Date: 25 March 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Brukinsa

International non-proprietary name: zanubrutinib
Pharmaceutical form: capsules
Dosage strength: 80 mg
Route(s) of administration: oral
Marketing Authorisation Holder: BeiGene Switzerland GmbH
Marketing Authorisation No.: 67998
Decision and Decision date: approved on 8 February 2022

Note:

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

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of the SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
WM	Waldenström's macroglobulinaemia

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

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

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan Drug Status was granted on 7 August 2020.

Authorisation human medical product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Brukinsa (zanubrutinib) is indicated for the treatment of patients with Waldenström's macroglobulinaemia (WM).

2.2.2 Approved Indication

Brukinsa (zanubrutinib) is used as monotherapy for the treatment of adult patients with Waldenström's Macroglobulinaemia (WM) who have received at least one prior therapy or as first-line therapy in adult patients who are not eligible for chemoimmunotherapy.

2.2.3 Requested Dosage

The recommended total daily oral dose of Brukinsa is 320 mg. Brukinsa may be taken as either 320 mg (four 80 mg capsules) once daily or 160 mg (two 80 mg capsules) twice daily.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	7 June 2021
Formal control completed	5 July 2021
Predecision	21 October 2021
Answers to Predecision	2 December 2021 and 13 December 2021
Labelling corrections	10 January 2022
Answers to Labelling corrections:	15 January 2022
Final Decision	8 February 2022
Decision	approval

Swissmedic has not assessed all the primary data of this application and is taking over the results of the assessment of the foreign reference authority Health Canada. The current SwissPAR refers to the publicly available Assessment Report for Brukinsa issued by Health Canada published 15 July 2021.

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3 Medical Context

Waldenström's macroglobulinaemia (WM) represents approximately 2% of all haematological malignancies. It constitutes a lymphoplasmacytic lymphoma and is primarily characterised by bone marrow invasion by a population of monoclonal small lymphocytes showing evidence of plasmacytoid differentiation along with the presence of IgM monoclonal gammopathy. The morbidity and mortality associated with WM are typically due to excessive concentration of serum IgM rather than mass effect from tumour infiltration. WM is more common in men and Caucasians, with a median age of 60–70 years. WM is an indolent non Hodgkin lymphoma (NHL) and remains an incurable disease.
The median survival in WM is reported to range from approximately 4 to 12 years, with patient mortality usually occurring due to disease progression, transformation to high-grade lymphoma and adverse treatment effects. Mortality is highly associated with symptom development since asymptomatic patients exhibit a similar life expectancy to the general population. The most frequent causes of death related to the disease are infections and secondary malignancies.
Only symptomatic patients are selected for therapy, whereas asymptomatic patients are monitored. The most common indications for initiating treatment in previously asymptomatic patients include anaemia, hyperviscosity, as well as neuropathy, bulky organomegaly and cytopaenia.

4 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is taking over the results of the assessment of the foreign reference authority Health Canada. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report for Brukinsa issued by Health Canada published 15 July 2021.

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5 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is taking over the results of the assessment of the foreign reference authority Health Canada. The current SwissPAR relating to nonclinical aspects refers to the publicly available Assessment Report for Brukinsa issued by Health Canada published 15 July 2021.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on a previous regulatory decision by Health Canada. The available assessment reports and approved product information from Health Canada were used as a basis for the clinical pharmacology evaluation.
For further details concerning clinical pharmacology aspects, see section 8.1 of this report.

6.2 Clinical Aspects

The evaluation of clinical data of this application has been carried out in reliance on a previous regulatory decision by Health Canada. The available assessment reports and approved product information from Health Canada were used as a basis for the evaluation of the recommended dose. In the pivotal Phase III ASPEN study, the patient population studied was either pre-treated or not eligible for a standard chemoimmunotherapy. Therefore, the indication wording was modified to limit the use of zanubrutinib monotherapy to adult patients with Waldenström's macroglobulinaemia who have received at least one prior therapy or who are not eligible for first line chemoimmunotherapy. This limitation to second-line treatment or unfit patients is also consistent from a regulatory perspective with other products in this indication.
For further details concerning clinical aspects, see section 8.1 of this report.

6.3 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

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

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8 Appendix

8.1 Approved Information for Healthcare Professionals

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

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

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

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Brukinsa 80 mg hard capsules

Composition

Active substances

Zanubrutinib

Excipients

Capsule contents
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Sodium lauryl sulphate
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac glaze (E904)
Iron oxide black (E172)
Propylene glycol (E1520)
Ammonium hydroxide (E527)

1 hard capsule contains 1.17 mg sodium.

Pharmaceutical form and active substance quantity per unit

Each hard capsule contains 80 mg zanubrutinib

Indications/Uses

BRUKINSA (zanubrutinib) is used as monotherapy for the treatment of adult patients with Waldenström’s Macroglobulinaemia (WM) who have received at least one prior therapy or as first-line therapy in adult patients who are not eligible for chemoimmunotherapy.

Dosage/Administration

Treatment with BRUKINSA should be prescribed and supervised by a physician experienced in cancer therapy.
In clinical studies, treatment with BRUKINSA was continued until disease progression or unacceptable toxicity.

Usual dosage

The usual dose is 320 mg daily, either once (four capsules) or twice daily (two capsules each in the morning and in the evening).

Dose adjustment following undesirable effects/interactions

Recommended dose adjustments of BRUKINSA for grade 3 or higher adverse reactions are listed in **Table** 1

Table 1: Recommended dose adjustment for adverse reactions

Event	**Occurrence of adverse reactions**	**Dose adjustment (Initial dose: 320 mg once or 160 mg twice daily)**
Grade 3 or higher non-haematologic toxicities Grade 3 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting longer than 10 consecutive days) Grade 4 thrombocytopenia (lasting longer than 10 consecutive days)	once	Interrupt BRUKINSA. Once toxicity resolves to grade 1 or less or baseline: Resume treatment with 160 mg twice daily or 320 mg once daily.
	twice	Interrupt BRUKINSA. Once toxicity resolves to grade 1 or less or baseline: Continue with 80 mg twice daily or 160 mg once daily.
	three times	Interrupt BRUKINSA. Once toxicity resolves to grade 1 or less or baseline: Continue with 80 mg once daily.
	four times	Definitively discontinue BRUKINSA.

Asymptomatic lymphocytosis is not considered a side effect; these patients may continue to take zanubrutinib.

Special dosage instructions

Recommended dose adjustments for use with CYP3A inhibitors or inducers are listed in **Table** 2.

Table 2: Use with CYP3A inhibitors or inducers

CYP3A	Concomitant medication	Recommended dose
Inhibition	Strong CYP3A inhibitor	80 mg once daily Treatment interruption according to recommendations in case of side effects.
	Mild CYP3A inhibitor	80 mg twice daily Dose adjustment according to recommendations in case of side effects.
Induction	Strong CYP3A inducer	Avoid concomitant use; consider alternative active substances with lower CYP3A induction.

After discontinuation of a CYP3A inhibitor, the previous BRUKINSA dosage must be resumed.

Patients with hepatic disorders

No dosage adjustment is recommended in patients with mild or moderate hepatic impairment. The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg twice daily. The safety of BRUKINSA has not been studied in patients with severe hepatic impairment. These patients should be closely monitored for side effects of BRUKINSA.

Patients with renal disorders

No dose adjustment is recommended in patients with mild to moderate renal impairment (CrCl ≥30 ml/min, estimated per Cockcroft-Gault). Patients with severe renal impairment (CrCl <30 ml/min) or on dialysis should be monitored for BRUKINSA side effects.

Elderly patients

No age-dependent dosage adjustment is required.

Children and adolescents

The safety and efficacy of zanubrutinib in paediatric patients has not been demonstrated.

Mode of administration

BRUKINSA hard capsules should be swallowed whole with water. BRUKINSA can be taken with or without food. Do not chew, dissolve or open the capsules. BRUKINSA must not be taken with grapefruit juice, grapefruit or Seville oranges (see “Interactions”).

Contraindications

BRUKINSA is contraindicated in patients who are hypersensitive to zanubrutinib or an excipient of the medicinal product. See section “Excipients” for complete list.

Warnings and precautions

Bleeding

Serious and fatal haemorrhagic events occurred in patients with haematologic malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events, including intracranial and gastrointestinal bleeding, haematuria, and haemothorax, were observed in 4% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 53% of patients with haematologic malignancies treated with BRUKINSA monotherapy.
BRUKINSA may increase the risk of bleeding in patients receiving antiplatelet agents or anticoagulants. Patients who recently had a stroke or intracranial haemorrhage or required warfarin or other vitamin K antagonists were excluded from the BRUKINSA clinical studies.
Patients should be monitored for signs of bleeding. Bleeding events should be managed with supportive care, including transfusions, and specialised care as needed. Dosage should be reduced or treatment interrupted or discontinued if needed (see Dosage/Administration). Treatment should be discontinued for any intracranial haemorrhage.

Consideration in operations

Depending on the type of surgery and the patient’s risk of bleeding, consideration should be given of whether to pause BRUKINSA administration for three to seven days before and after surgery.

Infections

Fatal and non-fatal bacterial, viral, or fungal infections have occurred in patients with haematologic malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 26.3% of patients treated with BRUKINSA monotherapy. The most common grade 3 or higher infection was pneumonia. Infections due to reactivation of the hepatitis B virus (HBV) have also occurred.
Prophylaxis according to standard of care should be considered in patients at increased risk of infection. Patients should be monitored for signs and symptoms of infection and treated appropriately.

Second primary malignancies

Second primary malignancies, including carcinomas other than skin cancers, occurred in 12.1% of patients with haematologic malignancies treated with BRUKINSA monotherapy. The most common second primary malignancy was skin cancer (basal cell and squamous cell carcinoma of the skin), which occurred in 8.1% of patients. Patients should be instructed to use sunscreen.

Atrial fibrillation and flutter

Atrial fibrillation and flutter occurred in 2.2% of patients with haematological malignancies treated with BRUKINSA monotherapy, particularly in patients with cardiac risk factors, hypertension, and acute infections. The signs and symptoms of atrial fibrillation and flutter should be monitored and treated as needed.

Cytopenia

Grade 3 or 4 cytopenia, including neutropenia (27.0%), thrombocytopenia (10.1%), and anaemia (6.6%) based on laboratory measurements, occurred in patients with haematologic malignancies treated with BRUKINSA monotherapy (see Undesirable effects). The complete blood count should be monitored regularly during treatment (see “Monitoring and laboratory tests”).

Interstitial lung disease

Suspected cases of interstitial lung disease, but not confirmed by biopsies, occurred in 0.8% of patients with haematologic malignancies treated with BRUKINSA monotherapy. Patients should be monitored for signs and symptoms of interstitial lung disease. If interstitial lung disease is suspected, treatment with BRUKINSA should be interrupted. If the suspected case is confirmed, treatment with BRUKINSA should be discontinued.

Teratogenic risk

BRUKINA may cause foetal harm or termination of pregnancy. Women should be advised of the potential risk to the foetus and should not become pregnant for one week after discontinuing BRUKINSA. Before starting treatment with BRUKINSA, women of childbearing potential should have a pregnancy test.

Use during pregnancy and breastfeeding

Women of childbearing potential or patients with a female partner of childbearing potential should use a very reliable method of contraception (see “Pregnancy, lactation”).

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, so it is “essentially sodium free”.

Interactions

Zanubrutinib is primarily metabolised by the cytochrome P450 enzyme 3A (CYP3A).

Active substances that may increase zanubrutinib plasma concentrations

Concomitant use of BRUKINSA and medicinal products that strongly or moderately inhibit CYP3A may increase zanubrutinib exposure.

Strong CYP3A inhibitors

Concomitant use of multiple doses of itraconazole (a strong CYP3A inhibitor) increased zanubrutinib Cmax 2.6-fold and AUC 3.8-fold in healthy subjects.

If a strong CYP3A inhibitor (e.g. posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir) has to be used, the dose of BRUKINSA should be reduced to 80 mg (one capsule) for the period of use of the inhibitor. Patients should be closely monitored for toxicity and, if necessary, the dose adjustment instructions should be followed (see section 4.2).

Moderate CYP3A inhibitors

Simulations of physiologically based PK (PBPK) suggest that concomitant use of multiple doses of a moderate CYP3A inhibitor may result in an approximately 2-fold increase in zanubrutinib Cmax and AUC. If a moderate CYP3A inhibitor (e.g. erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges) has to be used, the dose of BRUKINSA should be reduced to 160 mg (two capsules) for the period of inhibitor use. Patients should be closely monitored for toxicity and, if necessary, the dose adjustment instructions should be followed (see section 4.2).

Weak CYP3A inhibitors

Fasting simulations indicated that the weak CYP3A inhibitors (e.g. cyclosporine and fluvoxamine) may increase the AUC of zanubrutinib by <1.5-fold. No dose adjustment is required in combination with weak inhibitors. Patients should be closely monitored for toxicity and dose adjustment instructions should be followed as needed.

Grapefruit and Seville oranges should be used with caution during treatment with BRUKINSA as they contain moderate CYP3A4 inhibitors (see section 4.2).

Active substances that may decrease zanubrutinib plasma concentrations

Concomitant use of zanubrutinib with strong or moderate CYP3A inducers may decrease zanubrutinib plasma concentrations.

CYP3 inducers

Concomitant use of multiple doses of rifampin (a strong CYP3A inducer) reduced zanubrutinib Cmax by 92% and AUC by 93% in healthy subjects. Concomitant use with strong CYP3A inducers (carbamazepine, phenytoin, rifampin, St. John's Wort) and moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided (see section 4.2). Concomitant use of multiple doses of rifabutin (moderate CYP3A inducer) decreased Cmax by 48% and AUC by 44% in healthy subjects. Weak CYP3A inducers may be used with caution during treatment with BUKINSA.

Gastric acid-reducing active substances

No clinically significant differences in zanubrutinib pharmacokinetics were observed when co-administered with gastric acid-reducing active substances (proton pump inhibitors, H2 receptor antagonists).

Active substances whose plasma concentrations may be altered by zanubrutinib.

Zanubrutinib is a weak inducer of CYP3A and CYP2C19. Concomitant use of zanubrutinib may reduce the plasma concentrations of these substrates.

CYP3A substrate

Concomitant use of multiple doses of zanubrutinib decreased midazolam (a CYP3A substrate) Cmax by 30% and midazolam AUC by 47%. Medicinal products with a narrow therapeutic index that are metabolised by CYP3A (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) should be used with caution as zanubrutinib may reduce the plasma exposure of these medicines.

CYP2C19 substrate

Concomitant use of multiple doses of zanubrutinib reduced the Cmax of omeprazole (a CYP2C19 substrate) by 20% and the AUC of omeprazole by 36%. Medicinal products with a narrow therapeutic index that are metabolised by CYP2C19 (e.g. S-mephenytoin), should be used with caution, as zanubrutinib may reduce the plasma exposure of these medicines.

Other CYP substrates

No clinically significant differences in the pharmacokinetics of S-warfarin (a CYP2C9 substrate) were observed with concomitant use with zanubrutinib.

Concomitant use with transporter substrates/inhibitors

Concomitant use of multiple doses of zanubrutinib increased the Cmax of digoxin (a P-gp substrate) by 34% and the AUC of digoxin by 11%. No clinically significant differences in the pharmacokinetics of rosuvastatin (a BCRP substrate) were observed with concomitant use with zanubrutinib.

Concomitant use with oral P-gp substrates with a narrow therapeutic index (e.g. digoxin) should be used with caution, as zanubrutinib may increase their concentrations.

Pregnancy, lactation

Pregnancy

There are no clinical studies with BRUKINSA in pregnant women. Observations from animal studies suggest that BRUKINSA may cause foetal harm when administered to pregnant women. In animal reproductive studies, oral zanubrutinib administration to pregnant rats during the period of organogenesis was associated with foetal cardiac malformation (see “Preclinical data”).
BRUKINSA should not be used during pregnancy. Women of childbearing potential must use effective contraception while taking BRUKINSA and for at least one week after stopping BRUKINSA. A barrier method must also be used when using hormonal methods of contraception.
Male patients should use a highly effective method of contraception during treatment with BRUKINSA and for at least three months after the last treatment if their partner can become pregnant.
If the patient becomes pregnant while taking the drug, she must be informed of the possible risk to the foetus.

Lactation

It is not known whether BRUKINSA is excreted in human milk. Because many medicinal products are excreted in human milk, as well as the potential risk of serious adverse events with zanubrutinib in breastfed infants, breastfeeding should be discontinued during BRUKINSA treatment and breastfeeding should be avoided for two weeks after the last treatment

Fertility

There are no data on the effects of BRUKINSA on fertility in humans. No effects of zanubrutinib on fertility were observed in male or female rats, with morphological abnormalities in sperm and increased post-implantation loss at the highest dose tested (see Preclinical data).

Effects on ability to drive and use machines

No specific studies have been conducted to evaluate the effect of BRUKINSA treatment on the ability to drive or use heavy machinery. Fatigue, dizziness and asthenia have been reported in some

patients taking BRUKINSA and should be considered when assessing the ability to drive or use machines.

Undesirable effects

Summary of side effects

The overall safety profile of BRUKINSA is based on pooled data from 779 patients with B-cell malignancies treated with BRUKINSA in clinical studies.

The most common side effects (≥10%) were neutropenia, thrombocytopenia, upper respiratory tract infection, rash, haematoma including bruising, bleeding/haematoma including haematuria, anaemia, musculoskeletal pain including back pain and arthralgia, diarrhoea, pneumonia, cough, fatigue, urinary tract infection, constipation and dizziness.

Overall, serious adverse reactions occurred in 22.8% of patients. The most frequently reported serious adverse reactions were pneumonia (11.8%), neutropenia (3.1%), and bleeding (2.8%).

Of the 779 patients treated with BRUKINSA, 3.6% discontinued treatment due to side effects. The most common adverse reaction leading to treatment discontinuation was pneumonia (1.8%). Adverse reactions that led to a dose reduction occurred in 4.9% and an interruption of the dosage in 24.3% of patients. 1.4% of patients died due to side effects.

Tabulated list of adverse reactions

Adverse reactions in patients treated with BRUKINSA for B-cell malignancies are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (frequency cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented by decreasing severity.

Table 3: Side effects reported in patients with B-cell malignancies in clinical studies≠

MedDRA system organ classes	MedDRA terms	All grades* (%)	Grade 3 or higher (%)
Infections and infestations	Upper respiratory tract infection§	Very common (44.3)	2.6
	Pneumonia§ #	Very common (22.1)	11.6
	Pneumonia	Very common (16.3)	10.1
	Lower respiratory tract infection	Common (6.2)	0.8
	Urinary tract infection	Very common (15.5)	2.3
	Hepatitis B reactivation	Common (1.2)	0.8
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps	Non-melanoma skin cancer‡	Common (7.1)	1.0
Blood and lymphatic system disorders	Neutropenia†	Very common (56.2)	28.0
	Thrombocytopenia†	Very common (45.1)	11.4

	Anaemia†	Very common (28.9)	6.9
Immune system disorders	Interstitial lung disease‡	Uncommon (0.8)	0.8
Nervous system disorders	Dizziness§	Very common (11.7)	0.4
Cardiac disorders	Atrial fibrillation	Common (3.2)	1.0
Vascular disorders	Haematoma§	Very common (29.1)	0.1
	Bruising	Very common (21.1)	0.0
	Petechiae	Common (5.6)	0.0
	Ecchymosis	Common (2.3)	0.1
	Bleeding/Haematoma§#	Very common" (32.2)	3.1
	Haematuria	Very common (14.5)	0.6
	Epistaxis	Common (8.5)	0.1
	Gastrointestinal bleeding	Uncommon (0.5)	0.3
Respiratory, thoracic and mediastinal disorders	Cough	Very common (21.7)	0.1
Gastrointestinal disorders	Diarrhoea	Very common (23.6)	1.8
	Constipation	Very common (15.0)	0.4
Hepatobiliary disordersϰ	Alanine aminotransferase increased	Very common (13.0)	1.0
	Aspartate aminotransferase increased	Very common (11.0)	0
	Blood bilirubin increased	Very common (11.0)	1.0
Renal and urinary disordersϰ	Blood creatinine increased	Very common (31.0)	1.0
	Blood uric acid increased	Very common (14.0)	3.0
Skin and subcutaneous tissue disorders	Rash§	Very common (29.8)	0.4
	Toxic epidermal necrolysis#	Uncommon (0.1)	0.1
Musculoskeletal and connective tissue disorders	Musculoskeletal pain§	Very common (24.3)	2.4
	Back pain	Very common (11.7)	1.0
	Arthralgia	Very common (10.9)	1.0
General disorders and administration site conditions	Fatigue§	Very common (19.8)	1.5
	Fatigue	Very common (15.3)	1.2
	Asthenia	Common (3.6)	0.3

≠ Includes all patients (N=779)
ϰ Laboratory deviations (>10%) in patients from Cohort 1 of Study BGB-3111-302 (N=101)
* Grade was assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (NCI-CTCAE) Version 4.03.
† Based on laboratory values
‡ Causal relationship unclear
§ Includes multiple terms for these side effects.
# Includes events with fatal outcome.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for BRUKINSA overdose. Patients who experience an overdose should be closely monitored and receive appropriate supportive care.

Properties/Effects

ATC code

Pharmacotherapeutic group: Antineoplastic agents, Bruton's tyrosine kinase (BTK) inhibitors, ATC code: L01EL03.

Mechanism of action

Zanubrutinib is a BTK inhibitor. It forms a covalent bond with a cysteine residue in the active centre of the BTK, resulting in inhibition of BTK activity. BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signal transduction leads to activation of signalling pathways required for B-cell proliferation, trafficking, chemotaxis, and adhesion.
In non-clinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumour growth.

Pharmacodynamics

BTK occupancy in peripheral blood mononuclear cells and lymph node biopsies
Median steady-state BTK occupancy in peripheral blood mononuclear cells was maintained at 100% at a total daily dose of 320 mg BRUKINSA in patients with B-cell lymphomas over 24 hours. The median steady-state BTK occupancy in the lymph nodes was 94 and 100% after the recommended dose of 320 mg once daily and 160 mg twice daily respectively.

Cardiac electrophysiology
At the recommended doses (320 mg once daily or 160 mg twice daily), there were no clinically relevant effects on the QTc interval. At a single dose 1.5 times the maximum recommended dose (480 mg), zanubrutinib did not prolong the QT interval to any clinically relevant extent (≥10 ms). The maximum plasma exposure of zanubrutinib in this study was close to the maximum plasma exposure observed in patients following the recommended dose of 320 mg once daily.

The effect of BRUKINSA on the QTc interval above therapeutic exposure has not been studied.

Clinical efficacy

The safety and efficacy of BRUKINSA were studied in a randomised, open-label, multi-centre, comparative study of ibrutinib in 201 patients with Waldenström's Macroglobulinaemia (WM) carrying a MYD88 mutation (*MYD88*^{MUT}) (Cohort 1). In addition, a group of WD patients with the non-mutated *MYD88* gene (*MYD88*^{WT}) by gene sequencing (N=26) or with missing or unclear mutation status (N=2) was enrolled in a third, non-randomised study arm (Cohort 2) (Table 4).

Eligible patients were at least 18 years of age with a clinical and definitive histological diagnosis of relapsed/refractory (R/R) Waldenström's Macroglobulinaemia WM or first diagnosed who were considered unsuitable for standard chemoimmunotherapy. Patients had to meet at least one treatment criterion according to consensus panel criteria of the 7th International Workshop on Waldenström's Macroglobulinaemia (IWWM-7) and have measurable disease defined by a serum IgM level above 0.5 g/dl. Patients with *MYD88* mutation (*MYD88*^{MUT}) were assigned to Cohort 1 (N=201) and randomised 1:1 to receive either BRUKINSA 160 mg twice daily (Arm A) or ibrutinib 420 mg once daily (Arm B) until disease progression or unacceptable toxicity. Patients with a wild-type *MYD88* gene (*MYD88*^{WT}) by centrally confirmed gene sequencing (estimated presence in approximately 10% of enrolled patients) were enrolled in Cohort 2 (N=26) and received BRUKINSA 160 mg twice daily in a third non-randomised study arm (Arm C). In addition, those patients whose MYD88 mutation status was missing or inconclusive (N=2) were also assigned to Cohort 2, Arm C.

In Cohort 1, the median age was 70 years (range: 38 to 90 years), 28% were over 75 years of age (22% in the ibrutinib arm, 33% in the BRUKINSA arm), 67% were male, and 91% were Caucasian. At study entry, patients had a high International Prognostic Scoring System (IPSS) score derived from serum protein electrophoresis (SPEP) M-protein as follows: 44% of patients in the ibrutinib arm and 46% of patients in the BRUKINSA arm. 94% of patients had an ECOG performance status of 0 or 1 at baseline and 6% had an ECOG performance status of 2 at baseline. The median time from initial diagnosis was 4.6 years. Overall, 74 patients (37%) had IgM levels of at least 40 g/l. 164 patients (82%) had R/R WD. The median number of prior therapies was 1 (range: 1 to 8) and the median time from initial diagnosis was 5.6 years. The patient disposition and demographics of patients with R/R WD in Cohort 1 were generally comparable between the BRUKINSA and ibrutinib arms except for age. Compared with the ibrutinib treatment arm, the BRUKINSA treatment arm had a higher proportion of patients aged 75 years or older (32.5% vs. 19.8%) and under 65 years (43.4% vs. 32.1%).

In Cohort 2, the median age was 72 years (range: 39 to 87), 43% were over 75 years, 50% were male, and 96% were Caucasian. At study entry, 43% of patients had high IPSS score (derived by M-protein in the SPEP). The ECOG performance status score at baseline was 0 or 1 in 86% of patients and 14% of patients had a baseline ECOG performance status of 2. Median times from initial diagnosis were slightly shorter than in Cohort 1 (median 3.7 years vs. 4.6 years). 8 patients (29%) in Cohort 2 had IgM levels of at least 40 g/l. 23 of the 28 patients (82%) in Cohort 2 had R/R disease, with a median number of prior therapies of 1 (range: 1 to 5). Patient disposition and demographics of R/R WD *MYD88*^{WT} patients were similar to those of R/R WD *MYD88*^{MUT} patients in Cohort 1; only wild-type patients (R/R WD *MYD88*^{WT}) had a median of 4.0 years from first diagnosis whereas the median first diagnosis in mutant patients in Cohort 1 (R/R MW *MYD88*^{MUT}) was 5.6 years.

The primary endpoint was the rate of complete response (CR) or very good partial response (VGPR) in R/R *MYD88*^{MUT} WD patients, as assessed by an Independent Review Committee (IRC), adjusting for response criteria updated at the 6th IWWM. Secondary endpoints for Cohort 1 included investigator-assessed major response rate (MRR), duration of response, CR or VGPR rate, and progression-free survival (PFS).

Study results

The primary efficacy analysis for patients with R/R WD with *MYD88* mutation (*MYD88*^{MUT}), Cohort 1, was performed at a median treatment duration of 18.8 months in the ASPEN study. According to IRC assessment, the primary study results did not reach statistical significance in the R/R analysis set (two-sided, p=0.12), so the study did not meet the primary efficacy endpoint (Table 4). Consequently, all other endpoints are considered descriptive. Efficacy outcomes assessed by investigators were consistent with the primary efficacy analysis.

Table 4: Efficacy outcomes based on IRC in patients with Waldenström macroglobulinaemia (ASPEN study; Cohort 1)

Response category	Initially treated		Relapsed/Refractory		Total (ITT)	
	BRUKINSA (N=19)	**Ibrutinib (N=18)**	**BRUKINSA (N=83)**	**Ibrutinib (N=81)**	**BRUKINSA (N=102)**	**Ibrutinib (N=99)**
VGPR or CR rate, n (%)	**5 (26.3)**	**3 (16.7)**	**24 (28.9)**	**16 (19.8)**	**29 (28.4)**	**19 (19.2)**
95% CI[c]	(9, 51)	(4, 41)	(20, 40)	(12, 30)	(20, 38)	(12, 28)
Risk difference, %[d]	-		10.7		10.2	
95% CI	(-, -)		(-3, 24)		(-2, 22)	
P value[e]	-		0.12			

Abbreviations: CR: complete response, IRT: interactive response technology, ITT: intent-to-treat, MR: low response, MRR: higher response rate, NE: non-evaluable, ORR: overall response rate, PD: progressive disease, PR: partial response, SD: stable disease, VGPR: very good partial response
Cohort 1 includes patients with activating mutations in MYD88.
Percentages are based on N.
[a] The 95% CI was calculated using the Clopper-Pearson method.
[b] The common risk difference according to the Mantel-Haenszel method with 95% CI was calculated using normal approximation and Sato standard error stratified by stratification factors as per IRT (Strata CXCR4 WT and unknown will be combined) and age group (up to and over 65 years). Ibrutinib is the reference group.
[c] Based on the Cochran-Mantel-Haenszel test stratified by stratification factors as per IRT (Strata CXCR4 WT and unknown will be combined) and age group (up to and over 65 years). The p-value is two-sided.

MRRs were 78% (95% CI: 68, 87) and 80% (95% CI: 70, 88) in the BRUKINSA and ibrutinib arm of the primary efficacy set (R/R *WM MYD88*^{MUT}patients). MRRs for first-treated patients were 74% (95% CI: 49, 91) and 67% (95% CI: 41, 87) in the BRUKINSA and ibrutinib arm.

Median duration of response (DoR) of CR or VGPR and PFS were not reached in any arm of the primary efficacy set of R/R *MYD88*^{MUT} WD patients.

In the non-randomised exploratory subgroup of *MYD88^{WT}* WD patients treated with BRUKINSA (Cohort 2), the IRC-assessed rates of VGPR or CR were 20% (95% CI: 1, 72) for treatment-naïve patients (n=5) and 29% (95% CI: 11, 52) for R/R patients (n=21). No CRs were observed.

Pharmacokinetics

The pharmacokinetics (PK) of zanubrutinib have been studied in healthy subjects and patients with B-cell lymphomas. The maximum zanubrutinib plasma concentration (C_{max}) and the area under the plasma drug concentration curve over time (AUC) increase proportionally over a dose range of 40 mg to 320 mg (0.13 to 1 times the total recommended daily dose). Limited systemic accumulation of zanubrutinib was observed following repeated use.

The geometric mean (% CV) daily AUC for zanubrutinib at steady state is 2099 (42%) ng·h/ml after a dose of 160 mg twice daily and 1917 (59%) ng·h/ml after a dose of 320 mg once daily. The geometric mean (% CV) C_{max} for zanubrutinib at steady state is 299 (56%) ng/ml after a dose of 160 mg twice daily and 533 (55%) ng/ml after a dose of 320 mg once daily.

Absorption

Food effect: No clinically significant differences in the AUC or C_{max} of zanubrutinib were observed in healthy subjects following a high-fat meal (approx. 1,000 calories with 50% of total calorie content from fat).

Distribution

The geometric mean (% CV) apparent volume of zanubrutinib distribution at steady state during the terminal phase (Vz/F) was 537 l (73%) after a dose of 160 mg twice daily. Plasma protein binding of zanubrutinib is approximately 94% and the blood-to-plasma ratio is 0.7 to 0.8.

Metabolism

In vitro, zanubrutinib is primarily metabolised by cytochrome P450(CYP)3A.

Elimination

The mean half-life ($t_{½}$) of zanubrutinib is approximately two to four hours after a single oral zanubrutinib dose of 160 mg and 320 mg. The geometric mean (%CV) apparent oral clearance (CL/F) of zanubrutinib was 128 (58%) l/hr.

Following a single radio-labelled zanubrutinib dose of 320 mg in healthy subjects, approx. 87% of the dose was detected in stool (38% unchanged) and 8% in urine (less than 1% unchanged).

Hepatic impairment

The total AUC of zanubrutinib increased by 11% in patients with mild hepatic impairment (Child-Pugh class A), by 21% in patients with moderate hepatic impairment (Child-Pugh class B), and by 60% in patients with severe hepatic impairment (Child-Pugh class C) compared to patients with normal hepatic function. Zanubrutinib unbound AUC increased by 23% in patients with mild hepatic impairment (Child-Pugh class A), by 43% in patients with moderate hepatic impairment (Child-Pugh class B), and by 194% in patients with severe hepatic impairment (Child-Pugh class C) compared to patients with normal hepatic function.

Renal impairment

Zanubrutinib is only minimally eliminated renally. Based on the population PK analysis, mild or moderate renal impairment (CrCl ≥30 ml/min estimated as per the Cockcroft-Gault formula) did not affect zanubrutinib exposure. Only limited PK data are available in patients with severe renal impairment (CrCl <30 ml/min) or in patients requiring dialysis.

Elderly patients

Based on population pharmacokinetic analysis, age (19 to 90 years) had no clinically significant effect on zanubrutinib PK.

Children and adolescents

No pharmacokinetic studies have been conducted with zanubrutinib in patients under 18 years of age.

Preclinical data

Repeated dose toxicity

The general toxicological profiles of zanubrutinib were characterised by oral treatment in Sprague-Dawley rats for up to six months and in Beagle dogs for up to nine months.

In the six-month study, rats received a dose of 30, 100 or 300 mg/kg/day for 182 days or 1,000 mg/kg/day for up to 8 days. Mortality associated with the test item was only observed at a dose of 1,000 mg/kg/day after 5 days of treatment, and the most important toxicological findings were gastrointestinal toxicities associated with histopathological changes. Histopathological changes related to the test item were found in the pancreas, lungs, and skeletal muscles, most were completely or partially reversible. The NOAEL was assumed to be 300 mg/kg/day, with systemic exposure (AUC) in males approximately 25 times and in females 42 times the human exposure at the recommended dose.

In the nine-month study, dogs received 10, 30, or 100 mg/kg/day for 273 days. No mortalities occurred throughout the study. Toxicological findings or changes were minimal or mild and resolved during recovery, including abnormal stool, conjunctival hyperaemia, lymphoid depletion, or erythrophagocytosis in intestinal-associated lymphoid tissue. The NOAEL was assumed to be 100 mg/kg/day, with systemic exposure (AUC) in males approximately 20 times and in females 18 times the human exposure at the recommended dose.

Genotoxicity Zanubrutinib was non-mutagenic in a bacterial mutagenic test (Ames), non-clastogenic in a mammalian cell (CHO) chromosomal aberration test, and non-clastogenic in an *in vivo* bone marrow micronucleus test in rats.

Carcinogenicity

No carcinogenicity studies have been conducted with zanubrutinib.

Reproductive toxicity

A combined study of male and female fertility and early embryonic development was conducted in rats at oral zanubrutinib doses of 30 to 300 mg/kg/day. Male rats were dosed four weeks before mating and during mating and female rats were dosed two weeks before mating and up to gestation day seven. No effects on male or female fertility were noted, but at the high dose of 300 mg/kg/day, morphological abnormalities in sperm and increased post-implantation loss were noted. The 300 mg/kg/day dose is approximately 9 times the recommended human dose based on body surface area.

Embryo-foetal developmental toxicity studies have been conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Cardiac malformations (two or three heart chambers) were noted at all dose levels (incidence between 0.3 and 1.5%) without maternal toxicity. The lowest dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose.

Administration of zanubrutinib to pregnant rabbits in the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss and maternal toxicity at the highest dose. The dose of 70 mg/kg/day is approximately 25 times the exposure (AUC) of patients at the recommended dose.

In a pre- and post-natal development toxicity study in rats, zanubrutinib was administered orally at a dose of 30, 75, and 150 mg/kg/day from implantation until weaning. Offspring from the 75 mg/kg/day and 150 mg/kg/day groups had decreased body weight before weaning and all dose groups had adverse ocular findings (cataract, protruding eye, etc.). The dose of 30 mg/kg/day is approximately 4 times the exposure (AUC) in patients receiving the recommended dose.

Other information

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack.

36 months

Special precautions for storage

Store at 15-30°C.

Store in the original packaging.

Keep the container tightly closed.

Keep out of the reach of children.

Authorisation number

67998

Packs

White high-density polyethylene (HDPE) plastic bottle with a child resistant polypropylene cap.

Package size

Bottle with 120 hard capsules (A)

Marketing authorisation holder

BeiGene Switzerland GmbH

Aeschengraben 27

4051 Basel

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