For use in India only

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Acalabrutinib Capsules 100 mg

MSN Acalone 100
एम एस एन एकालन १००

To be sold by retail on the prescription of Oncologist only

PRESCRIBING INFORMATION

1. GENERIC NAME
Acalabrutinib Capsules 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Hard gelatin capsule contains:
Acalabrutinib dihydrate 107.740 mg equivalent to Acalabrutinib 100 mg

3. DOSAGE FORM AND STRENGTH
Capsules; 100 mg

4. CLINICAL PARTICULARS

4.1. Indications
Acalabrutinib is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
Acalabrutinib is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).

4.2. Posology and Method of Administration

Acalabrutinib as Monotherapy
For patients with MCL, CLL or SLL the recommended dose of Acalabrutinib is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

Acalabrutinib in Combination with Obinutuzumab
For patients with previously untreated CLL or SLL, the recommended dose of Acalabrutinib is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start Acalabrutinib at Cycle 1 (each cycle is 28 days). Start obinutuzumab at Cycle 2 for a total of 6 cycles and refer to the obinutuzumab prescribing information for recommended dosing. Administer Acalabrutinib prior to obinutuzumab when given on the same day. Advise patients to swallow capsule whole with water. Advise patients not to open, break or chew the capsules. Acalabrutinib may be taken with or without food. If a dose of Acalabrutinib is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra capsules of Acalabrutinib should not be taken to make up for a missed dose.

Recommended Dosage for Hepatic Impairment
Avoid administration of Acalabrutinib in patients with severe hepatic impairment. Dose modifications are not required for patients with mild or moderate hepatic impairment.

Recommended Dosage for Drug Interactions

Dose Modifications for Use with CYP3A Inhibitors or Inducers.
Table 1: Recommended Dose Modifications for Use with CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended Acalabrutinib use
Inhibition	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt Acalabrutinib.
	Moderate CYP3A inhibitor	100 mg once daily.
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase Acalabrutinib dose to 200 mg approximately every 12 hours.

Concomitant Use with Gastric Acid Reducing Agents
Proton Pump Inhibitors: Avoid concomitant use.
H2-Receptor Antagonists: Take Acalabrutinib 2 hours before taking a H2-receptor antagonist.
Antacids: Separate dosing by at least 2 hours.

Dose Modifications for Adverse Reactions
Recommended dose modifications of Acalabrutinib for Grade 3 or greater adverse reactions are provided in Table 2

Table 2: Recommended Dose Modifications for Adverse Reactions

Event	Adverse Reaction Occurrence	Dose Modification (Starting dose = 100 mg approximately every 12 hours)
Grade 3 or greater non- hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	First and Second	Interrupt Acalabrutinib. Once toxicity has resolved to Grade 1 or baseline level, Acalabrutinib may be resumed at 100 mg approximately every 12 hours.
	Third	Interrupt Acalabrutinib. Once toxicity has resolved to Grade 1 or baseline level, Acalabrutinib may be resumed at a reduced frequency of 100 mg once daily.
	Fourth	Discontinue Acalabrutinib.

Contraindications
Acalabrutinib is contraindicated in patients who are hypersensitive to the active substance.

4.4. Special Warnings and Precautions for Use

Serious and Opportunistic Infections
Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with Acalabrutinib. Serious or Grade 3 or higher infections (bacterial, viral, or fungal) were observed. Opportunistic infections in recipients of Acalabrutinib have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, Pneumocystis jiroveci pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with Acalabrutinib. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) with fatal hemorrhage was observed. Bleeding events of any grade, excluding bruising and petechiae, were also observed. Use of antithrombotic agents concomitantly with Acalabrutinib may further increase the risk of hemorrhage. Consider the risks and benefits of antithrombotic agents when co-administered with Acalabrutinib. Monitor patients for signs of bleeding.
Consider the benefit-risk of withholding Acalabrutinib for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia, anemia, thrombocytopenia, and lymphopenia, developed in patients with hematologic malignancies treated with Acalabrutinib. Grade 4 neutropenia was also developed in patients with hematologic malignancies. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted.

Second Primary Malignancies
Second primary malignancies, including skin cancers and other solid tumors occurred in patients exposed to Acalabrutinib. The most frequent second primary malignancy was skin cancer. Monitor patients for skin cancers and advise protection from sun exposure.

Atrial Fibrillation and Flutter
Grade 3 atrial fibrillation or flutter occurred in patients treated with Acalabrutinib. . The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

4.5. Drug Interactions

Table 3: Drug Interactions

Strong CYP3A Inhibitors		
Clinical Impact	• Co-administration of Acalabrutinib with a strong CYP3A inhibitor (itraconazole) increased Acalabrutinib plasma concentrations	
Prevention or Management	• Avoid co-administration of strong CYP3A inhibitors with Acalabrutinib. • Alternatively, if the inhibitor will be used short-term, interrupt Acalabrutinib.	
Moderate CYP3A Inhibitors		
Clinical Impact	• Co-administration of Acalabrutinib with a moderate CYP3A inhibitor may increase Acalabrutinib plasma concentrations. • Increased Acalabrutinib concentrations may result in increased toxicity.	
Prevention or Management	• When Acalabrutinib is co-administered with moderate CYP3A inhibitors, reduce Acalabrutinib dose to 100 mg once daily.	
Strong CYP3A Inducers		
Clinical Impact	• Co-administration of Acalabrutinib with a strong CYP3A inducer (rifampin) • Decreased acalabrutinib concentrations may reduce Acalabrutinib activity	
Prevention or Management	• Avoid co-administration of strong CYP3A inducers with Acalabrutinib • If a strong CYP3A inducer cannot be avoided, increase the Acalabrutinib dose to 200 mg approximately every 12 hours.	
Gastric Acid Reducing Agents		
Clinical Impact	Co-administration of Acalabrutinib with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations. Decreased Acalabrutinib concentrations may reduce Acalabrutinib activity. If treatment with a gastric acid reducing agent is required, consider using a H2 receptor antagonist (e.g., ranitidine or famotidine) or an antacid (e.g., calcium carbonate).	
Prevention or Management	Antacids	Separate dosing by at least 2 hours
	H2-receptor antagonists	Take Acalabrutinib 2 hours before taking the H2-receptor antagonist
	Proton pump inhibitors	Avoid co-administration. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with Acalabrutinib.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy
Based on findings in animals, Acalabrutinib may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

Lactation
No data are available regarding the presence of Acalabrutinib or its active metabolite in human milk, its effects on the breastfed child, or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from Acalabrutinib, advise lactating women not to breastfeed while taking Acalabrutinib and for at least 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pregnancy
Pregnancy testing is recommended for females of reproductive potential prior to initiating Acalabrutinib therapy.

Contraception
Females
Acalabrutinib may cause embryo-fetal harm and dystocia when administered to pregnant women. Advise female patients of reproductive potential to use effective contraception during treatment with Acalabrutinib and for at least 1 week following the last dose of Acalabrutinib. 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 a fetus.

Pediatric Use
The safety and efficacy of Acalabrutinib in pediatric patients have not been established.

Geriatric Use
Among patients 65 years of age or older, Grade 3 or higher adverse reactions were observed. Patients younger than age 65, had Grade 3 or higher adverse reactions. No clinically relevant differences in efficacy were observed between patients ≥ 65 years and younger.

Hepatic Impairment
Avoid administration of Acalabrutinib in patients with severe hepatic impairment. The safety of Acalabrutinib has not been evaluated in patients with moderate or severe hepatic impairment.

4.7. Effects on Ability to Drive and Use Machines
Acalabrutinib 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 until symptoms abate.

4.8. Undesirable Effects
The following are the adverse reactions experienced with Acalabrutinib.
- Serious and Opportunistic Infections
- Hemorrhage
- Cytopenias
- Second Primary Malignancies
- Atrial Fibrillation and Flutter

Table 4: **Adverse drug reactions* of patients with haematological malignancies treated with Acalabrutinib monotherapy**

MedDRA SOC	MedDRA Term	Overall Frequency (all CTCAE grades)	Frequency of CTCAE Grade ≥ 3†
Infections and infestations	Upper respiratory tract infection	Very common (22%)	0.8%
	Sinusitis	Very common (10.7%)	0.3%
	Pneumonia	Common (8.7%)	5.1%
	Urinary tract infection	Common (8.5%)	1.5%
	Nasopharyngitis	Common (7.4%)	0%
	Bronchitis	Common (7.6%)	0.3%
	Herpes viral infections†	Common (5.9%)	0.7%
	Aspergillus infections†	Uncommon (0.5%)	0.4%
	Hepatitis B reactivation	Uncommon (0.1%)	0.1%
Neoplasms benign, malignant and unspecified	Second Primary Malignancy† Non-melanoma skin malignancy† SPM excluding non- melanoma skin†	Very common (12.2%) Common (6.6%) Common (6.5%)	4.1% 0.5% 3.8%
Blood and lymphatic system disorders	Neutropenia†	Very common (15.7%)	14.2%
	Anaemia†	Very common (13.8%)	7.8%
	Thrombocytopenia†	Common (8.9%)	4.8%
	Lymphocytosis	Uncommon (0.3%)	0.2%
Metabolism and nutrition disorders	Tumour Lysis Syndrome±	Uncommon (0.5%)	0.4%
Nervous system disorders	Headache	Very common (37.8%)	1.1%
	Dizziness	Very common (13.4%)	0.2%
Cardiac disorders	Atrial fibrillation/Flutter†	Common (4.4%)	1.3%
Vascular disorders	Bruising† Contusion Petechiae Ecchymoses	Very common (34.1%) VeryCommon (21.7%) VeryCommon (10.7%) Common (6.3%)	0% 0% 0% 0%
	Haemorrhage/haematoma† Gastrointestinal haemorrhage Intracranial haemorrhage	Very common (12.6%) Common (2.3%) Common (1%)	1.8% 0.6% 0.5%
	Epistaxis	Common (7%)	0.3%
Gastrointestinal disorders	Diarrhoea	Very common (36.7%)	2.6%
	Nausea	Very common (21.7%)	1.2%
	Constipation	Very common (14.5%)	0.1%
	Vomiting	Very common (13.3%)	0.9%
	Abdominal pain†	Very common (12.5%)	1%
Skin and subcutaneous tissue disorders	Rash†	Very common (20.3%)	0.6%
Musculoskeletal and connective tissue disorders	Musculoskeletal Pain†	Very common (33.1%)	1.5%
	Arthralgia	Very common (19.1%)	0.7%
General disorders and administration site conditions	Fatigue	Very common (21.3%)	1.7%
	Asthenia	Common (5.3%)	0.8%
Investigations¶ (Findings based on test results)	Haemoglobin decreased§	Very common (42.6%)	10.1%
	Absolute neutrophil count decreased§	Very common (41.8%)	20.7%
	Platelets decreased§	Very common (31.1%)	6.9%

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
†Includes multiple ADR term.
±One case of drug-induced Tumour Lysis Syndrome was observed in Acalabrutinib arm in the ASCEND Study.
§Represents the incidence of laboratory findings, not of reported adverse events.
¶ Presented as CTCAE grade values.

Table 5: **Adverse drug reactions* of patients with haematological malignancies treated with Acalabrutinib combination therapy**

MedDRA SOC	MedDRA Term	Overall Frequency (all CTCAE grades)	Frequency of CTCAE Grade ≥ 3†
Infections and infestations	Upper respiratory tract infection	Very common (31.4%)	1.8%
	Sinusitis	Very common (15.2%)	0.4%
	Nasopharyngitis	Very common (13.5%)	0.4%
	Urinary tract infection	Very common (13%)	0.9%
	Pneumonia	Very common (10.8%)	5.4%
	Bronchitis	Common (9.9%)	0%
	Herpes viral infections†	Common (6.7%)	1.3%
	Progressive multifocal leukoencephalopathy	Uncommon (0.4%)	0.4%
	Hepatitis B reactivation	Uncommon (0.9%)	0.1%
	Aspergillus infections†	Very rare (0%)	0%
Neoplasms benign, malignant and unspecified	Second primary malignancy† Non-melanoma skin malignancy† SPM excluding non-melanoma skin†	Very common (13%) Common (7.6%) Common (6.3%)	4.0% 0.4% 3.6%
Blood and lymphatic system disorders	Neutropenia†	Very common (31.8%)	30%
	Thrombocytopenia†	Very common (13.9%)	9%
	Anaemia†	Very common (11.7%)	5.8%
	Lymphocytosis	Uncommon (0.4%)	0.4%
Metabolism and nutrition disorders	Tumour lysis syndrome±	Uncommon (1.8%)	1.3%
Nervous system disorders	Headache	Very common (43%)	0.9%
	Dizziness	Very common (23.8%)	0%
Cardiac disorders	Atrial fibrillation/flutter†	Common (3.1%)	0.9%
Vascular disorders	Bruising† Contusion Petechiae Ecchymoses	Very common (38.6%) Very common (27.4%) Very common (11.2%) Common (3.1%)	0% 0% 0% 0%
	Haemorrhage/haematoma† Gastrointestinal haemorrhage Intracranial haemorrhage	Very common (17.5%) Common(3.6%) Uncommon (0.9%)	1.3% 0.9% 0%
	Epistaxis	Common (8.5%)	0%
Gastrointestinal disorders	Diarrhoea	Very common (43.9%)	4.5%
	Nausea	Very common (26.9%)	0%
	Constipation	Very common (20.2%)	0%
	Vomiting	Very common (19.3%)	0.9%
	Abdominal pain†	Very common (14.8%)	1.3%
Skin and subcutaneous tissue disorders	Rash†	Very common (30.9%)	1.8%
Musculoskeletal and connective tissue disorders	Musculoskeletal pain†	Very common (44.8%)	2.2%
	Arthralgia	Very common (26.9%)	1.3%
General disorders and administration site conditions	Fatigue	Very common (30.5%)	1.8%
	Asthenia	Common (7.6%)	0.4%
Investigations¶ (Findings based on test results)	Absolute neutrophil count decreased§	Very common (57.4%)	35%
	Platelets decreased§	Very common (46.2%)	10.8%
	Haemoglobin decreased§	Very common (43.9%)	9%

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
†Includes multiple ADR term.
±One case of drug-induced Tumour Lysis Syndrome was observed in the Acalabrutinib arm in the ASCEND Study.
§Represents the incidence of laboratory findings, not of reported adverse events.
¶ Presented as CTCAE grade values.

4.9. Overdose
There is no specific treatment for acalabrutinib 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

Mechanism of action
Acalabrutinib is a small-molecule inhibitor of Bruton Tyrosine Kinase (BTK). Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant Bcell proliferation and tumor growth in mouse xenograft models.

In patients with B-cell malignancies dosed with 100 mg approximately every 12 hours, median steady state BTK occupancy of ≥ 95% in peripheral blood was maintained over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval.

Cardiac Electrophysiology
The effect of acalabrutinib on the QTc interval was evaluated in a randomized, double-blind, double-dummy, placebo- and positive-controlled, 4-way crossover thorough QTc study in 48 healthy adult subjects. Administration of a single dose of acalabrutinib that is the 4-fold maximum recommended single dose did not prolong the QTc interval to any clinically relevant extent (i.e., ≥ 10 ms).

5.2 Pharmacokinetic properties
Acalabrutinib exhibits dose-proportionality, and both Acalabrutinib and its active metabolite, ACP-5862, exposures increase with dose across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dose) in patients with B-cell malignancies. At the recommended dose of 100 mg twice daily, the geometric mean (% coefficient of variation [CV]) daily area under the plasma drug concentration over time curve (AUC_{24h}) and maximum plasma concentration (C_{max}) for acalabrutinib were 1843 (38%) ng•h/mL and 563 (29%) ng/mL, respectively, and for ACP-5862 were 3947 (43%) ng•h/mL and 451 (52%) ng/mL, respectively.

Absorption
The geometric mean absolute bioavailability of Acalabrutinib was 25%. Median [min, max] time to peak Acalabrutinib plasma concentrations (T_{max}) was 0.9 [0.5, 1.9] hours, and 1.6 [0.9, 2.7] hour for ACP-5862.

Effect of Food
Administration of a single 75 mg dose of acalabrutinib (0.75 times the approved recommended single dose) with a high-fat, high-calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions. Resulting C_{max} decreased by 73% and T_{max} was delayed 1-2 hours.

Distribution
Reversible binding to human plasma protein was 97.5% for Acalabrutinib and 98.6% for ACP-5862. The *in vitro* mean blood-to-plasma ratio was 0.8 for Acalabrutinib and 0.7 for ACP-5862. The geometric mean (% CV) steady-state volume of distribution (V_{ss}) was approximately 101 (52%) L for Acalabrutinib and 67 (32%) L for ACP-5862.

Elimination
The geometric mean (% CV) terminal elimination half-life ($t_{1/2}$) was 1 (59%) hour for Acalabrutinib and 3.5 (24%) hours for ACP-5862. The geometric mean (%CV) apparent oral clearance (CL/F) was 71 (35%) L/hr for Acalabrutinib and 13 (42%) L/hr for ACP-5862.

Metabolism
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 was 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.

Excretion
Following administration of a single 100 mg radiolabeled Acalabrutinib dose, 84% of the dose was recovered in the feces and 12% of the dose was recovered in the urine, with less than 2% of the dose excreted as unchanged Acalabrutinib in urine and feces.

Specific Populations
Age, Race, and Body Weight
Age (32 to 90 years), sex, race (Caucasian, African American), and body weight (40 to 149 kg) did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862.

Renal Impairment
No clinically relevant PK difference was observed in patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^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/1.73 m^2, MDRD) or renal impairment requiring dialysis.

Hepatic Impairment
The AUC of Acalabrutinib increased 1.9-fold in patients with mild hepatic impairment (Child-Pugh class A), 1.5-fold in patients with moderate hepatic impairment (Child-Pugh class B) and 5.3-fold in patients with severe hepatic impairment (Child-Pugh class C) compared to patients with normal liver function. No clinically relevant PK difference in ACP-5862 was observed in patients with severe hepatic impairment (Child-Pugh Class C) compared to subjects with normal liver function. No clinically relevant PK differences in acalabrutinib and ACP-5862 were observed in patients with mild or moderate hepatic impairment (total bilirubin less and equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin greater than ULN and any AST) relative to patients with normal hepatic function (total bilirubin and AST within ULN).

Drug Interaction Studies
Effect of CYP3A Inhibitors on Acalabrutinib
Co-administration with a strong CYP3A inhibitor (200 mg itraconazole once daily for 5 days) increased the Acalabrutinib C_{max} by 3.9-fold and AUC by 5.1-fold.
Physiologically based pharmacokinetic (PBPK) simulations with Acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased Acalabrutinib C_{max} and AUC approximately 2- to 3-fold.

Effect of CYP3A Inducers on Acalabrutinib
Co-administration with a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased Acalabrutinib C_{max} by 68% and AUC by 77%.

Gastric Acid Reducing Agents
Acalabrutinib solubility decreases with increasing pH. Co-administration with an antacid (1 g calcium carbonate) decreased Acalabrutinib AUC by 53%. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days) decreased Acalabrutinib AUC by 43%.

In Vitro Studies
Metabolic Pathways
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.

Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4; ACP-5862 weakly induces CYP3A4.

Based on *in vitro* data and PBPK modeling, no interaction with CYP substrates is expected at clinically relevant concentrations.

Drug Transporter Systems
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. 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 increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP. ACP-5862 does not inhibit BCRP at clinically relevant concentrations. Acalabrutinib does not inhibit MATE1, while ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been conducted with Acalabrutinib.
Acalabrutinib was not mutagenic in an *in vitro* bacterial reverse mutation (AMES) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or in an *in vivo* rat bone marrow micronucleus assay.
In a fertility study in rats, there were no effects of Acalabrutinib on fertility in male rats at exposures 11-times, or in female rats at exposures 9-times the AUC observed in patients at the recommended dose of 100 mg twice daily.

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities
None

7.2 Packing Information
60's count HDPE bottle 1×1 silica gel canister

7.3 Storage and Handling Instructions
Do not store above 30°C.
Keep out of reach of Children.

8. PATIENT COUNSELLING INFORMATION
Advise patients to read Prescribing Information.

Serious and Opportunistic Infections
Inform patients of the possibility of serious infection and to report signs or symptoms suggestive of infection.

Hemorrhage
Inform patients to report signs or symptoms of bleeding. Inform patients that Acalabrutinib may need to be interrupted for major surgeries.

Cytopenias
Inform patients that they will need periodic blood tests to check blood counts during treatment with Acalabrutinib.

Second Primary Malignancies
Inform patients that other malignancies have been reported in patients who have been treated with Acalabrutinib, including skin cancer and other solid tumors. Advise patients to use sun protection.

Atrial Fibrillation and Flutter
Counsel patients to report any signs of palpitations, dizziness, fainting, chest discomfort, and shortness of breath.

Pregnancy Complication
Acalabrutinib may cause fetal harm and dystocia. Advise women to avoid becoming pregnant during treatment and for at least 1 week after the last dose of Acalabrutinib.

Lactation
Advise females not to breastfeed during treatment with Acalabrutinib and for at least 2 weeks after the final dose.

Dosing Instructions
Instruct patients to take Acalabrutinib orally twice daily, about 12 hours apart. Acalabrutinib may be taken with or without food. Advise patients that Acalabrutinib capsules should be swallowed whole with a glass of water, without being opened, broken, or chewed.

Missed Dose
Advise patients that if they miss a dose of Acalabrutinib, they may still take it up to 3 hours after the time they would normally take it. If more than 3 hours have elapsed, they should be instructed to skip that dose and take their next dose of Acalabrutinib at the usual time. Warn patients they should not take extra capsules to make up for the dose that they missed.

Drug Interactions
Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins and herbal products.

9. DETAILS OF MANUFACTURER
MSN Laboratories Private Limited,
Formulation Division, Unit II,
Sy.no.1277, 1319 to 1324,
Nandigama (Village & Mandal),
Ranga Reddy District,
Telangana-509228,
India.

C030440-02

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
M.L.No.: 5/MN/TS/2014/F/G, 26/08/2019

11. DATE OF REVISION
November 2022