Summary Report of Benefit-Risk Assessment

HIBRUKA TABLET 50 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Orelabrutinib
Product Registrant	Labcorp Development (Asia) Pte. Ltd.
Product Registration Number	SIN16645P
Application Route	Abridged evaluation
Date of Approval	22 November 2022

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A INTRODUCTION

Hibruka is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

The active substance, orelabrutinib, is a small molecule inhibitor of Bruton's tyrosine kinase (BTK). BTK is a signalling molecule of the B-cell antigen receptor and cytokine receptor pathways. In B cells, BTK signalling results in activation of pathways necessary for B-cell migration, chemotaxis and adhesion. Orelabrutinib covalently binds to the active site of BTK, resulting in inhibition of BTK activity.

Hibruka is available as tablets containing 50 mg of orelabrutinib. Other ingredients in the tablet core are hydroxypropyl methylcellulose acetate succinate, mannitol, hydroxypropyl cellulose, croscarmellose sodium, silicon dioxide and magnesium stearate.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, orelabrutinib, is manufactured at Shanghai SynTheAll Pharmaceutical Co., Ltd., Shanghai, China. The drug product, Hibruka Tablet 50 mg, is manufactured at WuXi STA Pharmaceutical Co., Ltd., Jiangsu, China.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Shanghai SynTheAll Pharmaceutical Co., Ltd. was adequate to support the storage below 30°C with a shelf life of [redacted] months. The packaging is a [redacted].

Drug product:

The manufacturing process involves spray drying of the intermediate drug product to form an amorphous solid dispersion, followed by dry granulation and compression of the solid dispersion to produce the final tablet. The process is considered a standard process.

The manufacturing site involved is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30ºC. The container closure system is a 45-mL high density polyethylene bottles with child-resistant polypropylene cap and a 1-gram silica gel desiccant capsule, containing 30 tablets.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of orelabrutinib for the treatment of patients with relapsed or refractory MCL was based primarily on one pivotal Phase 1/2, multicentre, open-label, single-arm, non-randomised study (ICP-CL-00102) in MCL patients who had received at least one prior therapy.

The study was conducted in 2 stages. Stage I evaluated both the 100 mg twice daily (20 subjects) and 150 mg once daily (20 subjects) doses of orelabrutinib to determine the recommended therapeutic dose. In Stage I of the study, the primary endpoint was safety and the secondary endpoint was the overall response rate (ORR) assessed by the investigator.

Based on the acceptable safety profile and observed higher ORR in the 150 mg once daily group (ORR: 75.0%) compared to the 100 mg twice daily group (ORR: 66.7%), the 150 mg once daily dose was selected for Stage II. In Stage II of the study, all patients received orelabrutinib 150 mg once daily until disease progression, intolerability, death, withdrawal of consent, or termination of study.

The primary efficacy endpoint in Stage II was ORR, defined as complete response (CR) and partial response (PR), as assessed by the Independent Review Committee (IRC) based on computed tomography/magnetic resonance imaging (CT/MRI) and clinical results in accordance with the 2014 International Working Group (IWG) evaluation criteria for non-Hodgkin's lymphoma (i.e., the 2014 Lugano classification).

The secondary efficacy endpoints included ORR as assessed by the investigator, duration of response (DOR), time to response (TTR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). As an exploratory endpoint, complete response rate was assessed based on PET/CT/MRI imaging and clinical outcomes according to the 2014 Lugano classification in a subgroup of subjects who underwent PET examination. Tumour assessments were performed every 8 weeks during the first 48 weeks and every 12 weeks thereafter.

For the primary endpoint, ORR, the number and percentage of subjects with objective response were calculated based on the best overall response of subjects and the 95% confidence interval (CI) of the percentage was calculated using the Clopper-Pearson method. Based on the ORR of historical treatments for relapsed or refractory MCL ranging from 10% to 50%, and assuming an ORR of 65% for orelabrutinib compared to 45% in the historical control, at least 67 subjects were to be enrolled to maintain power >90% to demonstrate statistical significance at a one-sided alpha of 0.025 and lower limit of the 95% CI >45%. Considering safety issues and drop-out rates, approximately 80 subjects were planned to be

enrolled in the 150 mg once daily dose group. The statistical methods and sample size calculation were considered appropriate for the endpoint studied.

A total of 106 subjects were enrolled in the study, including 86 subjects in the 150 mg once daily dose group (20 subjects in Stage I and 66 subjects in Stage II) and 20 subjects who received 100 mg twice daily in Stage I. All 86 subjects in the 150 mg once daily (i.e., the recommended dosing regimen) group were treated and included in the full analysis set (FAS) for efficacy analyses. As of the data cut-off date of 10 April 2020, the median duration of follow-up was 15.0 months.

The median age of the 86 subjects in the 150 mg once daily dose group was 62.0 years (range 37 to 73 years), 31.4% of subjects were aged ≥65 years and 79.1% were males. The majority of the subjects scored 0 (47.7%) or 1 (50.0%) in ECOG performance status. Most subjects were in advanced stages of disease: 16 subjects (18.6%) were Stage III and 65 subjects (75.6%) were Stage IV. There were 19 subjects (22.1%) who had spleen involvement, 7 subjects (8.1%) had liver involvement, and 36 subjects (41.9%) had bone marrow infiltration.

All 86 subjects had received prior treatment, 40 subjects (46.5%) received prior first-line therapy and 46 subjects (53.5%) received second-line or above therapy. The majority of the subjects (90.7%) had previously received an anti-CD20 monoclonal antibody therapy (mainly rituximab), 69.8% of subjects were previously treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), 23.3% had previously received EPOCH (etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone), and 19.8% had received DHAP (dexamethasone, cisplatin, and cytarabine).

The efficacy of orelabrutinib was demonstrated in terms of an ORR by IRC assessment of 77.9% (95% CI: 67.7, 86.1), which met the primary endpoint set in the study (i.e., ORR >65.0%, lower limit of 95% CI >45.0%). The CR rate was 25.6% and the PR rate was 52.3%. The ORR by investigator assessment was 79.1% (95% CI: 69.0, 87.1).

The median DOR by IRC was not reached (95% CI: 14.46, NE). The median TTR by IRC was 1.9 months (95% CI: 1.84, 1.91), the median PFS by IRC was 16.6 months (95% CI: 10.97, not estimable), and the median OS was not reached with 18.6% death events as of the data cut-off date.

As an exploratory endpoint, the CR rate by PET/CT/MRI imaging was evaluated in a subgroup of 32 subjects who had baseline PET examination. The CR rate in this exploratory analysis was 37.5%.

Updated efficacy data in the total population with a data cut-off date of 31 December 2020 showed consistent results, as summarised in the table below.

Summary of efficacy results (FAS)

	Data cut-off 10 Apr 2020				**Data cut-off 31 Dec 2020**	
	150mg once daily (N=86)		**Total Population[a] (N=106)**		**Total Population[a] (N=106)**	
	IRC	**Investigator**	**IRC**	**Investigator**	**IRC**	**Investigator**
Overall response rate (ORR)						
ORR	67 (77.9%)	68 (79.1%)	86 (81.1%)	87 (82.1%)	86 (81.1%)	87 (82.1%)
CR	22 (25.6%)	22 (25.6%)	26 (24.5%)	29 (27.4%)	29 (27.4%)	37 (34.9%)
CRu	---	2 (2.3%)	---	5 (4.7%)	---	---
PR	45 (52.3%)	44 (51.2%)	60 (56.6%)	53 (50.0%)	57 (53.8%)	50 (47.2%)

SD	5 (5.8%)	5 (5.8%)	6 (5.7%)	6 (5.7%)	6 (5.7%)	6 (5.7%)
DCR	72 (83.7%)	73 (84.9%)	92 (86.8%)	93 (87.7%)	92 (86.8%)	93 (87.7%)
Duration of response (DOR)						
No. of events	23/67 (34.3%)	17/68 (25.0%)	31/86 (36.0%)	23/87 (26.4%)	---	---
Median (95% CI)	NR (14.46, NR)	NR (14.75, NR)	NR (14.46, NR)	NR (NR, NR)	22.9 (16.4, NR)	---
DOR rate 6 months 12 months 24 months	 82.0% 66.9% ---	 84.9% 75.4% ---	 80.1% 63.8% ---	 84.7% 73.7% ---	 --- --- 49.6%	---
Progression free survival (PFS)						
No. of events	41 (47.7%)	31 (36.0%)	49 (46.2%)	37 (34.9%)	---	---
Median (95% CI)	16.6 (10.97, NR)	NR (16.53, NR)	19.3 (11.30, NR)	NR (16.56, NR)	22.0 (13.8, NR)	---
PFS rate 6 months 12 months 24 months	 69.8% 57.7% ---	 78.9% 66.2% ---	 73.6% 60.0% ---	 81.0% 67.7% ---	 --- --- 46.5%	---
Overall Survival (OS)						
No. of events	16 (18.6%)		19 (17.9%)		---	
Median (95% CI)	NR (NR, NR)		NR (NR, NR)		NR (NR, NR)	
OS rate 6 months 12 months 24 months	 87.2% 83.6% ---		 89.6% 84.7% ---		 --- --- 74.3%	

CRu = unconfirmed complete response; SD = stable disease; DCR = disease control rate (CR + PR + SD); NR = not reached
[a] Total population (N=106) comprised 86 subjects who received the 150 mg once daily dose and 20 subjects who received the 100 mg twice daily dose.

As the single-arm, non-randomised, non-comparative study design does not allow meaningful conclusions to be made on the clinical benefit of orelabrutinib in terms of time-to-event endpoints such as PFS and OS, comparison was made to historical controls to contextualise the data. The ORR and DOR observed with orelabrutinib compared favourably with that documented for historical therapy used in the treatment of relapsed or refractory MCL (ORR ~20-30%) and fell within the range of that for other BTK inhibitors with reported ORRs ranging from 67% to 84% and median DOR ranging from 17.5 to 19.5 months.

Overall, there were limitations with the early phase single-arm study and the small sample size. Nonetheless, considering the rarity of the disease condition, the established role of BTK inhibitors in MCL and the comparable ORR and durable responses observed with orelabrutinib, the available data provided reasonable evidence to support the efficacy of orelabrutinib for the treatment of adult patients with MCL who have received at least one prior therapy.

A Phase 3, multicentre, randomised, open-label study (ICP-CL-00113) of orelabrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) compared to R-CHOP alone in patients with treatment-naïve MCL is currently ongoing. The final results of this study will be required to confirm the efficacy and safety of orelabrutinib in the treatment of patients with MCL.

D ASSESSMENT OF CLINICAL SAFETY

The safety evaluation of orelabrutinib for the treatment of patients with relapsed/refractory MCL was based primarily on the safety data from the pivotal study ICP-CL-00102 (n=106) in MCL.

In addition, data from four ongoing studies, ICP-CL-00103 (n=80) in CLL/SLL, ICP-CL-00104 (n=58) in marginal zone lymphoma (MZL), ICP-CL-00105 (n=25) in Waldenstrom's macroglobulinaemia (WM) and ICP-CL-00106 (n=35) in central nervous system lymphoma (CNSL), provided supportive safety evidence. The data from the above 5 studies were pooled to form a safety dataset comprising a total of 304 patients with B-cell lymphoma who were treated with orelabrutinib at ≥150 mg/day (referred to as "All lymphoma patients").

In the MCL study, the median duration of treatment was 11.93 months and the proportion of patients who have been treated for more than 12 months was 50.0%. The median duration of follow-up was 16.40 months. The size of the safety population and duration of exposure were considered adequate to reasonably assess the safety of orelabrutinib for the intended population.

Summary of treatment exposure

	MCL study (n=106)	**All lymphoma patients (n=304)**
Treatment duration (months)		
Mean (SD)	12.07 (6.139)	9.14 (6.151)
Median	11.93	9.25
Min, Max	0.5, 22.1	0.0, 22.1
Daily dose (mg/day)		
Mean (SD)	153.5 (23.61)	148.6 (16.84)
Median	150.0	150.0
Min, Max	79, 201	79, 201
Treatment duration, n (%)		
<2 months	12 (11.3%)	58 (19.1%)
2-4 months	2 (1.9%)	32 (10.5%)
4-6 months	9 (8.5%)	23 (7.6%)
6-9 months	5 (4.7%)	31 (10.2%)
9-12 months	25 (23.6%)	60 (19.7%)
12-15 months	15 (14.2%)	41 (13.5%)
15-18 months	14 (13.2%)	26 (8.6%)
>18 months	24 (22.6%)	33 (10.9%)
Follow-up duration (months)		
Mean (SD)	15.27 (5.842)	10.96 (6.677)
Median	16.40	11.70
Min, Max	0.5, 24.3	0.2, 24.3

Overview of treatment-emergent adverse events (AEs)

	MCL study* (n=106)	**All lymphoma patients (n=304)**
All AEs	100 (94.3%)	276 (90.8%)
Grade ≥3 AE	52 (49.1%)	125 (41.1%)
AE leading to dose reduction	7 (6.6%)	18 (5.9%)
AE leading to dose interruption	25 (23.6%)	55 (18.1%)
AE leading to treatment discontinuation	5 (4.7%)	21 (6.9%)
Serious AE (SAE)	32 (30.2%)	80 (26.3%)
SAE leading to death	7 (6.6%)	23 (7.6%)
All treatment-related AEs	96 (90.6%)	250 (82.2%)
Grade ≥3 AE	35 (33.0%)	87 (28.6%)
AE leading to dose reduction	7 (6.6%)	18 (5.9%)
AE leading to dose interruption	17 (16.0%)	41 (13.5%)
AE leading to treatment discontinuation	3 (2.8%)	9 (3.0%)
Serious AE (SAE)	17 (16.0%)	41 (13.5%)
SAE leading to death	0	4 (1.3%)

*data cut-off date 10 April 2020

In the MCL study, the most commonly reported AEs were platelet count decreased (30.2%), upper respiratory tract infection (25.5%), neutrophil count decreased (23.6%), white blood cell count decreased (18.9%), anaemia (17.9%), hypertension (16.0%), rash (16.0%) and hypokalaemia (15.1%). The most common treatment-related AEs observed were platelet count decreased (29.2%), neutrophil count decreased (21.7%), white blood cell count decreased (17.9%), hypertension (15.1%), rash (14.2%), anaemia (13.2%) and upper respiratory tract infection (12.3%).

SAEs were reported in 32/106 (30.2%) subjects and those occurring in more than one subject included platelet count decreased (7 subjects; 6.6%), pneumonia (6 subjects; 5.7%), disease progression (5 subjects; 4.7%), pneumonitis (4 subjects; 3.8%) and anaemia (2 subjects; 1.9%). The incidence of AEs leading to treatment discontinuation was low (5 subjects; 4.7%). Overall, the incidence and types of AEs, SAEs and AEs leading to treatment discontinuation are consistent with the known safety signals reported with BTK inhibitors.

In the MCL study, a total of 19 subjects died as of the data cut-off date (10 April 2020). Seven of the deaths occurred within 28 days after the last dose of the study drug, including 4 due to disease progression, 2 caused by AEs unrelated to the treatment, and 1 caused by unknown reason. Across all the 5 clinical studies, 4 subjects died of treatment-related AEs: fungal infection, cerebral haemorrhage, hepatitis and hepatitis B re-activation. Overall, the causes of deaths due to AEs reported in the clinical studies were either due to the known AEs associated with BTK inhibitors (e.g., infection, haemorrhage) or occurred in the setting of expected co-morbidities in the study population.

The AEs of special interest (AESIs) for orelabrutinib included infection, haemorrhage, cytopenia (neutrophil count decreased, platelet count decreased, anaemia), second primary malignancy, hypertension, diarrhoea, atrial fibrillation, and tumour lysis syndrome, which are known and expected AEs of BTK inhibitors.

Summary of AESIs

	MCL study* (n=106)	**All lymphoma patients (n=304)**
Any AESI	87 (82.1%)	232 (76.3%)
Grade ≥3 AESI	36 (34.0%)	92 (30.3%)
Infections Grade ≥3	55 (51.9%) 13 (12.3%)	147 (48.4%) 43 (14.1%)
Haemorrhage Grade ≥3	31 (29.2%) 0	98 (32.2%) 7 (2.3%)
Neutrophil count decreased Grade ≥3	25 (23.6%) 9 (8.5%)	80 (26.3%) 36 (11.8%)
Platelet count decreased Grade ≥3	32 (30.2%) 14 (13.2%)	79 (26.0%) 27 (8.9%)
Anaemia Grade ≥3	20 (18.9%) 8 (7.5%)	49 (16.1%) 16 (5.3%)
Hypertension Grade ≥3	21 (19.8%) 5 (4.7%)	28 (9.2%) 8 (2.6%)
Diarrhoea Grade ≥3	8 (7.5%) 0	19 (6.3%) 1 (0.3%)
Malignant neoplasms Grade ≥3	2 (1.9%) 2 (1.9%)	3 (1.0%) 3 (1.0%)
Atrial fibrillation Grade ≥3	1 (0.9%) 0	1 (0.3%) 0

*data cut-off date 10 April 2020

Cytopenia and infection AEs were the most common AESIs reported in the orelabrutinib clinical studies, and the profile is consistent with that known for other BTK inhibitors. The most commonly reported infection AEs in the MCL study were upper respiratory tract infection (25.5%), pneumonia (11.3%) and urinary tract infection (5.7%). Grade 5 (fatal) infection events included pneumonia in 2 subjects. None of the infection AEs led to treatment discontinuation, while dose interruption occurred in 6 subjects (5.7%) and dose reduction in 1 subject (0.9%). The package insert has included adequate warnings on cytopenias and infections, including recommendations for monitoring for complete blood count and signs and symptoms of infection.

Haemorrhage events were reported in 31 subjects (29.2%). The most frequently occurring haemorrhage events were blood urine present (7.5%), purpura (4.7%), petechiae (4.7%), post-traumatic punctate intraepidermal haemorrhage (2.8%) and haematuria (2.8%). There were no Grade ≥3 haemorrhage event reported in the MCL study. Across the other 4 clinical studies, Grade ≥3 haemorrhage events were reported in 7 subjects (2.3%) and 2 were Grade 5 (fatal) events (intracranial haemorrhage and cerebral haemorrhage). Adequate warnings on haemorrhagic events (including fatal events) have been included in the package insert, including recommendations for monitoring of bleeding.

The incidence of atrial fibrillation, hypertension, diarrhoea, and second primary malignancy was low and no AEs of tumour lysis syndrome were reported in the orelabrutinib clinical studies, which could be attributed to the limited exposure in the studies. Adequate warnings have been included in the package insert regarding these class-related safety events.

Overall, the spectrum of AEs observed across the orelabrutinib clinical studies in patients with MCL and other B-cell malignancies are consistent with the known safety profile of BTK inhibitors. The safe use of orelabrutinib should be guided by the warnings and precautionary information in the package insert.

E ASSESSMENT OF BENEFIT-RISK PROFILE

MCL is a rare and aggressive subtype of B-cell non-Hodgkin's lymphoma (NHL) and is a serious and life-threatening condition. Patients with relapsed or refractory MCL have an overall poor prognosis and a median survival of 1 to 2 years. Current treatment options for patients with relapsed or refractory disease consist of combination regimens or single-agents including bortezomib, lenalidomide, or the BTK inhibitors, ibrutinib, acalabrutinib or zanubrutinib, with overall response rates ranging from approximately 20% to >80% and median PFS and OS generally less than two years.

The use of orelabrutinib in relapsed or refractory MCL was supported by a Phase 2, single-arm study (ICP-CL-00102), which demonstrated a high and clinically meaningful ORR by IRC of 77.9% (95% CI: 67.7, 86.1) and CR rate of 25.6%. Based on investigator assessment, consistent ORR (79.1%; 95% CI: 69.0, 87.1) and CR rates (25.6%) were observed. The median DOR by IRC was not reached (95% CI: 14.46, NE) and the median PFS by IRC was 16.6 months (95% CI: 10.97, NE). The OS data was immature with 18.6% death events as of the data cut-off date.

While the absence of a comparator arm was a limitation of the single-arm study, the ORR and duration of response were comparable to that of other BTK inhibitors and historical therapies, thus providing preliminary evidence of efficacy for orelabrutinib in the target patient population.

The final results of the ongoing Phase 3 study (ICP-CL-00113) will be required to further confirm the efficacy demonstrated in Study ICP-CL-00102.

The safety profile of orelabrutinib is generally consistent with that documented for BTK inhibitors. The most common AEs were mainly haematological AEs (including platelet count decreased, neutrophil count decreased, white blood cell count decreased and anaemia), infections (including upper respiratory tract infection), hypertension, rash and hypokalaemia, which fall within that expected for this class of drugs. AEs of special interest included cytopenia (neutrophil count decreased, platelet count decreased, anaemia), infection and haemorrhage, which are known AEs of BTK inhibitors. These AEs have been adequately described in the package insert, including recommendations for monitoring and dose modifications.

Overall, based on the high response rates and durability of responses observed with orelabrutinib together with the safety profile that is acceptable in the target patient population, the benefit-risk profile of orelabrutinib in the treatment of patients with MCL who have received at least one prior therapy was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Hibruka for the treatment of adult patients with MCL who have received at least one prior therapy was deemed favourable and approval of the product registration was granted on 22 November 2022. The approval of this application is subject to the submission of the final results of the ongoing Phase 3 study (ICP-CL-00113) to confirm the efficacy and safety of orelabrutinib in the treatment of patients with MCL.

APPROVED PACKAGE INSERT AT REGISTRATION

Prescribing Information

HIBRUKA (Orelabrutinib) Tablet 50 mg

1 Name of Product

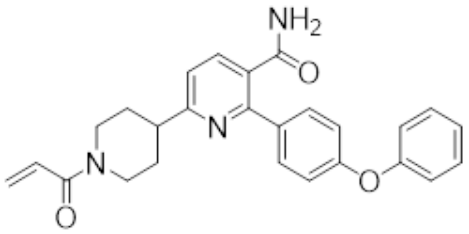
Nonproprietary name (INN) name: orelabrutinib tablet

2 Composition

The active ingredient is orelabrutinib.

Chemical name (IUPAC): 2-(4-phenoxyphenyl)-6-[1-(prop-2-enoyl) piperidin-4-yl] pyridine-3-carboxamide

Chemical Structure:



Empirical formula: $C_{26}H_{25}N_3O_3$

Molecular weight: 427.5

3 Product Description

HIBRUKA tablet is a round white or off-white solid tablet.

4 Indications

HIBRUKA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

5 Strength

50 mg

6 Dosage & Administration

HIBRUKA should be administered under the direction of a physician specialized in the diagnosis and treatment of patients with the intended indications.

HIBRUKA tablets should be taken orally once daily at approximately the same time each day, either before or after meal. Swallow the whole tablet with water. Do not break, crush or chew the tablets.

The recommended dose of HIBRUKA is 150 mg (three 50 mg tablets) orally once daily until disease progression or unacceptable toxicity.

Missed dose

If a dose is missed at the scheduled time, it should be taken as soon as possible only if it is at least 8 hours before the next dose, and return to the normal schedule in the following day. Do not take extra tablets to make up for the missed dose.

Dosage Adjustments

Recommended dose modifications are provided in Table 1.

Table 1: Recommended Dose Adjustments for Adverse Reactions

Adverse Reaction	Adverse Event Occurrence	Dose Modification (starting dose: 150 mg once daily)
• Grade 3 or higher non-haematological toxicity* • Grade 3 or higher febrile neutropenia • Grade 3 thrombocytopenia associated with significant bleeding • Grade 4 neutropenia • Grade 4 thrombocytopenia	1st occurrence	Withhold HIBRUKA. • If the toxicity has resolved to Grade 1 or baseline within 14 days, resume at 150 mg once daily. • If toxicity has resolved to Grade 1 or baseline after 14 days, resume at 150 mg or 100 mg, once daily, per physician's instruction.
	2nd occurrence	Withhold HIBRUKA. • If the toxicity has resolved to Grade 1 or baseline within 14 days, resume at 100 mg once daily. • If toxicity has resolved to Grade 1 or baseline after 14 days, resume at 100 mg or 50 mg, once daily, per physician's instruction.
	3rd occurrence	Withhold HIBRUKA. • If the toxicity has resolved to Grade 1 or baseline within 14 days, resume at 50 mg once daily. • If toxicity has resolved to Grade 1 or baseline after 14 days, resume 50 mg once daily or discontinue HIBRUKA, per physician's instruction.
	4th occurrence	Permanently discontinue HIBRUKA.

* Excluding hypertension that has been adequately controlled by oral medication, or asymptomatic laboratory abnormalities. Abnormal laboratory tests suggesting hepatic or renal impairment are not regarded as asymptomatic laboratory abnormalities.

Asymptomatic lymphocytosis is usually not regarded as an adverse reaction. Patients who have experienced such event can continue HIBRUKA under the direction of the treating physician.

Co-administration with CYP3A4 Inhibitors or Inducers

No clinical studies of drug-drug interaction have been conducted. Caution should be taken when co-administered with CYP3A4 inhibitors or inducers. Co-administration with strong and moderate CYP3A4 inhibitors or inducers should be avoided.

Use in Specific Populations

Hepatic Impairment

A pharmacokinetic study of orelabrutinib in patients with hepatic impairment has not been conducted. The use of orelabrutinib in patients with hepatic impairment is not recommended.

Renal Impairment

No dose modification is recommended in patients with mild renal impairment. Patients with moderate or severe renal impairment must use HIBRUKA with caution under the direction of a physician, and renal function should be closely monitored (See *9. Warnings and Precautions* and *17. Pharmacokinetics*).

Geriatric Use

No dose modification is required for elderly patients (See *12. Geriatric Use*).

Paediatric Use

The safety and efficacy of HIBRUKA in paediatric patients have not been established.

7 Adverse Reactions

For details of the following adverse reactions, see *9. Warnings and Precautions*

- Haemorrhage
- Infection
- Cytopenia
- Hepatitis B reactivation
- Second Primary Malignancy
- Hypertension
- Arrhythmia

Clinical Trials Experience

As different clinical trials are not conducted under the same conditions, the adverse reaction rates observed in one clinical trial cannot be directly compared to those from another clinical trial and may not reflect the rates observed in clinical practice.

Summary of Safety Profile

Currently, the safety profile of HIBRUKA is based on data from 5 clinical studies in patients with B-cell malignancies: ICP-CL-00102, ICP-CL-00103, ICP-CL-00104, ICP-CL-00105, ICP-CL-00106.

A total of 304 patients who received continuous treatment with HIBRUKA at a daily dose of 150 mg or above are included in HIBRUKA's safety profile analysis. The median duration of treatment with HIBRUKA was 9.3 months (range: 0.03 to 22.1 months). The most common adverse reactions (≥10%) were neutropenia, thrombocytopenia, leukopenia, haematuria, rash, anaemia, pneumonia, upper respiratory tract infection and arrhythmia. The incidence of Grade 3 or higher adverse reactions was 38.8%. See Table 2 below for common adverse reactions of any grade and of Grade 3 or higher.

Table 2: Common Adverse Reactions (≥5%) of Any Grade and of Grade 3 or higher in HIBRUKA-treated Patients with B-cell Malignancies

Body system and adverse reaction	HIBRUKA-treated patients (N=304)	
	All grades, n (%)	Grade 3 or higher, n (%)
Investigations		
Alanine aminotransferase increased	27 (8.9)	2 (0.7)
Blood bilirubin increased[1]	23 (7.6)	1 (0.3)
Lymphocyte count decreased	18 (5.9)	5 (1.6)
Aspartate aminotransferase increased	16 (5.3)	0
Blood and lymphatic system disorders		
Neutropenia	79 (26.0)	36 (11.8)
Thrombocytopenia	77 (25.3)	26 (8.6)
Leukopenia	52(17.1)	12 (3.9)
Anaemia[2]	45 (14.8)	17 (5.6)
Skin and subcutaneous tissue disorders		
Rash[3]	43 (14.1)	0
Bruise[4]	23 (7.6)	0
Purpura	22 (7.2)	0
Renal and urinary disorders		
Haematuria[5]	50 (16.4)	0
Infections and infestations		
Upper respiratory tract infection[6]	39 (12.8)	7 (2.3)
Pneumonia[7]	34 (11.2)	19 (6.3)
Herpes virus infection[8]	18 (5.9)	5 (1.6)
Circulatory system disorders		
Arrhythmia[9]	33 (10.9)	0
Haemorrhage[10]	29 (9.5)	5 (1.6)
Hypertension	26 (8.6)	8 (2.6)
Respiratory, thoracic and mediastinal disorders		
Pneumonitis[11]	29 (9.5)	6 (2.0)
Metabolism and nutrition disorders		
Hypokalemia	27 (8.9)	9 (3.0)
Hyperglycemia	21 (6.9)	2 (0.7)

[1] Blood bilirubin increased includes: blood bilirubin increased, conjugated bilirubin increased, blood unconjugated bilirubin increased.
[2] Includes anaemia, haemoglobin decreased, haemolytic anaemia.
[3] Includes rash, maculopapular rash, papular rash, macular rash.
[4] Includes ecchymosis, petechiae, post-traumatic punctate intraepidermal haemorrhage, contusion.
[5] Includes blood urine present, red blood cells urine positive, haematuria
[6] Includes upper respiratory tract infection, sinusitis, parainfluenza virus infection, respiratory tract infection, tonsillitis, nasopharyngitis, pharyngitis, influenza
[7] Includes pneumonia, bronchitis, tracheitis.
[8] Includes herpes zoster, Epstein-Barr virus infection, herpes simplex, oral herpes, herpes virus infection.
[9] Includes electrocardiogram QT prolonged, electrocardiogram PR prolongation, supraventricular extrasystoles, ventricular extrasystoles, atrioventricular block first degree, atrial tachycardia, atrioventricular block second degree.

[10] Includes haemorrhage subcutaneous, skin haemorrhage, haemorrhage subepidermal, mucocutaneous haemorrhage, epistaxis, haemoptysis, bronchial haemorrhage, mouth haemorrhage, gingival bleeding, angina bullosa haemorrhagica, cerebral haemorrhage, haemorrhage intracranial, conjunctival haemorrhage, vitreous haemorrhage.
[11] Includes pneumonitis, interstitial lung disease, granulomatous pneumonitis.

The incidence of serious adverse reactions was 23.4%, among which the common ones (≥1%) were pneumonia (5.9%), thrombocytopenia (3.3%), anaemia (2.0%), pneumonitis (2.0%), herpes virus infection (1.0%) and haemorrhage (1.0%). Adverse reactions leading to dose interruption occurred in 16.8% of patients, among which the common ones (≥1%) were thrombocytopenia (3.0%), pneumonia (2.0%), pneumonitis (2.0%), neutropenia (1.6%) and pyrexia (1.0%). Adverse reactions leading to dose reduction occurred in 5.9% of patients, among which the common ones (≥1%) were neutropenia (1.3%), thrombocytopenia (1.3%) and haemorrhage (1.0%). Adverse reactions leading to treatment discontinuation occurred in 6.3% of patients, among which the only common one (≥1%) was thrombocytopenia (1.0%).

Mantle Cell Lymphoma (MCL)

The adverse reaction information of HIBRUKA in MCL patients who have received at least one prior therapy mainly comes from an open-label, multi-centre, phase II pivotal clinical trial (ICP-CL-00102). The trial included 106 patients with a median age of 62 years (range: 37 to 73 years). Most patients had a baseline ECOG performance status of 0 or 1 (46.2% and 50.0%, respectively). The median duration of treatment was 11.9 months (range: 0.5 to 22.1 months). 86 patients received HIBRUKA at 150 mg once daily, with a median duration of treatment of 11.1 months (range: 0.5 to 22.1 months).

Most common adverse reactions (≥10%) in the MCL clinical trial (ICP-CL-00102) were thrombocytopenia (29.2%), neutropenia (23.6%), leukopenia (18.9%), hypertension (17.9%), anaemia (17.0%), rash (16.0%), arrhythmia (16.0%), upper respiratory tract infection (14.2%), pneumonitis (12.3%), hyperglycaemia (11.3%), haematuria (11.3%) and pneumonia (11.3%).

The incidence of Grade 3 or higher adverse reactions was 45.3%, among which the common ones were thrombocytopenia (12.3%), neutropenia (8.5%), anaemia (7.5%), pneumonia (4.7%), hypertension (4.7%), lymphocyte count increased (3.8%), pneumonitis (3.8%), skin and soft tissue infection (2.8%), and white blood cell count increased (2.8%). The incidence of serious adverse reactions was 26.4%, with thrombocytopenia (5.7%), pneumonia (5.7%) and pneumonitis (2.8%) were being the common ones.

Adverse reactions leading to dose interruption occurred in 20.8% of patients, among which the common ones were thrombocytopenia (5.7%), pneumonia (2.8%), and pneumonitis (2.8%). Adverse reactions leading to dose reduction occurred in 6.6% of patients, among which thrombocytopenia (2.8%) was the common ones. 4.7% of patients discontinued treatment due to adverse reactions.

8 Contraindications

HIBRUKA is contraindicated in patients with:

- Severe hepatic impairment;
- Hypersensitivity (manifested by symptoms such as anaphylactic or anaphylactoid reaction) to HIBRUKA or to any of the excipients (see *18 List of Excipients*).

9 Warnings and Precautions

Haemorrhage

Fatal haemorrhagic events have occurred in patients treated with HIBRUKA and other BTK inhibitors. In patients treated with HIBRUKA, 1.6% had Grade 3 or higher haemorrhagic events, including haemorrhage subcutaneous (0.7%), vitreous haemorrhage (0.3%) and haemorrhage intracranial (0.6%). Haemorrhagic events of any grade, including haematuria, bruise, and purpura, occurred in 31.6% of the patients. Haemorrhagic events leading to dose reduction, interruption, and discontinuation occurred in 1.3%, 1.3%, and 1.0% of the patients, respectively.

Treating physician should pay close attention to the risk of haemorrhage during treatment. It is not recommended for patients with severe active haemorrhage to take HIBRUKA. Patients who require anticoagulant or antiplatelet therapies during treatment should be monitored for signs of haemorrhage. Treatment should be discontinued in case of haemorrhage of Grade 3 or higher or intracranial haemorrhage of any grade.

For patients who plan to have a surgery during the treatment, a benefit-risk assessment should be conducted based on the type of surgery and the risk of haemorrhage; HIBRUKA should be withheld at least 3 days pre-surgery and 7 days post-surgery.

Infection

It was observed in clinical studies that HIBRUKA might increase the risk of infection during long-term treatment of patients with B-cell malignancies. The most common infections were upper respiratory tract infection and pneumonia, and there were reports of opportunistic infections. Grade 3 or higher infection occurred in 12.8% of patients, of which pneumonia (6.3%) was common.

Patients with severe infections before taking HIBRUKA can only start the treatment after the infection has been effectively controlled. For patients who are at increased risk of opportunistic infections, prophylaxis should be considered according to standard of care. Symptoms and signs of infections, including pyrexia, should be monitored and evaluated during the treatment, and appropriate treatment should be given if need. In case of infection of Grade 3 or higher, HIBRUKA should be withheld until the infection has been effectively controlled.

Cytopenia

In HIBRUKA-treated patients with B-cell malignancies, cytopenia was very common. Grade 3 or higher cytopenia occurred in 18.4% of patients, among which neutropenia (11.8%), thrombocytopenia (8.6%), anaemia (5.6%) and leukopenia (3.9%) were common. Dose reduction, interruption, and discontinuation due to cytopenia occurred in 2.6%, 4.9%, and 1.0% of patients, respectively.

Close monitoring of complete blood count is recommended during the treatment. In case of cytopenia, symptomatic treatment should be given as indicated; if necessary, withhold the treatment, and re-initiate the treatment after the relevant haematological adverse reactions have been resolved to an acceptable level (see *6.Dosage & Administration* for details).

Hepatitis B reactivation

Hepatitis B reactivation occurred in 1.0% of HIBRUKA-treated patients with B-cell malignancies. In clinical trials, patients with active hepatitis B were excluded. The status of

hepatitis B should be determined before commencing treatment with HIBRUKA. For patients who currently suffer from or have a history of hepatitis B virus infection, it is recommended to consult a hepatitis specialist before initiating HIBRUKA treatment and monitor the patient according to standard medical practice to prevent hepatitis B recurrence.

Second Primary Malignancies

Second primary malignancies events have been observed in the treatment by other BTK inhibitors. They occurred in 0.7% of HIBRUKA-treated patients with B-cell malignancies, including acute myeloid leukaemia (0.3%) and rectal cancer recurrent (0.3%).

Hypertension

Adverse events of hypertension have been reported in clinical trials and post-marketing experiences of other BTK inhibitors. Hypertension of any grade and of Grade 3 or higher occurred in 8.6% and 2.6%, respectively, of HIBRUKA-treated patients with B-cell malignancies. Among patients with hypertensive events, 34.8% had a history of hypertension, and 30.4% of patients had their blood pressure returned to normal within 3 days without medical intervention, and no serious adverse events related to hypertension occurred.

During the treatment with HIBRUKA, it is recommended to closely monitor the patients whose blood pressure is elevated and consult specialist if needed. For patients with a history of hypertension, blood pressure should be closely monitored during treatment with HIBRUKA, and anti-hypertensive treatment should be given or adjusted as needed.

Arrhythmia

Atrial fibrillation, atrial flutter and ventricular tachycardia have been observed in clinical trials and post-marketing experiences of other BTK inhibitors. Among the HIBRUKA-treated patients with B-cell malignancies, 10.9% of the patients reported arrhythmia (see *7. Adverse Reactions)*, and the common ones were electrocardiogram QT prolonged (3.9%), supraventricular extrasystoles (3.0%), ventricular extrasystole (3.0%), first-degree atrioventricular block (1.3%) and atrial tachycardia (1.3%). No Grade 3 or higher arrhythmias were reported, and no adverse reactions of atrial fibrillation or atrial flutter were reported.

During the treatment with HIBRUKA, patients with cardiovascular risk factors or hypertension, acute infection and a history of previous arrhythmia should be monitored for arrhythmia based on clinical manifestations. If a patient has symptoms or signs of arrhythmia (such as palpitations, dizziness, syncope, chest discomfort, newly-onset dyspnoea, etc.), an electrocardiogram (ECG) examination should be performed and consult specialist as needed. For patients with prolonged QT interval, ECG should be monitored closely and concomitant use of drugs that may prolong the QT/QTc interval should be avoided; if the QTc interval is ≥ 500 ms, the dose should be withheld and adjusted promptly (see *6. Dosage & Administration*).

Tumour Lysis Syndrome

Tumour lysis syndrome has been observed in other BTK inhibitors. This adverse reaction has not been reported in clinical trials of HIBRUKA. Baseline risk (e.g., high tumour burden) should be assessed and precautions should be taken accordingly. Monitor patients closely and provide appropriate treatments if need.

Special populations

Hepatic Impairment

Orelabrutinib is primarily metabolized in the liver. Patients with moderate and severe hepatic impairment were excluded from clinical studies, so there have been no clinical data of HIBRUKA treatment in such population of patients. Data in patients with mild hepatic impairment (n=2) in the clinical studies is limited. A pharmacokinetic study of orelabrutinib in patients with hepatic impairment has not been conducted. The use of orelabrutinib in patients with hepatic impairment is not recommended. (see *6. Dosage & Administration*, *8. Contraindications; 17.Pharmacokinetics*).

Renal Impairment

Renal excretion is not the main route of elimination of parent HIBRUKA (see *17. Pharmacokinetics*). Dose modification is not recommended in patients with mild renal impairment (see *6. Dosage & Administration*). Patients with moderate to severe renal impairment (serum creatinine > 1.5 times ULN) were excluded from clinical studies, as there have been no clinical data for HIBRUKA treatment in such population of patients. Patients with moderate or severe renal impairment must use HIBRUKA with caution under the direction of the treating physician, and renal function should be monitored closely (See *17. Pharmacokinetics*).

Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy test (for women of childbearing potential only) should be performed before initiating HIBRUKA treatment.

Contraception

Females: Female patients of child-bearing potential are advised to avoid pregnancy during HIBRUKA treatment and for at least 1 month after the last dose.

There are no available data in pregnant women to evaluate the risk associated with the use of HIBRUKA. Female patients of child-bearing potential must use highly effective method of contraception during HIBRUKA treatment and for at least 1 month after the last dose. Hormonal contraceptive method must be combined with an additional barrier contraceptive method.

If HIBRUKA is used during pregnancy or if the patient becomes pregnant while taking HIBRUKA, the patient should be apprised of the potential risk to a fetus.

Males: Males patients should take effective contraceptive measures during the treatment with HIBRUKA and for at least 3 months after the last dose.

Impact on the ability to drive and operate machinery

No study has been conducted to evaluate the effect of HIBRUKA on the ability to drive and operate machinery.

Others

Keep this product out of reach of children.

10 Pregnant and Lactating Women

Pregnant woman

Advise female patients of child-bearing potential to avoid pregnancy during HIBRUKA treatment and for at least 1 month after the last dose. If HIBRUKA is used during pregnancy

or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus (see *9. Warnings and Precautions*).

Lactation

No peri- and postnatal toxicology study has been conducted, and there is no research data on the use of HIBRUKA in lactating women. There is no information regarding the presence of orelabrutinib or its metabolites in human milk, nor the effects on the breastfed child or milk production. Advise lactating women not to breastfeed baby while taking HIBRUKA and for at least 2 weeks after the final dose.

11 Paediatric Use

The safety and efficacy of HIBRUKA in paediatric patients have not been established.

12 Geriatric Use

In the pivotal clinical trials in chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) (ICP-CL-00103) and MCL (ICP-CL-00102), patients ≥ 65 years of age accounted for 27.5% and 28.3%, respectively, of the total patients enrolled. No overall difference in safety or efficacy was observed between elderly and young patients.

13 Drug Interactions

No clinical studies of drug-drug interaction have been conducted. *In vitro* studies showed that orelabrutinib was mainly metabolized by CYP3A4. Caution should be taken when using HIBRUKA concomitantly with CYP3A4 inhibitors or inducers. Co-administration of HIBRUKA with strong and moderate CYP3A4 inhibitors or inducers should be avoided.

14 Overdosage

There has been no experience in the management of HIBRUKA overdose in patients. There is no effective antidote for overdose with HIBRUKA either. In case of suspected overdose, the patient should be closely monitored and appropriate supportive treatment should be provided.

No dose-limiting toxicity was observed in healthy subjects during the tolerability study at doses up to 400 mg single-dose of orelabrutinib. One accidental overdose of 450 mg per day for consecutive 8 days was reported in a patient during the clinical trials, and no hepatic or renal abnormalities were reported.

15 Clinical Trials

Mantle Cell Lymphoma (MCL)

Study ICP-CL-00102

In an open-label, multi-centre phase II clinical trial (ICP-CL-00102) carried out in China, the safety and efficacy of HIBRUKA were evaluated in MCL patients who had received at least one prior therapy. A total of 86 patients were treated at the dose of 150 mg once daily. The median follow-up was 15.0 months (range: 0.5 to 24.3 months).

The median age of patients was 62 years (range: 37 to 73 years); 79.1% was male. 18.6% of

the patients were in stage III and 75.6% were in stage IV; 30.2% of patients had lymph nodes ≥ 5 cm but < 10 cm in the longest diameter, 10.5% with that ≥ 10 cm, and 41.9% of patients were positive for bone marrow infiltration. 53.5% of patients had received at least two lines of prior treatment.

Efficacy of MCL patients was evaluated by an Independent Review Committee based on CT/MRI and according to the International Working Group 2014 response criteria for Non-Hodgkin's lymphoma. Summary of result is shown in Table 4.

Table 4: Efficacy Result for Patients with Relapsed or Refractory MCL from Study ICP-CL-00102

Endpoint(s)	Overall (N= 86)
Overall Response Rate (%)	77.9
95% confidence interval (%)	(67.7, 86.1)
Complete Response (%)	25.6
Partial Response (%)	52.3
Median duration of response (month)	not reached

16 Pharmacology and Toxicology

Pharmacology

Orelabrutinib is a selective Bruton tyrosine kinase (BTK) inhibitor with an IC_{50} of 1.6 nM for BTK inhibition. BTK is a signalling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. The signalling pathway activated by BCR is necessary for B-cell migration, chemotaxis, and adhesion. Orelabrutinib can inhibit BTK-mediated signalling and subsequent B cell activation and proliferation.

Toxicology Studies

Genotoxicity

Orelabrutinib was negative in the Ames test, *in vitro* chromosomal aberration test using Chinese hamster lung fibroblast cells, and the micronucleus test in rats.

Reproductive toxicity

In the fertility and early embryo developmental toxicity study in rats, oral administration of orelabrutinib at doses of 25 (female)/50 (male), 100, and 400 mg/kg (equivalent to 1.6/3.2-, 6.5-, and 26-fold of recommended human dose of 150 mg/day, respectively, based on body surface area) did not result in any test article-related adverse effects on the fertility and early embryonic development in male and female rats.

In the embryo-fetal developmental toxicity study, oral administration of 50, 150, 400 mg/kg of orelabrutinib (AUC values, equivalent to 5-, 15-, and 37-fold of AUC at the recommended human dose of 150 mg/day) to pregnant rats during organogenesis did not result in significant maternal and embryo-fetal developmental toxicity. Oral administration of 10, 30, 100 mg/kg of orelabrutinib to pregnant rabbits during organogenesis resulted in a decrease in maternal food intake at 100 mg/kg, and non-observed-adverse-effect level (NOAEL) in maternal females and on embryo-fetal development in rabbits were 30 mg/kg and 100 mg/kg, respectively (AUC values at NOAEL equivalent to 3- and 13-fold of AUC at the recommended human dose of 150 mg/day).

Carcinogenesis

Carcinogenicity studies have not been conducted with orelabrutinib.

17 Pharmacokinetics

The pharmacokinetic profile of orelabrutinib shows no significant differences between healthy subjects, CLL/SLL and MCL patients. The exposure of orelabrutinib AUC and C_{max} increases proportionally over a dosage range from 20 mg to 400 mg. At the dose of 150 mg once daily, the mean orelabrutinib steady-state AUC_{0-t} values observed in patients with CLL/SLL and MCL were 7280 ± 1750 h•ng/mL and 7970 ± 1850 h•ng/mL (mean ± SD), respectively, and the mean steady-state C_{max} values were 1580 ± 376 and 1330 ± 384 ng/mL (mean ± SD), respectively, and the mean half-life ($t_{1/2}$) values were 4.04 ± 0.313 hours and 4.41 ± 0.663 hours (mean ± SD), respectively. No systemic accumulation of orelabrutinib and no significant changes in the pharmacokinetic profile were observed following repeated administration.

Absorption

The median time to maximum concentration (t_{max}) for oral administration of orelabrutinib was approximately 2 hours. The mean AUC and C_{max} of orelabrutinib after a high-fat and high-calorie meal (containing approximately 1000 calories with approximately 50% of total caloric content from fat) were about 110% and 74.8%, respectively of those under fasted condition. No clinically significant food effects were observed.

Distribution

Reversible binding of orelabrutinib to human plasma protein *in vitro* was 93.5%, with no concentration dependence in the range of 0.1-10 μM. The *in vitro* blood-to-plasma ratio of orelabrutinib was about 0.9. At the dose of 150 mg once daily, the apparent volume of distribution (V_z/F) values in CLL/SLL and MCL patients were 123 ± 23.1 L and 122 ± 27.7 L (mean ± SD), respectively.

Elimination

After repeated doses of 150 mg once daily, the mean terminal elimination half-life ($t_{1/2}$) values of orelabrutinib in CLL/SLL and MCL patients were 4.04 ± 0.313 hours and 4.41 ± 0.663 hours (mean ± SD), respectively, and the apparent clearance (CL/F) values were 21.3 ± 4.76 L/h and 19.7 ± 6.53 L/h (mean ± SD), respectively, in CLL/SLL and MCL patients.

Metabolism is the main route of elimination for orelabrutinib. *In vitro* studies showed that orelabrutinib was mainly metabolized by CYP3A4.

Orelabrutinib is eliminated primarily in the form of metabolites via feces and urine. After a single oral administration of radio labelled [^{14}C] orelabrutinib in healthy subjects, approximately 83.6% of radioactivity was excreted within 336 hours, with 49.4% excreted in feces and 34.3% in urine. Parent orelabrutinib accounted for less than 1.0% in feces, and about 1.0% in urine of the administered dose.

Pharmacokinetics in Special Populations

There have been no pharmacokinetic data in patients with hepatic impairment, renal impairment, the elderly, and the paediatric populations.

Pharmacokinetic Interaction

No clinical studies of drug-drug interaction have been conducted.

In vitro studies suggested that at the recommended clinical dose, orelabrutinib is unlikely to inhibit the activity of CYP1A2, CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4, nor likely to induce the activity and gene expression of CYP1A2, CYP2B6, and CYP3A4.

18 List of Excipients

HIBRUKA tablet contains the following excipients: Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS), Mannitol, Hydroxypropyl Cellulose, Croscarmellose Sodium, Silicon Dioxide, Magnesium Stearate.

19 Storage

Do not store above 30℃. Protect from moisture and light.

20 Pack Presentation

HIBRUKA tablets are packaged in high-density polyethylene (HDPE) bottle with a polypropylene child-resistant bottle cap system, containing silica gel desiccant in a HDPE cylinder. Don’t open the desiccant cylinder and keep it in the bottle.

Each bottle contains 30 tablets.

21 Shelf Life

36 months.

22 Product Owner

Beijing InnoCare Pharma Tech Co., Ltd.

Bldg 8, Community No.1, No. 8 Courtyard, Life Park Road, ZGC Life Science Park, Changping District, Beijing PRC 102206

23 Date of Last Revision

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