly population (65 years of age or above)

No dose adjustment is required in patients 65 years of age or above.

Method of administration

BACRELBA should be taken orally without food. Food consumption should be avoided for at least 2 hours before and 1 hour after taking BACRELBA (see section 4.5 and 5).

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

4.3 Contraindications

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

Based on the severity of thrombocytopenia and/or neutropenia, the BACRELBA dose should be reduced, temporarily withheld or permanently discontinued as described in Table 2 (see section 4.2).

Pancreatic toxicity

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

Serum lipase and amylase levels should be assessed monthly during treatment with BACRELBA, 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 BACRELBA dose should be reduced, temporarily withheld or permanently discontinued as described in Table 2 (see section 4.2).

QT prolongation

Electrocardiogram QT prolongation occurred in patients receiving BACRELBA (see section 4.8). It is recommended that an electrocardiogram is performed prior to the start of treatment with BACRELBA and monitored during treatment as clinically indicated. Hypokalaemia and hypomagnesaemia should be corrected prior to BACRELBA administration and monitored during treatment as clinically indicated.

Caution should be exercised when administering BACRELBA at a total daily dose of 80 mg concomitantly with medicines known to cause torsades de pointes. Co-administration of BACRELBA at 200 mg twice daily concomitantly with medicines known to cause torsades de pointes should be avoided (see section 4.5 and 5).

Hypertension

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

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

Hypersensitivity

Hypersensitivity events occurred in 169 of 556 (30.4 %) patients receiving BACRELBA. with ≥ grade 3 events reported in 8 (1.4 %) 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 BACRELBA. HBV carriers who require treatment with BACRELBA should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Embryo-foetal toxicity

Based on findings from animal studies, BACRELBA can cause foetal harm when administered to a pregnant woman. Pregnant women and females of reproductive potential should be advised of the potential risk to a foetus if BACRELBA is used during pregnancy or if the patient becomes pregnant while taking BACRELBA. The pregnancy status of females of reproductive potential should be verified prior to starting treatment with BACRELBA. Sexually active females of reproductive potential should use effective contraception during treatment with BACRELBA and for at least 3 days after the last dose (see section 4.6).

Lactose

BACRELBA contains lactose (see section 2). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose- galactose malabsorption should not use BACRELBA.

BACRELBA contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet that is to say essentially “sodium free”.

4.5 Interaction with other medicines and other forms of interaction

Medicines that may increase asciminib plasma concentrations

Strong CYP3A4 inhibitors

Physiologically-based pharmacokinetic (PBPK) models predict that co-administration of BACRELBA at 200 mg twice daily with a strong CYP3A4 inhibitor (clarithromycin) would increase asciminib AUC_{tau} and C_{max} by 77 % and 49 %, respectively.

Caution should be exercised during concomitant administration of BACRELBA 200 mg twice daily with strong CYP3A4 inhibitors including but not limited to clarithromycin, telithromycin, troleandomycin, itraconazole, ketoconazole, voriconazole, ritonavir, indinavir, nelfinavir or saquinavir. Dose adjustment of BACRELBA is not required.

Medicines that may decrease asciminib plasma concentrations

Strong CYP3A4 inducers

Co-administration of a strong CYP3A4 inducer (rifampicin) decreased asciminib AUC_{inf} by 14.9 %, while increasing asciminib C_{max} by 9 % in healthy subjects receiving a single BACRELBA dose of 40 mg.

PBPK models predict that co-administration of asciminib at 80 mg once daily with rifampicin would decrease asciminib AUC_{tau} and C_{max} by 52 % and 23 %, respectively, while co-administration of asciminib at 200 mg twice daily with rifampicin would decrease asciminib AUC_{tau} and C_{max} by 63 % and 47 %, respectively.

Caution should be exercised during concomitant administration of BACRELBA at all recommended doses with strong CYP3A4 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin or St. John's wort (*Hypericum perforatum*).
Dose adjustment of BACRELBA is not required.

Medicines that may have their plasma concentrations altered by asciminib

CYP3A4 substrates with narrow therapeutic index

Co-administration of asciminib with a CYP3A4 substrate (midazolam) increased midazolam AUC_{inf} and C_{max} by 28 % and 11 %, respectively, in healthy subjects receiving BACRELBA 40 mg twice daily.

PBPK models predict that co-administration of asciminib at 80 mg once daily would increase midazolam AUC_{inf} and C_{max} by 24 % and 17 %, respectively, while co-administration of asciminib at 200 mg twice daily would increase midazolam AUC_{inf} and C_{max} by 88 % and 58 %, respectively.

Caution should be exercised during concomitant administration of BACRELBA at all recommended doses 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). Dose adjustment of BACRELBA is not required.

CYP2C9 substrates

Co-administration of asciminib with a CYP2C9 substrate (warfarin) increased S-warfarin AUC_{inf} and C_{max} by 41 % and 8 %, respectively, in healthy subjects receiving BACRELBA 40 mg twice daily.

PBPK models predict that co-administration of asciminib at 80 mg once daily would increase S-warfarin AUC_{inf} and C_{max} by 52 % and 4 %, respectively, while co-administration of asciminib at 200 mg twice-daily would increase S-warfarin AUC_{inf} and C_{max} by 314 % and 7 %, respectively.

Caution should be exercised during concomitant administration of BACRELBA at 80 mg total daily dose with CYP2C9 substrates known to have a narrow therapeutic index, including, but not limited to, phenytoin or warfarin (see section 5). Dose adjustment of BACRELBA is not required.

Concomitant administration of BACRELBA at 200 mg twice daily with CYP2C9 sensitive substrates and CYP2C9 substrates known to have a narrow therapeutic index should be avoided and alternative medications should be considered (see section 5). If co-administration cannot be avoided, the CYP2C9 substrates dose should be reduced. If co-administration with warfarin cannot be avoided, the frequency of international normalized ratio (INR) monitoring should be increased as the anti-coagulant effect of warfarin may be enhanced.

Substrates of OATP1B, of BCRP or of both transporters

PBPK models predict that co-administration of asciminib at 40 mg twice daily and 80 mg once daily with an OATP1B substrate (pravastatin) would increase pravastatin C_{max} by 43 % and 63 % and AUCinf by 37 % and 51 %, respectively, while co-administration of asciminib at 200 mg twice daily would increase pravastatin Cmax and AUCinf by 141 % and 137 %, respectively.

PBPK models predict that co-administration of asciminib at 40 mg twice daily and 80 mg once daily with an OATP1B, CYP3A4 and P-gp substrate (atorvastatin) would increase atorvastatin Cmax by 97 % and 143 % and AUCinf by 81 % and 122%, respectively, while co-administration of asciminib at 200 mg twice daily would increase atorvastatin Cmax and AUCinf by 300 % and 326 %, respectively.

PBPK models predict that co-administration of asciminib at 40 mg twice daily and 80 mg once daily with a BCRP substrate (sulfasalazine) would increase sulfasalazine Cmax by 334 % and 342 % and AUCinf by 333 % and 340 %, respectively, while co-administration of asciminib at 200 mg twice daily would increase sulfasalazine Cmax and AUCinf by 353 % and 359 %, respectively.

PBPK models predict that co-administration of asciminib at 40 mg twice daily and 80 mg once daily with a BCRP and OATP1B substrate (rosuvastatin) would increase rosuvastatin Cmax by 453 % and 530 % and AUCinf by 190 % and 202 %, respectively, while co-administration of asciminib at 200 mg twice daily would increase rosuvastatin Cmax and AUCinf by 732 % and by 311 %, respectively.

Caution should be exercised during concomitant administration of BACRELBA at all recommended doses with substrates of OATP1B, BCRP or both transporters, including, but not limited to sulfasalazine, methotrexate, pravastatin, atorvastatin, pitavastatin, rosuvastatin and

simvastatin. Refer to OATP1B and BCRP substrates' dose reductions, as recommended in their prescribing information.

Concomitant administration of BACRELBA at all recommended doses with rosuvastatin should be avoided and alternative statins should be considered. If co-administration cannot be avoided, rosuvastatin dose should be reduced, as recommended in its prescribing information (see section 5.2).

P-gp substrates

Co-administration of BACRELBA with a medicine that is a substrate of P-gp may result in a clinically relevant increase in the plasma concentration of P-gp substrates, where minimal concentration changes may lead to serious toxicities (e.g. P-gp substrates with narrow therapeutic index such as digoxin).

QT prolongation

Caution should be exercised during concomitant administration of BACRELBA at 80 mg total daily dose and medicines known to cause torsades de pointes, including, but not limited to, bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozide (see section 5).

Concomitant administration of BACRELBA at 200 mg twice-daily dose and medicines known to cause torsades de pointes should be avoided (see section 5).

Drug-food interactions

The bioavailability of asciminib decreases on consumption of food (see sections 4.2 and 5).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception

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

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.

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). BACRELBA can cause foetal harm when administered to a pregnant woman.

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.

Breastfeeding

It is not known if asciminib is transferred into human milk after administration of BACRELBA. There are no data on the effects of asciminib on the breastfed child or on milk production.

Because of the potential for serious adverse drug reactions in the breastfed child, breast-feeding is not recommended during treatment with BACRELBA and for at least 3 days after the last dose.

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

Patients experiencing dizziness, visual impairment or other undesirable effects with a potential impact on the ability to safely drive or use machines should refrain from these activities as long as these undesirable effects persist. (See section 4.8).

4.8 Undesirable effects

Summary of safety profile

The overall safety profile of BACRELBA has been evaluated in 556 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 J12301 (ASC4FIRST) (N = 200 newly diagnosed Ph+

CML-CP patients), the pivotal phase III study A2301 (ASCEMBL) (N = 156 Ph+ CML-CP patients previously treated with two or more TKIs) and the phase I study X2101, including patients with:

- Ph+ CML-CP (N = 115),
- Ph+ CML-CP harbouring the T315I mutation (N = 70),
- Ph+ CML-AP (N = 15).

The safety pool (N = 556) includes patients receiving BACRELBA at doses ranging from 10 to 200 mg twice daily and 80 to 200 mg once daily. In the pooled dataset, the median duration of exposure to BACRELBA was 83.29 weeks (range: 0.1 to 439 weeks), with 79.3 % of patients exposed for at least 48 weeks and 42.4 % of patients exposed for at least 96 weeks, respectively.

The most common adverse drug reactions of any grade (incidence ≥ 20 %) in patients receiving BACRELBA were musculoskeletal pain (32.9 %), thrombocytopenia (28.1 %), fatigue (25 %), upper respiratory tract infections (23.7 %), headache (21.8 %), neutropenia (21.6 %), and diarrhoea (22.5 %). The most common adverse drug reactions of ≥ grade 3 (incidence ≥ 5 %) in patients receiving BACRELBA were thrombocytopenia (16.5 %), neutropenia (13.7 %), increased pancreatic enzymes (9.4 %) and hypertension (8.6 %).

Serious adverse drug reactions occurred in 9.5 % of patients receiving BACRELBA. The most frequent serious adverse drug reactions (incidence ≥ 1 %) were pleural effusion (1.6 %), lower

respiratory tract infections (1.4 %), thrombocytopenia (1.3 %), pancreatitis (1.1 %) and pyrexia (1.1 %).

Tabulated summary of adverse reactions

Adverse drug reactions from clinical studies (Table 3) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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 drug reactions observed with BACRELBA in clinical studies

System organ class	**Frequency category**	**Adverse reaction**
Infections and infestations	Very common	Upper respiratory tract infection[3]
	Common	Lower respiratory tract infection[4], influenza
Blood and lymphatic system disorders	Very common	Thrombocytopenia[5], neutropenia[6], anaemia[7]
	Uncommon	Febrile neutropenia

Immune system disorders	Uncommon	Hypersensitivity
Endocrine disorders	Common	Hypothyroidism[8]
Metabolism and nutrition disorders	Very common	Dyslipidaemia[9]
	Common	Decreased appetite
Nervous system disorders	Very common	Headache, dizziness
Eye Disorders	Common	Vision blurred, dry eye
Cardiac disorders	Common	Palpitations
Vascular disorders	Very common	Hypertension[10]
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Pleural effusion, dyspnoea, non-cardiac chest pain

Gastrointestinal disorders	Very common	Pancreatic enzymes[11] increased, vomiting, diarrhoea, nausea, abdominal pain[12]
	Common	Pancreatitis[13]
Hepatobiliary disorders	Very common	Hepatic enzymes increased[14]
	Common	Blood bilirubin increased[15]
Skin and subcutaneous tissue disorders	Very common	Rash[16], pruritus
	Common	Urticaria
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[17], Arthralgia
General disorders and administration site conditions	Very common	Fatigue[18]
	Common	Pyrexia[20], oedema[19]
Investigations	Common	Blood creatine phosphokinase increased,

	Uncommon	Electrocardiogram QT prolonged

1 Asciminib median duration of exposure: 83.29 weeks (range: 0.1 to 439 weeks)

2 Frequency based on the safety pool (J12301, A2301 and X2101) for asciminib all grade reactions (N=556).

3 Upper respiratory tract infection includes: upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis;

4 Lower respiratory tract infections includes: pneumonia, bronchitis and tracheobronchitis;

5 Thrombocytopenia includes: thrombocytopenia and platelet count decreased;

6 Neutropenia includes: neutropenia and neutrophil count decreased;

7 Anaemia includes: anaemia and haemoglobin decreased;

8 Hypothyroidism includes: hypothyroidism, autoimmune thyroiditis, blood thyroid stimulating hormone increased, autoimmune hypothyroidism and primary hypothyroidism

9 Dyslipidaemia includes: hypertriglyceridaemia, blood cholesterol increased, hypercholesterolaemia, blood triglycerides increased, hyperlipidaemia and dyslipidaemia;

10 Hypertension includes: hypertension and blood pressure increased;

11 Pancreatic enzymes increased includes: lipase increased, amylase increased and hyperlipasaemia;

12 Abdominal pain includes: abdominal pain and abdominal pain upper;

13 Pancreatitis includes: pancreatitis and pancreatitis acute;

14 Hepatic enzyme increased includes: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, and hypertransaminasaemia;

15 Blood bilirubin increased includes: blood bilirubin increased, bilirubin conjugated increased and hyperbilirubinaemia;

16 Rash includes: rash, rash maculopapular and rash pruritic;

17 Musculoskeletal pain includes: pain in extremity, back pain, myalgia, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain, and musculoskeletal discomfort;

18 Fatigue includes: fatigue and asthenia;

19 Oedema includes: oedema and oedema peripheral;

20 Pyrexia includes: pyrexia and body temperature increased.

Description of selected adverse drug reactions

Myelosuppression

Thrombocytopenia occurred in 156 of 556 (28.1 %) patients receiving BACRELBA, with grade 3 and 4 reactions reported in 39 (7 %) and 53 (9.5 %) of patients, respectively. Among the patients with thrombocytopenia ≥ grade 3, the median time to first occurrence of reactions was 6 weeks (range: 0.14 to 64.14 weeks) with median duration of any occurring event of 1.57 weeks (95 % CI, range: 1.43 to 2 weeks). BACRELBA was permanently discontinued in 119 (2 %) of patients, while BACRELBA was temporarily withheld in 70 (12.6 %) patients due to thrombocytopenia.

Neutropenia occurred in 120 of 556 (21.6 %) patients receiving BACRELBA, with grade 3 and 4 reactions reported in 41 (7.4 %) and 35 (6.3 %) patients, respectively. Among the patients with neutropenia ≥ grade 3, the median time to first occurrence of reactions was 7.07 weeks (range: 0.4 to 180.14 weeks) with median duration of any occurring reactions of 1.86 weeks (95 % CI, range: 1.29 to 2 weeks). BACRELBA was permanently discontinued in 7 (1.3 %) of patients, while BACRELBA was temporarily withheld in 52 (9.4 %) patients due to the neutropenia.

Anaemia occurred in 70 of 556 (12.6 %) patients receiving BACRELBA, with grade 3 reaction occurring in 22 (4 %) patients. Among the patients with anaemia ≥ grade 3, the median time to first occurrence of reaction was 22.21 weeks (range: 0.14 to 207 weeks) with median duration of any occurring reaction of 0.79 weeks (95 % CI, range: 0.29 to 1.71 weeks). BACRELBA was temporarily withheld in 2 (0.4 %) due to anaemia.

Pancreatic toxicity

Pancreatitis occurred in 11 of 556 (2 %) patients receiving asciminib with grade 3 reactions occurring in 6 (1.1 %) patients. Asciminib was permanently discontinued in 3 (0.5%) patients, while asciminib was temporarily withheld in 6 (1.1 %) patients due to pancreatitis. Asymptomatic elevation of serum lipase and amylase occurred in 107 of 556 (19 %) patients receiving asciminib, with grade 3 and 4 reactions occurring in 41 (7.4%) and 11 (2%) patients, respectively. Asciminib was permanently discontinued in 11 (2 %) patients due to asymptomatic elevation of serum lipase and amylase.

QT prolongation

Electrocardiogram QT prolongation occurred in 5 of 556 (0.9 %) patients receiving asciminib. In the ASCEMBL clinical study, one patient had a prolonged QTcF greater than 500 ms together with more than 60 ms QTcF increase from baseline, and another patient had prolonged QTcF with more than 60 ms QTcF increase from baseline (See sections 4.4, 4.5 and 5.1).

Hypertension

Hypertension occurred in 88 of 556 (15.8 %) patients receiving asciminib, with grade 3 and 4 reactions reported in 47 (8.5 %) and 1 (0.2 %) patient, respectively. Among the patients with hypertension ≥ grade 3, the median time to first occurrence of reactions was 21.29 weeks (range: 0.14 to 365 weeks). Asciminib was temporarily withheld in 5 (0.9 %) patients due to the adverse reaction (see section 4.4).

Laboratory abnormalities

In the ASCEMBL study, decrease in phosphate levels occurred as a laboratory abnormality in 17.9 % (all grades) and 7.1 % (grade ¾) of 156 patients receiving asciminib at 40 mg twice daily. In the ASC4FIRST study, decrease in phosphate levels based on normal ranges occurred as a laboratory abnormality in 13 % (all grades) of 200 patients receiving asciminib at 80 mg once daily.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine

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

Category and class: A 26 Cytostatic agents

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 pocket.

Pharmacodynamics (PD)

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 or the T315I mutant form of BCR-ABL1, asciminib inhibits cell growth with mean IC_{50} values of 0.61 ±0.21 and 7.64 ±3.22 nanomolar, respectively.

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

Cardiac electrophysiology

Asciminib treatment is associated with an exposure-related prolongation of the QT interval. The correlation between asciminib concentration and the estimated 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 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 asciminib 40 mg twice-daily dose, 3.64 ms (upper bound of 90 % CI: 4.68 ms) for the 80 mg once-daily dose and 5.37 ms (upper bound of 90 % CI: 6.77 ms) for the 200 mg twice-daily dose.

Clinical efficacy and safety

Newly diagnosed Ph+ CML-CP

The clinical efficacy and safety of asciminib in the treatment of patients with newly diagnosed Philadelphia chromosome-positive myeloid leukaemia in chronic phase (Ph+ CML-CP) were demonstrated in the multi-centre, randomized, active-controlled and open-label phase III study ASC4FIRST.

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

asciminib or IS-TKIs, and continued treatment until unacceptable toxicity or treatment failure occurred.

Patients were 36.8 % female and 63.2 % male, with median age 51 years (range: 18 to 86 years). Of the 405 patients, 23.5 % were 65 years or older, while 6.2% were 75 years or older. Patients were Caucasian (53.8 %), Asian (44.4 %), Black (1 %) and 0.7 % unknown. The demographic characteristics within the 1G (N = 203) and the 2G TKIs (N = 202) strata were:

- Median age: 55 years and 43 years, respectively;
- ELTS high risk group: 8.4 % and 13.9 %, respectively;
- Framingham cardiovascular disease high risk group: 35.5 % and 17.8 %, respectively.

The demographic characteristics were balanced across asciminib and IS-TKIs, as well as across the two arms within the 1G and 2G TKIs strata.

Of the 405 patients, 200 received asciminib, while 201 received IS-TKIs. Of the 201 patients receiving IS-TKIs, 99 received 1G and 102 received 2G TKIs. Four patients did not receive any treatment.

The median duration of treatment was 69.8 weeks (range: 0.7 to 107.7 weeks) for patients receiving asciminib and 64.3 weeks (range: 1.3 to 103.1 weeks) for patients receiving IS-TKIs. By 48 weeks, 90 % of patients on asciminib and 80.6 % of patients on IS-TKIs were still receiving treatment.

The study had multiple primary objectives assessing major molecular response rate (MMR) at 48 weeks. One primary objective evaluated asciminib compared to IS-TKIs. The other primary objective evaluated asciminib compared to IS-TKIs, within the 1G TKI stratum. A secondary

objective evaluated MMR at 48 weeks evaluating asciminib compared to IS-TKIs, within the 2G TKIs stratum.

The main efficacy outcomes from ASC4FIRST are summarized in Table 4.

Table 4 Efficacy results in patients with newly diagnosed Ph+ CML-CP (ASC4FIRST)

Asciminib 80 mg once daily		IS-TKIs 100-400 mg once or twice daily			Difference (95% CI)[1]	p-value
		All patients (N = 204)	1G TKI stratum (N = 102)	2G TKIs stratum (N = 102)		
MMR rate, % (95 % CI) at 48 weeks						
All patients (N = 201)	67.66 (60.72, 74.07)	49.02 (41.97, 56.10)			18.88 (9.59, 28.17)	<0.001[2]
1G TKI stratum (N = 101)	69.31 (59.34, 78.10)		40.2 (30.61,50.37)		29.55 (16.91, 42.18)	<0.001[3]
2G TKIs stratum (N = 100)	66 (55.85, 75.18)			57.84 (47.66, 67.56)	8.17 (-5.14, 21.47)	

Abbreviations: MMR, major molecular response (BCR::ABL1^{IS} ≤ 0.1%); IS-TKIs, investigator-selected tyrosine kinase inhibitors; 2G TKIs, second generation tyrosine kinase inhibitors; PRS-TKI, pre-randomization selection of TKI.

[1] Estimated using a common risk difference stratified by PRS-TKI and baseline ELTS risk groups.

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

[3] Adjusted p-value using a Cochran-Mantel-Haenszel 1-sided test stratified by baseline ELTS risk groups

The predicted MMR rate at 48 weeks for the asciminib 40 mg twice-daily dose is comparable to the MMR rate at 48 weeks observed in ASC4FIRST with the asciminib 80 mg once-daily dose, based on exposure-response analysis.

Median time to MMR in patients receiving asciminib, IS-TKIs, IS-TKIs within the 1G TKI stratum, and IS-TKIs within the 2G TKIs stratum were: 24.3 weeks (95 % CI: 24.1 to 24.6 weeks), 36.4 weeks (95 % CI: 36.1 to 48.6 weeks), 48.6 weeks (95 % CI: 36.1 to 59.6 weeks), and 36.1 weeks (95 % CI: 24.4 to 48.1 weeks), respectively.

MMR rates at 48 weeks by ELTS risk group in patients receiving asciminib, IS-TKIs, IS-TKIs within the 1G TKI stratum, and IS-TKIs within the 2G TKIs stratum were: 72.1 %, 57.6 %, 50 % and 65.6 % for low risk, respectively; 64.3 %, 36.8 %, 26.7 % and 48.2 % for intermediate risk, respectively; 52.2 %, 31.8 %, 12.5 % and 42.9 % for high risk, respectively.

By 48 weeks, MR4.0 achieved by patients receiving asciminib, IS-TKIs, IS-TKIs within the 1G TKI stratum, and IS-TKIs within the 2G TKIs stratum was: 40.8 %, 22.1 %, 15.7 %, and 28.4 %, respectively. By 48 weeks, MR4.5 achieved by patients receiving asciminib, IS-TKIs, IS-TKIs within the 1G TKI stratum and IS-TKIs within 2G TKIs stratum was: 19.9 %, 11.8 %, 5.9 %, and 17.7 %, respectively.

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

The clinical efficacy and safety of asciminib in the treatment of patients with Ph+ CML-CP previously treated with two or more tyrosine kinase inhibitors were demonstrated in the multicentre, randomized, active-controlled and open-label phase III study ASCEMBL.

In this study, a total of 233 patients were randomized in a 2:1 ratio and stratified according to major cytogenetic response (MCyR) status at baseline to receive either Asciminib 40 mg twice daily (N = 157) or a second generation [2G] TKI once daily (N = 76). Patients continued treatment until unacceptable toxicity or treatment failure occurred.

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 asciminib and 31 weeks (range: 1 to 188 weeks) for patients receiving the 2G TKI.

The predicted Major Molecular Response (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.

Table - 5 Efficacy results in Ph+ CML-CP patients previously treated with two or more tyrosine kinase inhibitors (ASCEMBL)

	BACRELBA 40 mg twice daily	**2G TKI 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]
CCyR rate, %	**N = 103**[3] 40.78 (31.20, 50.9)	**N = 62**[3]	17.3 (3.62, 30.99)	0.019[2,4]

(95 % CI) at 24 weeks		24.19 (14.22, 36.74)		

[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*

In ASCEMBL, 12.7 % of patients treated with BACRELBA and 13.2 % of patients receiving the 2G TKI 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 BACRELBA with or without any BCR-ABL1 mutation at baseline, respectively. MMR at 24 weeks was observed in 25 % and 11.1 % of patients receiving bosutinib with or without any mutation at baseline, respectively. The MMR rate at 24 weeks in patients in whom the randomized treatment represented the third, fourth, fifth or more line of TKI was 29.3 %, 25 %, and 16.1 % in patients treated with BACRELBA and 20 %, 13.8 %, and 0 % in patients receiving the 2G TKI, respectively.

The MMR rate at 48 weeks was 29.3 % (95 % CI: 22.32, 37.08) in patients receiving BACRELBA and 13.2 % (95 % CI: 6.49, 22.87) in patients receiving the 2G TKI. The Kaplan

Meier estimated proportion of patients receiving BACRELBA and maintaining MMR for at least 48 weeks was 96.1 % (95 % CI: 85.4, 99).

Patients with Ph+ CML-CP harbouring the T315I mutation

The clinical efficacy and safety of asciminib in the treatment of patients with Ph+ CMLCP harbouring the T315I mutation were assessed in the first in human, multicentre, open label phase I study X2101.

In this study, a total of 185 patients with Ph+ CML-CP without (N = 115) or with (N = 70) the T315I mutation received BACRELBA at doses ranging from 10 to 200 mg twice daily or 80 to 200 mg once daily. Among these, 48 patients with Ph+ CML-CP harbouring the T315I mutation received BACRELBA at a dose of 200 mg twice daily. Patients continued treatment until unacceptable toxicity or treatment failure occurred.

Patients who had previously received 1, 2, 3, 4 and 5 or more TKIs were 16.7 %, 31.3 %, 35.4 %, 14.6 % and 2.1 %, respectively. The median duration of treatment was 108 weeks (range: 2 to 215 weeks). MMR by 24 weeks was achieved in 42.2% of the evaluable patients (N = 45) treated with BACRELBA (95 % CI: 27.7-57.8 %).

5.2 Pharmacokinetic properties

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 asciminib at 80 mg once-daily and 40 mg twice-daily doses, respectively. The geometric mean (geoCV %) of C_{max} at steady state is 5642 ng/ml (40 %) following administration of asciminib at 200 mg twice-daily dose. The geometric mean (geoCV %) of AUCtau is 5262 ng*h/ml (48%) following administration of asciminib at 40 mg twice-daily dose.

PBPK models predict that the asciminib absorption is approximately 100 %, while bioavailability is approximately 73 %.

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

Food effect

Food consumption decreases asciminib bioavailability, with a high-fat meal having a higher impact on asciminib pharmacokinetics than a low-fat meal. Asciminib AUC is decreased by 62.3 % with a high-fat meal and by 30 % with a low-fat meal compared to the fasted state, independent of the dose (see sections 4.2 and 4.5).

Distribution

Asciminib apparent volume of distribution at steady state is 111 L, 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/metabolism

Asciminib is primarily metabolized via CYP3A4-mediated oxidation (36 %), UGT2B7- 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 accumulation half-life ($T_{1/2}$) of asciminib is 5.2 hours at 80 mg total daily dose.

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. In addition, asciminib reversibly inhibits CYP2C8 and CYP2C19 at plasma concentrations reached at 200 mg twice-daily dose.

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. Based on PBPK models, asciminib increases the exposure to P-gp OATP1B and BCRP substrates (see section 4.5). The clinical relevance of the interaction with OCT1 is currently unknown at asciminib 200 mg twice-daily dose.

Multiple pathways

Asciminib is metabolized by several pathways including, the CYP3A4, UGT2B7 and UGT2B17 enzymes and biliary secreted by the transporter BCRP.

Medicines inhibiting or inducing multiple pathways may alter asciminib exposure.

Asciminib inhibits several pathways including CYP3A4, CYP2C9, OATP1B, P-gp and BCRP. Asciminib may increase the exposure of medicinal products, which are substrates of these pathways (see section 4.5).

Special populations

Geriatric patients (65 years of age or above)

Among the 556 patients receiving asciminib in the ASC4FIRST, ASCEMBL and X2101 studies, 130 (23.4 %) were 65 years of age or older and 31 (5.6 %) were 75 years of age 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.

Gender/Race/Body weight

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

Renal impairment

A dedicated renal impairment study including 6 subjects with normal renal function (absolute glomerular filtration rate [aGFR] ≥ 90 mL/min) and 8 subjects with severe renal impairment not requiring dialysis (aGFR 15 to < 30 mL/min) has been conducted. Asciminib AUC_{inf} and C_{max} were increased by 56 % and 8 %, respectively, in subjects with severe renal impairment compared to subjects with normal renal function, following oral administration of a single 40 mg dose of asciminib (see section 4.2).

Population 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 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} 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

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 200-fold, 100-fold or 30-fold higher when compared to asciminib free C_{max} in patients at the 40 mg twice-daily, 80 mg once-daily or 200 mg twice-daily doses, 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, hematopoietic system, adrenal gland and gastro-intestinal tract as target organs of asciminib.

Pancreatic effects (serum amylase and lipase increases, acinar cell lesions) occurred in dogs at AUC exposures below those achieved in patients on 40 mg twice daily, 80 mg once daily or 200 mg twice daily. A trend towards recovery was observed.

Elevations in liver enzymes and/or bilirubin were observed in rats, dogs and monkeys. Histopathological hepatic changes (centrilobular hepatocyte hypertrophy, slight bile duct

hyperplasia, increased individual hepatocyte necrosis and diffuse hepatocellular hypertrophy) were seen in rats and monkeys. These changes occurred at AUC exposures either equivalent to (rats) or 8- to 18-fold (dogs and monkeys) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily. AUC exposures were below (rats), equivalent (dogs) or approximately 2-fold higher (monkeys) than the exposure in patients on 200 mg twice daily. These changes were fully reversible.

Effects on the haematopoietic system (reduction in red blood cells 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. AUC exposures were below (rats), equivalent (dogs) or approximately 2-fold higher (monkeys) than the exposure in patients on 200 mg twice daily. These changes were fully reversible.

Minimal mucosal hypertrophy/hyperplasia (increase in thickness of the mucosa with frequent elongation of villi) was present in the duodenum of rats, at AUC exposures 30-fold or 22-fold higher than those achieved in patients on 40 mg twice daily or 80 mg once daily, respectively. AUC exposure was 4-fold higher than those achieved in patients on 200 mg twice daily. This change was fully reversible.

Minimal or slight hypertrophy of the adrenal gland and mild to moderate decreased vacuolation in the zona fasciculata occurred at AUC exposures either equivalent to (monkeys) or 13- to 19-fold (rats) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily, respectively. AUC exposures were below (monkeys) or 2-fold higher (rats) than the exposure in patients on 200 mg twice daily, respectively. These changes were fully reversible.

Carcinogenicity and mutagenicity

Asciminib did not have mutagenic, clastogenic or aneugenic potential neither *in vitro* nor *in vivo*. In a 2-year rat carcinogenicity study no asciminib-related neoplastic or hyperplastic findings were noted in male or female rats at any dose level. AUC exposures to asciminib in rats at the highest dose were generally 8-fold or 5-fold higher than those achieved in patients at the dose of 40 mg twice daily or 80 mg once daily, respectively. AUC exposure to asciminib in rats at the highest dose was equivalent to those achieved in patients at the dose of 200 mg twice daily.

Reproductive toxicity

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 embryo-foetal 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 embryo-foetal 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 the foetal NOAEL of 25 mg/kg/day, the AUC exposures were equivalent to or below those achieved in patients at the 40 mg twice-daily or 80 mg once-daily doses, respectively. At the foetal NOAEL of 25 mg/kg/day, the AUC exposures were below those achieved in patients at the 200 mg twice daily dose.

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. At the foetal NOAEL of 15 mg/kg/day, the AUC exposures were below those achieved in patients at the 200 mg twice-daily dose.

Fertility

In the rat fertility study, asciminib did not affect reproductive function in male and female rats. A slight effect on male sperm motility and sperm count was observed at doses of 200 mg/kg/day, likely at AUC exposures 19-fold, 13-fold or 2-fold higher than those achieved in patients at the 40 mg twice-daily, 80 mg once-daily or 200 mg twice-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 C_{max} in plasma was 15-fold, 6-fold or 2-fold higher than the exposure in patients on 40 mg twice daily, 80 mg once daily or 200 mg twice daily, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

20 mg film-coated tablets:

Lactose monohydrate, microcrystalline cellulose (E460i), hydroxypropylcellulose (E463), croscarmellose sodium (E468), polyvinyl alcohol (E1203), titanium dioxide (E171), magnesium stearate, talc (E553b), colloidal silicon dioxide, iron oxide (E172, yellow and red), lecithin (E322), xanthan gum (E415).

40 mg film-coated tablets:

Lactose monohydrate, microcrystalline cellulose (E460i), hydroxypropylcellulose (E463), croscarmellose sodium (E468), polyvinyl alcohol (E1203), titanium dioxide (E171), magnesium

stearate, talc (E553b), colloidal silicon dioxide, iron oxide (E172, black and red), lecithin (E322), xanthan gum (E415).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture and light.

Keep blisters in the carton until required for use.

6.5 Nature and contents of container

Transparent, laminated colourless plastic film made of polychlorotrifluoroethylene (PCTFE) and polyvinyl chloride (PVC) sealed to an aluminium push through lidding foil.

Each blister strip containing 10 film-coated tablets is enclosed in a cardboard carton.

Pack sizes: 20 or 60 film coated tablets.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

011 346 6600

8. REGISTRATION NUMBER(S)

BACRELBA 20 mg film-coated tablets: 56/26/0824

BACRELBA 40 mg film-coated tablets: 56/26/0825

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

25 July 2023

10. DATE OF REVISION OF THE TEXT

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