

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

HIBRUKA® (ORELABRUTINIB) TABLETS

1 NAME OF THE MEDICINE

Orelabrutinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg orelabrutinib.

For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**

3 PHARMACEUTICAL FORM

50 mg, white or off-white round tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

HIBRUKA has provisional approval in Australia for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). The decision to approve this indication has been made on the basis of overall response rate (ORR). Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with HIBRUKA should be initiated and supervised by a physician experienced in the use of anticancer therapies

Dosage

The recommended dose of HIBRUKA is 150 mg taken orally once daily until disease progression or unacceptable toxicity.

Method of Administration

Advise patients of the following:

- Swallow whole tablets with water. Do not break, crush, or chew the tablets.
- Take HIBRUKA at the same time each day. HIBRUKA can be taken with or without food.

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.

Dose Modification Guidelines

Recommended dose modifications of HIBRUKA for Grade 3 or greater adverse reactions are provided in [Table 1](#).

Table 1 Dosage modification for adverse reactions

Adverse Reaction	Adverse Reaction 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	First	Interrupt HIBRUKA - If the toxicity has resolved to Grade 1 or baseline within 14 days, resume at 150 mg once daily. - If the toxicity has resolved to Grade 1 or baseline after 14 days, resume at 150 mg or 100 mg, once daily, per physician's instruction.
	Second	Interrupt HIBRUKA - If the toxicity has resolved to Grade 1 or baseline within 14 days, resume at 100 mg once daily. - If the toxicity has resolved to Grade 1 or baseline after 14 days, resume at 100 mg or 50 mg, once daily, per physician's instruction.
	Third	Interrupt HIBRUKA - If the toxicity has resolved to Grade 1 or baseline within 14 days, resume at 50 mg once daily. - If the toxicity has resolved to Grade 1 or baseline after 14 days, resume 50 mg once daily or discontinue HIBRUKA, per physician's instruction.
	Fourth	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 an event can continue HIBRUKA under the direction of the treating physician.

Special Populations

Renal Impairment

No dose modification is recommended in patients with mild and moderate renal impairment (creatinine clearance [CrCl] ≥ 30 mL/min, as estimated by Cockcroft-Gault equation). Use HIBRUKA with caution under the direction of the treating physician, and monitor for HIBRUKA adverse reactions in patients with severe renal impairment (CrCl < 30 mL/min) or on dialysis.

Hepatic impairment

Based on the NCI-ODWG criteria, the recommended dose of HIBRUKA for patients with moderate hepatic impairment (total bilirubin > 1.5 to $\leq 3 \times$ upper limit of normal [ULN] and any aspartate aminotransferase [AST]) is 100 mg orally once daily. No dosage adjustment of HIBRUKA is recommended in patients with mild hepatic impairment (total bilirubin $\leq$ ULN and AST $>$ ULN or total bilirubin > 1 to $\leq 1.5 \times$ ULN and any AST). The use of HIBRUKA in patients with severe hepatic impairment (total bilirubin $> 3 \times$ ULN and any AST) should be avoided. Monitor for HIBRUKA adverse reactions in patients with hepatic impairment.

Geriatric Use

No dose modification is required for elderly patients (See **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE-Use in the Elderly**).

Paediatric Use

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

Interactions Requiring Dose Adjustments

Dose modification for use with CYP3A inhibitors or inducers:

Table 2 Dose Modifications for Use with CYP3A Inhibitors or Inducers

Co-administered Drug	Recommended HIBRUKA Dose
Strong CYP3A inhibitor	50 mg once daily Interrupt dose as recommended for adverse reactions [see 4.2 DOSE AND METHOD OF ADMINISTRATION].
Moderate CYP3A inhibitor	100 mg once daily Modify dose as recommended for adverse reactions [see 4.2 DOSE AND METHOD OF ADMINISTRATION].
Strong CYP3A inducer	Avoid concomitant use.
Moderate CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase HIBRUKA dose to 200 mg once daily.

4.3 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 **6.1 LIST OF EXCIPIENTS**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haemorrhage

Serious haemorrhagic events, including fatal events, have occurred in the combined safety database of 630 patients with haematological malignancies treated with HIBRUKA monotherapy. Grade 3 or higher bleeding events have been reported in 2.1% of patients treated with HIBRUKA monotherapy, mainly including haemorrhage subcutaneous (0.5%), vitreous haemorrhage (0.3%). Bleeding events of any grade, including purpura and petechiae, occurred in 31.7% of patients treated with HIBRUKA monotherapy. Haemorrhagic events leading to dose reduction, interruption, and discontinuation occurred in 1.0%, 2.2%, and 0.6% of the patients, respectively.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of HIBRUKA with antiplatelet or anticoagulant medications may further increase the risk of haemorrhage.

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.

Infections

Serious infections (including bacterial, viral, or fungal) including fatal events and opportunistic infections have occurred in the combined safety database of 630 patients with haematological malignancies treated with HIBRUKA monotherapy. Grade 3 or higher infections occurred in 24.1% of patients treated with HIBRUKA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred. Grade 3 or higher hepatitis B reactivation occurred in 0.3% of patients. In clinical trials, patients with active hepatitis B were excluded.

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.

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.

Effects on Laboratory Tests-Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (12.7%), thrombocytopenia (7.0%), anaemia (6.8%) and leukopenia (3.8%) based on laboratory measurements, were reported in the combined safety database of 630 patients treated with HIBRUKA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 4.4% of the total 630 patients treated with HIBRUKA monotherapy. The most frequent second primary malignancy was nonmelanoma skin cancer (basal cell carcinoma, Bowen's disease, and squamous cell carcinoma of skin), reported in 1.4% of patients. Advise patients to use sun protection.

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 10.3% and 4.1%, respectively, of HIBRUKA-treated patients with B-cell malignancies.

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 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.

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 needed.

Use in the Elderly

Of the patients with MCL who received the 150 mg dose of HIBRUKA in studies ICP-CL-00102 and ICP-CL-00107, 48 (37.2%) were 65 years of age and older and 6 (4.7%) were 75 years and older [see **5.1 PHARMACODYNAMIC PROPERTIES- Clinical trials**]. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

Paediatric Use

Safety and effectiveness in paediatric patients have not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of Other Drugs on HIBRUKA

Table 3 Drug Interactions that Affect HIBRUKA

Moderate and Strong CYP3A Inhibitors	
<i>Clinical Impact</i>	Co-administration with a moderate or strong CYP3A inhibitor increases orelabrutinib C_{max} and AUC [see 5.2 PHARMACOKINETIC PROPERTIES] which may increase the risk of HIBRUKA toxicities.
<i>Prevention management</i> or	Reduce HIBRUKA dosage when co-administered with moderate or strong CYP3A inhibitors [see 4.2 DOSE AND METHOD OF ADMINISTRATION]
Moderate and Strong CYP3A Inducers	
<i>Clinical Impact</i>	Co-administration with a moderate or strong CYP3A inducer decreases orelabrutinib C_{max} and AUC [see 5.2 PHARMACOKINETIC PROPERTIES] which may reduce HIBRUKA efficacy
<i>Prevention management</i> or	Avoid co-administration of HIBRUKA with moderate or strong CYP3A inducers. If concomitant use with moderate CYP3A inducers is unavoidable, increase the HIBRUKA dose [see 4.2 DOSE AND METHOD OF ADMINISTRATION]

Effect of HIBRUKA on Other Drugs

Sensitive CYP2D6, CYP2C19 or P-gp Substrates

HIBRUKA is a weak CYP2D6 and CYP2C19 inhibitor. Concomitant use of HIBRUKA with sensitive CYP2D6 or CYP2C19 substrates increased their systemic exposure, which may increase the risk of adverse reactions related to these substrates for drugs which are sensitive to minimal exposure changes. HIBRUKA modestly increased the C_{max} of digoxin (P-gp substrate), but had no significant effect on AUC. Follow recommendations for sensitive CYP2D6, CYP2C19, or P-gp substrates provided in their approved product labelling.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes:

Orelabrutinib did not inhibit CYP1A2, CYP2C19, CYP2B6 or CYP2C8; and was an inhibitor of intestinal CYP3A4, systemic CYP2C9 and CYP2D6 at clinically relevant.

Orelabrutinib induced CYP3A4 mRNA expression at 1.0 µM, induced CYP2B6 mRNA expression at 10.0 µM, and did not induce CYP1A2 mRNA expression at all when tested at concentrations in the range of 0.3 to 30.0 µM.

Transporter Systems:

Orelabrutinib was a substrate of P-gp, and not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 or MATE2-K.

Orelabrutinib was a potential inhibitor of intestinal and systemic P-gp, and intestinal BCRP, but not of hepatic BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K at clinically relevant concentrations.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Oral administration of orelabrutinib had no adverse effects on fertility and early embryonic development (FEED) in rats. The plasma exposure (AUC) of orelabrutinib in male and female rats at NOAEL of 400 mg/kg/day, was approximately 7- and 19-fold, respectively, of exposure in human at the maximum recommended human dose (MRHD) for B cell malignancy treatment.

Use in Pregnancy– Pregnancy Category C

In the animal embryo-fetal development (EFD) studies, oral administration of orelabrutinib to pregnant rats and rabbits during the period of organogenesis did not result in malformations or embryo-fetal lethality up to the highest doses tested (400 and 100 mg/kg/day in the respective species). The corresponding plasma exposure (AUC) at NOAELs in rats and rabbits was 36- and 12-fold, respectively, of exposure in humans at the MRHD for B-cell malignancy treatment.

Based on the results of animal EFD studies, HIBRUKA has a low risk of causing embryo-fetal malformations or pregnancy loss when administered to pregnant women. However, there are no data available on HIBRUKA use in pregnant women to evaluate a drug-associated risk. Additionally, owing to its pharmacological action, orelabrutinib may pose a risk for immunosuppression through B-cell suppression in the newborn. Advise female patients of childbearing potential to use effective contraception during treatment with HIBRUKA and for at least 1 month following the last dose of HIBRUKA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus. Advise men to avoid fathering a child while receiving HIBRUKA and for at least 3 months following the last dose of HIBRUKA.

Use in lactation.

There are no data available on the presence of HIBRUKA in human milk or the effects on the breastfed child or milk production. Orelabrutinib was present in the milk of lactating rats at a concentration lower than plasma concentration. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with HIBRUKA and for at least 2 weeks after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

Fatigue and dizziness have been reported in some patients taking HIBRUKA and should be considered when assessing a patient's ability to drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety profile is based on pooled data from 630 patients with B-cell malignancies

treated with HIBRUKA in 8 clinical trials, including ICP-CL-00102, ICP-CL-00103, ICP-CL-00104, ICP-CL-00105, ICP-CL-00106, ICP-CL-00107, ICP-CL-00111, and ICP-CL-00127. Among 630 patients receiving HIBRUKA, 74.6% were exposed for 6 months or longer, 63.2% were exposed for greater than one year and 45.9% were exposed for greater than two years.

In this pooled safety population, the most common adverse reactions in $\geq 20\%$ of patients who received HIBRUKA were thrombocytopenia, upper respiratory tract infection, neutropenia, anaemia and COVID-19. The most common grade 3 or above adverse reactions ($\geq 5\%$) were pneumonia, neutropenia, thrombocytopenia, anaemia and COVID-19.

Other clinically relevant adverse reactions include: sinus bradycardia (7.5%), peripheral edema (7.3%), and atrial fibrillation or flutter (1.1%).

Mantle Cell Lymphoma (MCL)

The safety of HIBRUKA was evaluated in 129 patients with MCL who received at least one prior therapy in two single-arm clinical trials of ICP-CL-00102 [NCT03494179] and ICP-CL-00107 [NCT04014205] [see **5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials**]. The median duration of treatment was 16.9 months.

The median age of patients who received HIBRUKA in studies ICP-CL-00102 and ICP-CL-00107 was 62.0 years (range: 37 to 84): 81.4% were male, 66.7% were Asian, 32.6% were White, and 52.7% had an ECOG performance status of 0. 42.6% of patients have received at least 2 lines of prior treatments. Patients received HIBRUKA 150 mg once daily. Among patients receiving HIBRUKA, 79.1% were exposed for 6 months or longer and 65.1% were exposed for greater than one year.

The most common adverse reactions ($\geq 20\%$) in the MCL clinical trial (ICP-CL-00102 and ICP-CL-00107) were thrombocytopenia, anaemia, upper respiratory tract infection, neutropenia, rash, and diarrhoea.

The incidence of Grade 3 or higher adverse reactions was 54.3%, among which the common ones ($\geq 2\%$) were thrombocytopenia, neutropenia, anaemia, pneumonia, hypertension, hypokalaemia, leukopenia, and abdominal pain.

The incidence of serious adverse reactions was 38.8%. Adverse reactions leading to dose interruption occurred in 36.4% of patients. Adverse reactions leading to dose reduction occurred in 6.2% of patients. 9.3% of patients discontinued treatment due to adverse reactions.

Table 4 Adverse Reactions (≥ 10%) in Patients with MCL Receiving HIBRUKA in ICP-CL-00102 and ICP-CL-00107

	HIBRUKA 150 mg once daily N=129	
	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders		
Thrombocytopenia*	36 (27.9)	15 (11.6)
Anaemia*	33 (25.6)	13 (10.1)
Neutropenia*	29 (22.5)	14 (10.9)
Leukopenia*	21 (16.3)	3 (2.3)
Infections and infestations		
Upper respiratory tract infection*	32 (24.8)	0
Pneumonia*	24 (18.6)	12 (9.3)
COVID-19*	14 (10.9)	2 (1.6)
	HIBRUKA 150 mg once daily N=129	
	All Grades (%)	Grade 3 or 4 (%)
Urinary tract infection*	13 (10.1)	1 (0.8)
Gastrointestinal disorders		
Diarrhoea*	26 (20.2)	1 (0.8)
Abdominal pain*	16 (12.4)	3 (2.3)
Metabolism and nutrition disorders		
Hyperglycaemia*	26 (20.2)	1 (0.8)
Hypokalaemia*	19 (14.7)	4 (3.1)
Vascular disorders		
Hypertension*	25 (19.4)	10 (7.8)
Haemorrhage*	20 (15.5)	1 (0.8)
Skin and subcutaneous tissue disorders		
Rash*	28 (21.7)	0
Respiratory, thoracic and mediastinal disorders		
Cough*	26 (20.2)	0
General disorders and administration site conditions		
Fatigue*	23 (17.8)	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	19 (14.7)	1 (0.8)
Nervous system disorders		
Dizziness*	15 (11.6)	0
Investigations		
Blood bilirubin increased	14 (10.9)	0

* Includes multiple adverse reaction terms

Adverse events were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V4.03 for study ICP-CL-00102 and V5.0 for study ICP-CL-00107.

Table 5 summarizes laboratory abnormalities in ICP-CL-00102 and ICP-CL-00107.

Table 5 Selected Laboratory Abnormalities ($\geq 20\%$) that Worsened from Baseline in Patients with MCL Who Received HIBRUKA in ICP-CL-00102 and ICP-CL-00107

Laboratory Abnormality	HIBRUKA 150 mg once daily N=129	
	All Grades (%)	Grade 3 or 4 (%)
Haematology		
Platelet count decreased	61 (47.7)	20 (15.6)
Anaemia	43 (33.6)	17 (13.3)
Neutrophil count decreased	42 (32.8)	21 (16.4)
Chemistry		
Aspartate aminotransferase increased	26 (20.3)	1 (0.8)
Hyperuricemia	9 (20.9)	9 (20.9)

Grades were evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V4.03 for study ICP-CL-00102 and V5.0 for study ICP-CL-00107.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific antidote for overdose with HIBRUKA. 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 a 400 mg single-dose of HIBRUKA. One accidental overdose of 450 mg per day for a consecutive 8 days was reported.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

Pharmacodynamic effects

BTK Occupancy in PBMCS

In patients with MCL, orelabrutinib achieved nearly complete and persistent BTK occupancy up to 24 hours after a therapeutic dose of 150 mg QD.

Cardiac Electrophysiology

After a single 400 mg dose (2.7 times of the clinically recommended dosage), orelabrutinib had no clinically meaningful effect on the QTc interval.

Clinical trials

Mantle Cell Lymphoma

The efficacy of HIBRUKA was assessed in study ICP-CL-00102 (NCT03494179), a phase 2, open-label, multicentre, single-arm clinical trial of 86 previously treated patients with MCL who had received at least one prior therapy. HIBRUKA was given orally at a dose of 150 mg once daily until disease progression or unacceptable toxicity. The median follow-up was 47.1 months (range: 0.5 to 65.3 months).

The median age of patients was 62 years (range: 37 to 73 years); 79.1% were male. 18.6% of the patients were in stage III and 75.6% were in stage IV; 29.1% of patients had lymph nodes ≥ 5 cm but < 10 cm in the longest diameter, 9.3% 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 IRC based on CT/MRI and according to the International Working Group 2014 response criteria for non-Hodgkin's lymphoma. The summary of the results is shown in [Table 6](#).

The efficacy of HIBRUKA was also assessed in study ICP-CL-00107 (NCT04014205), a phase 2, open-label, multicentre, single-arm clinical trial of 43 patients previously treated with MCL who had received at least one prior therapy. HIBRUKA was given orally at a dose of 150 mg once daily until disease progression or unacceptable toxicity. The median follow-up was 16.8 months (range: 5.4 to 46.5 months).

The median age of patients was 64.0 years (range: 39 to 84 years); 86.0% were male. 20.9% of the patients were in stage III and 69.8% were in stage IV; 27.9% of patients had lymph nodes ≥ 5 cm but < 10 cm in the longest diameter, no patients with lymph nodes ≥ 10 cm, and 48.8% of patients were positive for bone marrow infiltration. The median number of previous therapies was 1 (range: 1 to 4).

Efficacy of MCL patients was evaluated by an IRC based on CT/MRI and according to the International Working Group 2014 response criteria for Non-Hodgkin's lymphoma. The summary of the results is shown in [Table 6](#).

Table 6 Efficacy Results in Patients with MCL by Independent Review Committee

Endpoint(s)	Study ICP-CL-00102 Overall (N= 86)	Study ICP-CL-00107 Overall (N= 43)	Total (N=129)
Overall Response Rate (%)	72.1	83.7	76.0
95% confidence interval (%)	(61.4, 81.2)	(69.3, 93.2)	(67.7, 83.1)
Complete Response (%)	33.7	39.5	35.7
Partial Response (%)	38.4	44.2	40.3
Median duration of response (range) (month)	NE (1.9, 53.5+)	NE (0.0+, 42.3+)	NA (0.0+, 53.5+)

Per 2014 Lugano Classification.

NE: non-evaluable.

+: censoring.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic profile of orelabrutinib shows no significant differences between healthy subjects and MCL patients. The exposure of orelabrutinib AUC and C_{max} increases proportionally over a dosage range from 20 mg to 400 mg. No systemic accumulation of orelabrutinib and no significant changes in the pharmacokinetic profile were observed following repeated administration.

At a dose of 150 mg once daily, the mean (CV%) of orelabrutinib steady-state AUC_{0-24} was 7555 (24.54%) h•ng/mL, and the mean (CV%) of the steady-state C_{max} was 1240 (31.94%) ng/mL.

Absorption

The median time to maximum concentration (t_{max}) for oral administration of orelabrutinib was approximately 2 hours.

Food effect

The geometric mean AUC and C_{max} of orelabrutinib after a high-fat and high-calorie meal (containing approximately 1,000 calories with approximately 50% of total caloric content from fat) were 111% and 76.55%, respectively of those under fasted conditions. No clinically significant food effects were observed.

Distribution

Human plasma protein binding of orelabrutinib was 93.5%. The *in vitro* blood-to-plasma ratio of orelabrutinib was about 0.9. At a dose of 150 mg once daily, the mean (CV%) of the apparent volume of distribution (V_z/F) was 123 (21.58%) L.

Metabolism

Metabolism is the main route of elimination for orelabrutinib. Orelabrutinib is primarily metabolized by CYP3A4.

Excretion

After repeated doses of 150 mg once daily, the mean terminal elimination half-life ($t_{1/2}$) value of orelabrutinib was approximately 4 hours, and the mean (CV%) of the apparent clearance (CL/F) values was 20.9 (29.81%) L/h.

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

Specific Populations

No clinically meaningful differences in the pharmacokinetics of orelabrutinib were observed based on age (18 to 90 years), sex, race (White and Asian), body weight (42 to 128 kg), or mild to moderate renal impairment (creatinine clearance [CrCl] ≥ 30 mL/min, as estimated by Cockcroft-Gault equation). The effect of severe renal impairment ($\text{CrCl} < 30$ mL/min) and dialysis on orelabrutinib pharmacokinetics is unknown.

Hepatic Impairment

Based on the Child-Pugh classification, the total AUC of orelabrutinib increased by 65% in subjects with mild hepatic impairment (Child-Pugh class A) and by 93% in subjects with moderate hepatic impairment (Child-Pugh class B) relative to subjects with normal liver function. The unbound AUC of orelabrutinib increased by 71% in subjects with mild hepatic impairment and by 162% in subjects with moderate hepatic impairment relative to subjects with normal liver function. Based on the NCI-ODWG classification, the total AUC of orelabrutinib in subjects with mild hepatic impairment (total bilirubin $\leq$ ULN and aspartate aminotransferase (AST) $>$ ULN or total bilirubin > 1 to $\leq 1.5 \times$ ULN and any AST) had no significant difference, and increased by 50% in subjects with moderate hepatic impairment (total bilirubin > 1.5 to $\leq 3 \times$ ULN and any AST) and by 83% in subjects with severe hepatic impairment (total bilirubin $> 3 \times$ upper limit of normal (ULN) and any AST) relative to subjects with normal liver function. The unbound AUC of orelabrutinib increased by 21% in subjects with mild hepatic impairment, by 102% in subjects with moderate hepatic impairment, and by 199% in subjects with severe hepatic impairment relative to subjects with normal liver function.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

CYP3A Inhibitors:

Co-administration of multiple doses of itraconazole (strong CYP3A inhibitor) increased the orelabrutinib C_{max} by 59% and AUC by 110%.

Co-administration of multiple doses of fluconazole (moderate CYP3A inhibitor) was predicted to increase orelabrutinib C_{max} by 30% and AUC by 70%.

Co-administration of multiple doses of cimetidine (weak CYP3A inhibitor) was predicted of no clinically significant interaction.

CYP3A Inducers:

Co-administration of multiple doses of rifampin (strong CYP3A inducer) decreased the orelabrutinib C_{max} by 75% and AUC by 87%.

Co-administration of multiple doses of efavirenz (moderate CYP3A inducer) was predicted to decrease orelabrutinib C_{max} by 34% and AUC by 53%.

Co-administration of multiple doses of dexamethasone (weak CYP3A inducer) was predicted to decrease orelabrutinib C_{max} by 18% and AUC by 30%.

Gastric Reducing Agents:

The impact of administration of proton pump inhibitors (PPI) on the plasma exposure of orelabrutinib is predicted to be not clinically significant.

CYP3A4 Substrates:

Orelabrutinib had no clinically meaningful effect on the plasma exposure of midazolam (CYP3A substrate).

CYP2D6 Substrates:

Orelabrutinib increased the AUC and C_{max} of dextromethorphan (CYP2D6 substrate) by 29% and 37%, respectively.

CYP2C9 Substrates:

Orelabrutinib had no clinically meaningful effect on the plasma exposure of S-warfarin (CYP2C9 substrate).

CYP2C19 Substrates:

Orelabrutinib increased the AUC of omeprazole (CYP2C19 substrate) by 27% and had no clinically significant impact on C_{max} .

CYP1A2 Substrates:

Orelabrutinib had no clinically meaningful effect on the plasma exposure of caffeine (CYP1A2 substrate).

CYP2B6 Substrate:

Orelabrutinib was predicted to have no DDI risk when co-administered with bupropion (CYP2B6 substrate).

P-gp Substrates:

Multiple doses of orelabrutinib increased the C_{max} of digoxin (P-gp substrate) by 52% and had no clinically significant impact on AUC.

BCRP Substrates:

Multiple doses of orelabrutinib had no clinically significant impact on the plasma exposure of rosuvastatin (BCRP substrate).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Orelabrutinib was not genotoxic in the *in vitro* bacterial mutagenicity assay (Ames test) and chromosomal aberration assay as well as in the *in vivo* micronucleus test in rats.

Carcinogenicity

Carcinogenicity studies have not been conducted for orelabrutinib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Hypromellose acetate succinate
Mannitol,
Hyprolose,
Croscarmellose Sodium,
Silicon Dioxide,
Magnesium Stearate

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.3 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Keep in original container. Keep lid tightly closed. Protect from light.

6.4 NATURE AND CONTENTS OF CONTAINER

HIBRUKA tablets are packed in high-density polyethylene (HDPE) bottles with a polypropylene child-resistant bottle cap system, containing silica gel desiccant in a HDPE cylinder. Do not open the desiccant cylinder. Keep it in the bottle.

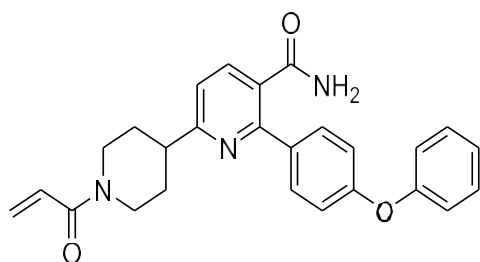
Each bottle contains 30 tablets.

6.5 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.6 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

1655504-04-3

Molecular formula

C₂₆H₂₅N₃O₃

Molecular weight

427.50 g/mol

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription-only medicine (Schedule 4)

8 SPONSOR

Innocare Pharma Australia Pty Ltd

SUITE 1903
 109 PITT STREET
 Sydney
 NSW 2000

E-mail: Product_inquiry@innocarepharma.com

9 DATE OF FIRST APPROVAL

XXXXXX

10 DATE OF REVISION

Summary table of changes

Section Changed	Summary of new information