Professional Information For:

ACALABRUTINIB Cipla 100 mg Capsules

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ACALABRUTINIB CIPLA (100 mg hard gelatin capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 100 mg of acalabrutinib.

Sugar free

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Hard gelatin capsules.

ACALABRUTINIB CIPLA capsules: White to off white to light yellow blend, filled in size “1” Opaque, hard gelatin capsules, with pink cap and white body, printed with black ink “Cipla” on the cap and “100 mg” on the body.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

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

ACALABRUTINIB CIPLA is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL).

4.2 Posology and method of administration

Treatment with ACALABRUTINIB CIPLA should be initiated and supervised by a medical practitioner experienced in the use of anticancer therapies.

Posology

MCL

The recommended dose of ACALABRUTINIB CIPLA for the treatment of MCL is 100 mg (1 capsule) twice a day.

CLL

The recommended dose of ACALABRUTINIB CIPLA for the treatment of MCL is 100 mg (1 capsule) twice a day, either as monotherapy or in combination with Obinutuzumab. Refer to the Obinutuzumab prescribing information for recommended Obinutuzumab dosing information. Doses should be separated by approximately 12 hours.

Treatment with ACALABRUTINIB CIPLA should continue until disease progression or unacceptable toxicity.

Missed Dose

If a patient misses a dose of ACALABRUTINIB CIPLA by more than 3 hours, instruct the patient to take the next dose at its regularly scheduled time. Extra capsules of ACALABRUTINIB CIPLA should not be taken to make up for a missed dose.

Dose Adjustment

Adverse Reactions

Recommended dose modifications of ACALABRUTINIB CIPLA for Grade ≥ 3 adverse reactions are provided in Table 1**.**

Table 1. Recommended Dose Adjustments for Adverse Reactions

Adverse Reaction Occurrence	**Dose Modification (Starting dose = 100 mg twice a day)**
First and Second	Restart at 100 mg twice daily
Third	Restart at 100 mg daily.
Fourth	Discontinue ACALABRUTINIB CIPLA

Table 2: Dose Modifications for use with CYP3A Inhibitors or Inducers and Gastric Acid Reducing medicines

	Co-administered medicine	**Recommended ACALABRUTINIB CIPLA use**
CYP3A Inhibitors	Strong CYP3A inhibitors	Consider alternative therapies to strong CYP3A inhibitors. Monitor patients closely for adverse reactions if taking strong CYP3A inhibitors.
CYP3A Inducers	Strong CYP3A inducers	Consider alternative therapies to strong CYP3A inducers If these inducers cannot be avoided, increase ACALABRUTINIB CIPLA dose to 200mg twice daily.
Gastric Acid Reducing medicines	Proton Pump Inhibitors	Avoid concomitant use.
	H2-Receptor Antagonists	Take ACALABRUTINIB CIPLA, 2 hours before taking a H2-receptor antagonist.
	Antacids	Separate dosing by at least 2 hours.

SPECIAL POPULATIONS

Elderly population

No dose adjustment is required for elderly patients aged ≥ 65 years, see **section 5.2**.

Renal impairment

No dose adjustment is recommended in patients with mild to moderate renal impairment, [eGFR greater than or equal to 30 mL/min/1,73m^2 as estimated by MDRD (modification of diet in renal disease equation)]

The pharmacokinetics and safety of ACALABRUTINIB CIPLA in patients with severe renal impairment (eGFR less than 29 mL/min/1,73m^2) or end-stage renal disease have not been studied (see **section 5.2**).

Hepatic impairment

No dose adjustment is recommended in patients with mild or moderate hepatic impairment (Child-Pugh A, Child-Pugh B or total bilirubin between 1,5 to 3 times upper limit of normal [ULN] and any AST). It is not recommended to administer ACALABRUTINIB CIPLA in patients with severe hepatic impairment (Child-Pugh C, or total bilirubin between > 3 times the ULN and any AST) (see **section 5.2**).

Paediatric population

The safety and efficacy of ACALABRUTINIB CIPLA in children and adolescents aged less than 18 years have not been established.

Method of administration

Oral use.

ACALABRUTINIB CIPLA should be swallowed whole with water at approximately the same time each day.

ACALABRUTINIB CIPLA can be taken with or without food. The capsule should not be chewed, dissolved, or opened.

4.3. Contraindications

ACALABRUTINIB CIPLA is contraindicated for the following:

- Hypersensitivity to acalabrutinib or any of the excipients listed in **section 6.1**.

4.4. Special warnings and precautions for use

Haemorrhagic events

Serious haemorrhagic events, including fatal events, have been reported in patients with haematologic malignancies (n=1040) treated with acalabrutinib monotherapy.

The mechanism for the bleeding events is not well understood. Patients receiving antithrombotic medicines may be at increased risk of haemorrhage. Use caution with antithrombotic medicines and consider additional monitoring for signs of bleeding when concomitant use is medically necessary.

Consider the benefit-risk of withholding ACALABRUTINIB CIPLA for at least 3 days pre- and post-surgery.

Infections

Serious infections (bacterial, viral or fungal), including fatal events have been reported in patients with haematologic malignancies (n=1040) treated with acalabrutinib monotherapy. Grade 3 or higher infections occurred in these patients. The most frequently reported Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation, aspergillosis, and progressive multifocal leukoencephalopathy (PML) have occurred. Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Cytopenia's

Treatment-emergent Grade 3 or 4 cytopenia's, including neutropenia, anaemia and thrombocytopenia based on laboratory measurements, has been reported in patients with haematologic malignancies (n=1040) treated with acalabrutinib monotherapy. Monitor complete blood counts as medically appropriate.

Second Primary Malignancies

Second primary malignancies, including non-skin cancers have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy reported is skin cancer. Skin cancers should be monitored.

Atrial Fibrillation and Flutter

In patients with haematologic malignancies (n=1040) treated with acalabrutinib monotherapy, Grade 3 atrial fibrillation/flutter have been reported in 1% of patients, and Grade 1 or 2 in 3% of patients. Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) of atrial fibrillation and atrial flutter and obtain an ECG as appropriate.

ACALABRUTINIB CIPLA contains sodium starch glycolate

ACALABRUTINIB CIPLA contains less than 1 mmol sodium (23 mg) per dose, essentially 'sodium-free'.

4.5. Interaction with other medicines and other forms of interaction

Active substances that may increase acalabrutinib plasma concentrations

CYP3A Inhibitors

Co-administration of acalabrutinib with a strong CYP3A inhibitor (itraconazole) increases acalabrutinib plasma concentrations, which may result in increased toxicity.

Consider alternative therapies that do not strongly inhibit CYP3A activity. Patients taking strong CYP3A inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, ritonavir, telaprevir, posaconazole, voriconazole) with ACALABRUTINIB CIPLA should be monitored more closely for adverse reactions.

Active substances that may decrease acalabrutinib plasma concentrations

CYP3A Inducers

Co-administration of acalabrutinib with a strong CYP3A inducer (rifampin) decreases acalabrutinib plasma concentrations, which may result in reduced ACALABRUTINIB CIPLA activity.
Consider alternative therapies to strong inducers of CYP3A activity (e.g., phenytoin, rifampin, carbamazepine). Avoid St. John's wort which may unpredictably decrease acalabrutinib plasma concentrations. If a strong CYP3A inducer cannot be avoided, increase the ACALABRUTINIB CIPLA dose to 200 mg twice daily.

Gastric Acid Reducing medicines

Acalabrutinib solubility decreases with increasing pH. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days), decreased acalabrutinib AUC by 43 %.
If treatment with an acid reducing medicine is required, consider using an antacid (e.g., calcium carbonate), or an H2-receptor antagonist (e.g., ranitidine or famotidine). For use with antacids, separate dosing by at least 2 hours. For H2-receptor antagonists, take ACALABRUTINIB CIPLA 2 hours before taking the H2-receptor antagonist.
Due to the long-lasting effect of proton pump inhibitors, separation of doses with proton pump inhibitors may not eliminate the interaction with ACALABRUTINIB CIPLA.

Active substances whose plasma concentrations may be altered by ACALABRUTINIB CIPLA

CYP3A Substrates

Based on in vitro data and PBPK modelling, no interaction with CYP substrates is expected at the clinically relevant concentrations (see **section 5.2**).

Effects of Acalabrutinib and its active metabolite, ACP-5862, on Drug Transport Systems

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP (see **section 5.2**).

ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1 (see **section 5.2**).

4.6. Fertility, pregnancy, and lactation

Women of childbearing potential

ACALABRUTINIB CIPLA should not be used by women of childbearing potential, and they should be advised to avoid becoming pregnant while receiving ACALABRUTINIB CIPLA.

Pregnancy

ACALABRUTINIB CIPLA should not be used during pregnancy.

Breastfeeding

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk. Breastfeeding mothers should not breastfeed during treatment with ACALABRUTINIB CIPLA and for 2 days after receiving the last dose.

Fertility

There are no data on the effect of ACALABRUTINIB CIPLA on human fertility.

4.7. Effects on ability to drive and use machines

ACALABRUTINIB CIPLA has no or negligible influence on the ability to drive and use machines. However, during treatment with acalabrutinib, fatigue and dizziness have been reported and patients who experience these symptoms should be advised not to drive or use machines.

4.8. Undesirable effects

a) Summary of the safety profile

The most frequent reported adverse drug reactions of any grade in patients treated with acalabrutinib monotherapy, are infection, headache, diarrhoea, bruising, musculoskeletal pain, nausea, fatigue, and rash.

The most frequently reported Grade ≥ 3 adverse drug reactions are infection, neutropenia, and anaemia.

b) Tabulated list of adverse reactions

Tables 3 present the frequency category of adverse reactions observed in patients with Haematological malignancies treated with ACALABRUTINIB CIPLA.

System Organ Class	All Grades	Grade ≥ 3 Adverse Reactions /Frequency
Infections and infestations	**Frequent** Infection	**Frequent** Infection
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	**Frequent** Second primary malignancy Non-melanoma skin cancer Second primary malignancy excluding non-melanoma skin	**Frequent** Second primary malignancy Second primary malignancy excluding non-melanoma skin **Less Frequent** Non-melanoma skin cancer

Blood and lymphatic system disorders	**Frequent** Leukopenia Neutropenia Anaemia Thrombocytopenia	**Frequent** Leukopenia Neutropenia Anaemia Thrombocytopenia
Metabolism and nutrition disorders	**Less Frequent** Tumour Lysis Syndrome	**Less Frequent** Tumour Lysis Syndrome
Nervous system disorders	**Frequent** Headache Dizziness	**Frequent** Headache **Less Frequent** Dizziness
Cardiac disorders	**Frequent** Atrial fibrillation /Flutter	**Frequent** Atrial fibrillation /Flutter
Vascular disorders	**Frequent** Haemorrhage/ Hematoma	**Less Frequent** Haemorrhage/ Hematoma
Respiratory, thoracic, and mediastinal disorders	**Frequent** Epistaxis	**Less Frequent** Epistaxis
Gastrointestinal disorders	**Frequent** Diarrhoea Nausea Abdominal pain Constipation Vomiting	**Frequent** Diarrhoea Nausea Abdominal pain **Less Frequent** Constipation Vomiting
Skin and subcutaneous tissue disorders	**Frequent** Bruising Rash	**Less Frequent** Rash
Musculoskeletal and connective tissue disorders	**Frequent** Arthralgia Musculoskeletal Pain	**Frequent** Musculoskeletal Pain **Less Frequent** Arthralgia
General disorders and administration site conditions	**Frequent** Fatigue Asthenia	**Frequent** Fatigue **Less Frequent** Asthenia
Investigations	**Frequent**	**Frequent**

	Decreased haemoglobin Decreased platelets Decreased absolute neutrophil count	Decreased haemoglobin Decreased platelets Decreased absolute neutrophil count

Other special populations

Elderly

No clinically relevant differences in safety or efficacy observed between patients ≥ 65 years and younger.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or drugsafetysa@cipla.com

4.9. Overdose

There is no specific treatment for ACALABRUTINIB CIPLA overdose and symptoms of overdose have not been established. In the event of an overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors.

ATC code: L01EL02.

Mechanism of action

Acalabrutinib is a selective small-molecule inhibitor of Bruton tyrosine kinase (BTK). BTK is a signalling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, chemotaxis.

Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK (IC50 ≤ 5 nM) with minimal off-target interactions.

In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signalling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival and had minimal activity on other immune cells (T cells and NK cells).

5.2. Pharmacokinetic properties

Acalabrutinib exhibits dose-proportionality, and both acalabrutinib and its active metabolite, ACP-5862 exhibit almost linear PK across a dose range of 75 to 250 mg. Population PK modelling suggests that the PK of acalabrutinib and ACP-5862 does not differ significantly in patients with different B-cell malignancies. At the recommended dose of 100 mg twice daily in patients with B-cell malignancies, the geometric mean steady state daily area under the plasma drug concentration over time curve (AUC24h) and maximum plasma concentration (C_{max}) of acalabrutinib were 1893 ng•h/mL and 466 ng/mL, respectively, and for ACP-5862 were 4091 ng•h/mL and 420 ng/mL, respectively.

Absorption

The median time to peak acalabrutinib plasma concentrations (T_{max}) was 0,75 hours, and 1,0 hour for ACP-5862. The geometric mean absolute bioavailability of acalabrutinib is 25 %.

Distribution

Reversible binding to human plasma protein is 97,5 % for acalabrutinib and 98,6 % for ACP-5862. The *in vitro* mean blood-to-plasma ratio is 0,8 for acalabrutinib and 0,7 for ACP-5862. The mean steady-state volume of distribution (V_{ss}) is approximately 34 L for acalabrutinib.

Biotransformation

Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis, based on *in vitro* studies. ACP-5862 is identified as the major active metabolite in plasma with a geometric mean exposure (AUC) that was approximately 2-to 3-fold higher than the exposure of acalabrutinib. ACP-5862 is approximately 50 % less potent than acalabrutinib with regard to BTK inhibition.

In vitro, acalabrutinib is a weak inhibitor of CYP3A4/5, CYP2C8 and CYP2C9, but does not inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, UGT1A1, and UGT2B7. ACP-5862 is a weak inhibitor of CYP2C8, CYP2C9 and CYP2C19, but does not inhibit CYP1A2, CYP2B6, CYP2D6, CYP3A4/5, UGT1A1, and UGT2B7 in vitro. Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4 mRNA; ACP-5862 weakly induces CYP3A4.

Interactions with transport proteins

In vitro, acalabrutinib and its active metabolite, ACP-5862, are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein(BCRP). Acalabrutinib is not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1 and OATP1B3, *in vitro*. ACP-5862 is not a substrate of OATP1B1 or OATP1B3.

Acalabrutinib and ACP-5862 do not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, and MATE2-K at clinically relevant concentrations.

Acalabrutinib may inhibit intestinal BCRP substrates (see **section 4.5**), while ACP-5862 may inhibit MATE1 (see **section 4.5**) at clinically relevant concentrations. Acalabrutinib does not inhibit MATE1, while ACP-5862 does not inhibit BCRP at clinically relevant concentrations.

Elimination

Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life ($t_{1/2}$) of acalabrutinib is 0,9 (range: 0,6 to 2,8) hours. The median $t_{1/2}$ of the active metabolite, ACP-5862, is 6,9 hours (range: 2,7 to 9,1) hours.

Following administration of a single 100 mg radiolabelled acalabrutinib dose in healthy subjects, 84 % of the dose was recovered in the faeces and 12 % of the dose was recovered in the urine, with less than 2 % of the dose excreted as unchanged acalabrutinib in urine and faeces.

Pharmacokinetics in Special Populations

No clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862 based age, sex, race and body weight.

Renal impairment

No clinically relevant PK difference is observed in patients with mild renal impairment (eGFR between 60 and 89 mL/min/1,73m^2) or moderate renal impairment (eGFR between 30 and 59 mL/min/1,73m^2, as estimated by MDRD (modification of diet in renal disease equation). Acalabrutinib PK has not been evaluated in patients with severe renal impairment (eGFR < 29 mL/min/1,73m^2, MDRD) or renal impairment requiring dialysis.

Hepatic impairment

Acalabrutinib is metabolised in the liver.

Based on a population PK analysis, no clinically relevant difference has been observed within patients with mild (n = 79) or moderate (n = 6) hepatic impairment (total bilirubin between 1,5 to 3 times ULN and any AST) relative to subjects with normal (n = 651) hepatic function (total bilirubin and AST within ULN).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Magnesium stearate (Vegetable Grade)

Pregelatinized starch (Starch 1500)

Silicified Microcrystalline Cellulose (Prosolv SMCC 90)

Sodium starch glycolate (Primogel Type- A)

Hard gelatin capsule: The composition of empty hard gelatin capsule is:

Gelatin

Iron Oxide red E172

Purified water

Titanium dioxide E171

Composition of ink used for printing on Capsule Shell are:

Black Iron Oxide E172

Butyl Alcohol

Dehydrated Alcohol E1510

Isopropyl Alcohol

Potassium Hydroxide E525

Propylene Glycol E1520

Purified water

Shellac E904

Strong Ammonia Solution E527

6.2. Incompatibilities

Not applicable

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5. Nature and contents of container

ACALABRUTINIB CIPLA is packed in a 75cc white HDPE bottle, with 38 mm White Child Resistant cap. Pack size of 60`s capsules.

6.6. Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

57/26/0033

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 July 2023

Date of latest renewal: TBC

10. DATE OF REVISION OF THE TEXT