BARCODE

ACABRUNAT

(Acalabrutinib 100 mg hard capsules)

1. Name of the medicinal product

ACABRUNAT (Acalabrutinib 100 mg hard capsules)

2. Qualitative and quantitative composition

Each hard gelatin capsule contains, Acalabrutinib dihydrate 107.740 mg, equivalent to Acalabrutinib 100 mg.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Hard-gelatin capsule (capsule).
Hard gelatin capsule size '1' with dark blue opaque color cap and yellow opaque body and printed with "NAT 100 mg" on body in black ink.

4. Clinical particulars

4.1 Therapeutic indications

Acalabrutinib as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
Acalabrutinib as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

4.2 Posology and method of administration

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

The recommended dose is 100 mg Acalabrutinib twice daily (equivalent to a total daily dose of 200 mg). Refer to obinutuzumab prescribing information for recommended obinutuzumab dosing information.
The dose interval is approximately 12 hours.
Treatment with Acalabrutinib should be continued until disease progression or unacceptable toxicity.

Dose adjustments

Adverse reactions

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

Table 1. Recommended dose adjustments for adverse reactions*

Adverse reaction	Adverse reaction occurrence	Dose modification (Starting dose = 100mg approximately every 12 hours)
Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia Or Grade 4 neutropenia lasting longer than 7 days Grade 3 or greater non-haematological toxicities	First and second	Interrupt Acalabrutinib Once toxicity has resolved to Grade 1 or baseline, Acalabrutinib may be resumed at 100mg approximately every 12 hours
	Third	Interrupt Acalabrutinib Once toxicity has resolved to Grade 1 or baseline, Acalabrutinib may be resumed at a reduced frequency of 100mg once daily
	Fourth	Discontinue Acalabrutinib

*Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events

Interactions

Recommendations regarding use of Acalabrutinib with CYP3A inhibitors or inducers and gastric acid reducing agents are provided in Table 2 (see section 4.5).

Table 2. Use with CYP3A inhibitors or inducers and gastric acid reducing agents

	Co-administered medicinal product	Recommended Acalabrutinib use
CYP3A inhibitors	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	No dose adjustment. Monitor patients closely for adverse reactions if taking moderate CYP3A inhibitors.
	Mild CYP3A inhibitor	No dose adjustment.
CYP3A inducers	Strong CYP3A inducer	Avoid concomitant use.
Gastric acid reducing agents	Proton pump inhibitors	Avoid concomitant use.
	H2-receptor antagonists	Take Acalabrutinib 2 hours before (or 10 hours after) taking a H2-receptor antagonist.
	Antacids	The interval between taking the medicinal products should be at least 2 hours.

Missed dose

If a patient misses a dose of Acalabrutinib by more than 3 hours, the patient should be instructed to take the next dose at its regularly scheduled time. Double dose of Acalabrutinib should not be taken to make up for a missed dose.

Special populations

Elderly

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

Renal impairment

No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in Acalabrutinib clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained, and serum creatinine levels monitored periodically. Acalabrutinib should be administered to patients with severe renal impairment (< 30mL/min creatinine clearance) only if the benefit outweighs the risk and these patients should be monitored closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis (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 1.5-3 times the upper limit of normal [ULN] and any AST). However, patients with moderate hepatic impairment should be closely monitored for signs of toxicity. It is not recommended to use Acalabrutinib in patients with severe hepatic impairment (Child-Pugh C or total bilirubin >3 times ULN and any AST) (see section 5.2).

Severe cardiac disease

Patients with severe cardiovascular disease were excluded from Acalabrutinib clinical studies.

Paediatric population

The safety and efficacy of Acalabrutinib in children and adolescents aged 0 to 18 years have not been established. No data are available.

Method of administration

Acalabrutinib is for oral use. The capsules should be swallowed whole with water at approximately the same time each day, with or without food (see section 4.5). The capsules should not be chewed, dissolved or opened as this may affect the absorption of the medicinal product into the body.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Haemorrhage

Major haemorrhagic events including central nervous system and gastrointestinal haemorrhage, some with fatal outcome, have occurred in patients with haematologic malignancies treated with Acalabrutinib monotherapy and in combination with obinutuzumab. These events have occurred in patients both with and without thrombocytopenia. Overall, the bleeding events were less severe events including bruising and petechiae (see section 4.8).
The mechanism for the bleeding events is not well understood.
Patients receiving antithrombotic agents may be at increased risk of haemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. Warfarin or other vitamin K antagonists should not be administered concomitantly with Acalabrutinib.
Consider the benefit-risk of withholding Acalabrutinib for at least 3 days pre- and post-surgery.

Infections

Serious infections (bacterial, viral or fungal), including fatal events have occurred in patients with haematologic malignancies treated with Acalabrutinib monotherapy and in combination with obinutuzumab. These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Infections due to hepatitis B virus (HBV) and herpes zoster virus (HZV) reactivation, aspergillosis and progressive multifocal leukoencephalopathy (PML) have occurred (see section 4.8).

Viral reactivation

Cases of hepatitis B reactivation have been reported in patients receiving Acalabrutinib. Hepatitis B virus (HBV) status should be established before initiating treatment with Acalabrutinib. If patients have positive hepatitis B serology, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation.
Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of Acalabrutinib within the context of a prior or concomitant immunosuppressive therapy. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected, then appropriate diagnostic evaluations should be undertaken and treatment with Acalabrutinib should be suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be considered.
Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anaemia and thrombocytopenia, occurred in patients with haematologic malignancies treated with Acalabrutinib monotherapy and in combination with obinutuzumab. Monitor complete blood counts as medically indicated (see section 4.8).

Second primary malignancies

Second primary malignancies, including skin and non-skin cancers, occurred in patients with haematologic malignancies treated with Acalabrutinib monotherapy and in combination with obinutuzumab. Skin cancers were commonly reported. Monitor patients for the appearance of skin cancers and advise protection from sun exposure (see section 4.8).

Atrial fibrillation

Atrial fibrillation/flutter occurred in patients with haematologic malignancies treated with Acalabrutinib monotherapy and in combination with obinutuzumab. Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated (see sections 4.5 and 4.2). In patients who develop atrial fibrillation on therapy with Acalabrutinib, a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk for thromboembolic disease, tightly controlled treatment with anticoagulants and alternative treatment options to Acalabrutinib should be considered.

Other medicinal products

Co-administration of strong CYP3A inhibitors with Acalabrutinib may lead to increased acalabrutinib exposure and consequently a higher risk for toxicity. On the contrary, co-administration of CYP3A inducers may lead to decreased acalabrutinib exposure and consequently a risk for lack of efficacy. Concomitant use with strong CYP3A inhibitors should be avoided. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), treatment with Acalabrutinib should be interrupted. Patients should be closely monitored for signs of toxicity if a moderate CYP3A inhibitor is used (see sections 4.2 and 4.5). Concomitant use with strong CYP3A4 inducers should be avoided due to risk for lack of efficacy.

Acalabrutinib contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Acalabrutinib and its active metabolite are primarily metabolised by cytochrome P450 enzyme 3A4 (CYP3A4), and both substances are substrates for P-gp and breast cancer resistance protein (BCRP).

Active substances that may increase acalabrutinib plasma concentrations

CYP3A/P-gp inhibitors

Co-administration with a strong CYP3A/P-gp inhibitor (200 mg itraconazole once daily for 5 days) increased acalabrutinib C_{max} and AUC by 3.9-fold and 5.0-fold in healthy subjects (N=17), respectively.
Concomitant use with strong CYP3A/P-gp inhibitors should be avoided. If the strong CYP3A/*P-gp* inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, ritonavir, telaprevir, posaconazole, voriconazole) will be used short-term, treatment with Acalabrutinib should be interrupted (see section 4.2).
Co-administration with moderate CYP3A inhibitors (400 mg fluconazole as single dose or 200 mg isavuconazole as repeated dose for 5 days) in healthy subjects increased acalabrutinib Cmax and AUC by 1.4-fold to 2-fold while the active metabolite ACP-5862 Cmax and AUC was decreased by 0.65-fold to 0.88-fold relative to when acalabrutinib was dosed alone. No dose adjustment is required in combination with moderate CYP3A inhibitors. Monitor patients closely for adverse reactions (see Section 4.2).

Active substances that may decrease acalabrutinib plasma concentrations

CYP3A inducers

Co-administration of a strong CYP3A inducer (600 mg rifampicin once daily for 9 days) decreased acalabrutinib C_{max} and AUC by 68% and 77% in healthy subjects (N=24), respectively.
Concomitant use with strong inducers of CYP3A activity (e.g., phenytoin, rifampicin, carbamazepine) should be avoided. Concomitant treatment with St. John's wort, which may unpredictably decrease acalabrutinib plasma concentrations, should be avoided.

Gastric acid reducing medicinal products

Acalabrutinib solubility decreases with increasing pH. Co-administration of acalabrutinib with an antacid (1 g calcium carbonate) decreased acalabrutinib AUC by 53% in healthy subjects. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days) decreased acalabrutinib AUC by 43%.
If treatment with an acid reducing agent is required, consider using an antacid (e.g., calcium carbonate), or an H2-receptor antagonist (e.g., ranitidine or famotidine). For use with antacids, the interval between taking the medicinal product should be at least 2 hours (see section 4.2). For H2-receptor antagonists, Acalabrutinib should be taken 2 hours before (or 10 hours after) 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 and therefore concomitant use should be avoided (see section 4.2).

Active substances whose plasma concentrations may be altered by Acalabrutinib

CYP3A substrates

Based on *in vitro* data, it cannot be excluded that acalabrutinib is an inhibitor of CYP3A4 at the intestinal level and may increase the exposure of CYP3A4 substrates sensitive to gut CYP3A metabolism. Caution should be exercised if co-administering acalabrutinib with CYP3A4 substrates with narrow therapeutic range administered orally (e.g., cyclosporine, ergotamine, pimozide).

Effect of acalabrutinib on CYP1A2 substrates

In vitro studies indicate that acalabrutinib induces CYP1A2. Co-administration of acalabrutinib with CYP1A2 substrates (e.g., theophylline, caffeine) may decrease their exposure.

Effects of acalabrutinib and its active metabolite, ACP-5862, on medicinal product transport systems

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP (see section 5.2). To minimise the potential for an interaction in the Gastrointestinal (GI) tract, oral narrow therapeutic range BCRP substrates such as methotrexate should be taken at least 6 hours before or after acalabrutinib.
ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1 (see section 5.2). Patients taking concomitant medicinal products with disposition dependent upon MATE1 (e.g., metformin) should be monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving Acalabrutinib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Acalabrutinib.

Pregnancy

There are no or limited amount of data from the use of acalabrutinib in pregnant women. Based on findings from animal studies, there may be a risk to the foetus from exposure to acalabrutinib during pregnancy. Dystocia (difficult or prolonged labour) was observed in the rat and administration to pregnant rabbits was associated with reduced foetal growth (see section 5.3).
Acalabrutinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with acalabrutinib.

Breast-feeding

It is not known whether acalabrutinib is excreted in human milk. There are no data on the effect of acalabrutinib on the breast-fed child or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. A risk to the breast-fed child cannot be excluded. Breast-feeding mothers are advised not to breast-feed during treatment with Acalabrutinib and for 2 days after receiving the last dose.

Fertility

There are no data on the effect of Acalabrutinib on human fertility. In a non-clinical study of acalabrutinib in male and female rats, no adverse effects on fertility parameters were observed (see section 5.3).

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

Summary of the safety profile

Of the 1040 patients treated with Acalabrutinib monotherapy, the most common (≥ 20%) adverse drug reactions (ADRs) of any grade reported in patients were infection (66.7%), headache (37.8%), diarrhoea (36.7%), bruising (34.1%), musculoskeletal pain (33.1%), nausea (21.7%), fatigue (21.3%), cough (21%) and rash (20.3%). The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were infection (17.6%), leukopenia (14.3%), neutropenia (14.2%), and anaemia (7.8%).
Of the 223 patients treated with Acalabrutinib combination therapy, the most common (≥ 20%) ADRs of any grade reported in patients were infection (74%), musculoskeletal pain (44.8%), diarrhoea (43.9%), headache (43%), leukopenia (31.8%), neutropenia (31.8%), cough (30.5%), fatigue (30.5%), arthralgia (26.9%), nausea (26.9%), dizziness (23.8%), and constipation (20.2%). The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were leukopenia (30%), neutropenia (30%), infection (21.5%), thrombocytopenia (9%) and anaemia (5.8%).

Tabulated list of adverse reactions

The following adverse drug reactions (ADRs) have been identified in clinical studies with patients receiving Acalabrutinib as treatment for haematological malignancies. The median duration of Acalabrutinib treatment across the pooled dataset was 26.2 months.
Adverse drug reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are sorted by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each ADR is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse drug reactions* of patients with haematological malignancies treated with acalabrutinib monotherapy (n=1040)

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%) Very Common (21.7%) Very Common (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 4. Adverse drug reactions* of patients with haematological malignancies treated with acalabrutinib combination therapy (n=223)

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.

Description of selected adverse reactions

Discontinuation and dose reduction due to adverse reactions

Of the 1,040 patients treated with Acalabrutinib monotherapy, discontinuation due to adverse reactions were reported in 9.3% of the patients. These main adverse reactions included pneumonia, thrombocytopenia and diarrhoea. Dose reductions due to adverse reactions were reported in 4.2% of patients. These main adverse reactions included hepatitis B reactivation, sepsis, and diarrhoea.
Of the 223 patients treated with Acalabrutinib combination, discontinuation due to adverse reactions were reported in 10.8% of the patients. These main adverse reactions included pneumonia, thrombocytopenia and diarrhoea. Dose reductions due to adverse reactions were reported in 6.7% of patients. These main adverse reactions included neutropenia, diarrhoea and vomiting.

Elderly

Of the 1,040 patients in clinical studies of Acalabrutinib monotherapy, 41% were greater than 65 years and less than 75 years of age and 22% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.
Of the 223 patients in clinical studies of Acalabrutinib in combination of obinutuzumab therapy, 47% were greater than 65 years and less than 75 years of age and 26% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients and ≥ 65 years and younger.

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

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EL02.

Mechanism of action

Acalabrutinib is a selective 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, and 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 with minimal off-target interactions.

Pharmacodynamic effects

In patients with B-cell malignancies dosed with acalabrutinib100 mg twice daily, 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 46 healthy male and female subjects in a randomised, double-blind thorough QT study with placebo and positive controls. At a supratherapeutic dose, 4-times the maximum recommended dose, Acalabrutinib did not prolong the QT/QTc interval to any clinically relevant extent (e.g., not greater than or equal to 10 ms) (see sections 4.4, 4.8 and 5.3).

Clinical efficacy and safety

Patients with previously untreated CLL

The safety and efficacy of Acalabrutinib in previously untreated CLL were evaluated in a randomised, multi-centre, open-label Phase 3 study (ELEVATE-TN) of 535 patients. Patients received Acalabrutinib plus obinutuzumab, Acalabrutinib monotherapy, or obinutuzumab plus chlorambucil. Patients 65 years of age or older, or between 18 and 65 years of age with coexisting medical conditions, were included in ELEVATE-TN, 27.9% patients had a CrCl of < 60 mL/min. Of the patients who were < 65 years of age, 16.1% had a median CIRS-G score of 8. The study allowed patients to receive antithrombotic agents. Patients who required anticoagulation with warfarin or equivalent vitamin K antagonists were excluded.
Patients were randomised in a 1:1:1 ratio into 3 arms to receive

- Acalabrutinib plus obinutuzumab (Acalabrutinib +G): Acalabrutinib 100 mg was administered twice daily starting on Cycle 1 Day 1 until disease progression or unacceptable toxicity. Obinutuzumab was administered starting on Cycle 2 Day 1 for a maximum of 6 treatment cycles. Obinutuzumab 1,000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 2 followed by 1,000 mg on Day 1 of Cycles 3 up to 7. Each cycle was 28 days.
- Acalabrutinib monotherapy: Acalabrutinib 100 mg was administered twice daily until disease progression or unacceptable toxicity.
- Obinutuzumab plus chlorambucil (GClb): Obinutuzumab and chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1,000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by 1,000 mg on Day 1 of Cycles 2 up to 6. Chlorambucil 0.5 mg/kg was administered on Days 1 and 15 of Cycles 1 up to 6. Each cycle was 28 days.

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2) and geographic region (North America and Western Europe versus Other). After confirmed disease progression, 45 patients randomised on the GClb arm crossed over to Acalabrutinib monotherapy. Table 5 summarises the baseline demographics and disease characteristics of the study population.

Table 5. Baseline patient characteristics in (ELEVATE-TN) patients with previously untreated CLL

Characteristic	Acalabrutinib plus obinutuzumab N=179	Acalabrutinib monotherapy N=179	Obinutuzumab plus chlorambucil N=177
Age, years; median (range)	70 (41-88)	70 (44-87)	71 (46-91)
Male; %	62	62	59.9
Caucasian; %	91.6	95	93.2
ECOG performance status 0-1; %	94.4	92.2	94.4
Median time from diagnosis (months)	30.5	24.4	30.7
Bulky disease with nodes ≥ 5 cm; %	25.7	38	31.1
Cytogenetics/FISH Category; %			
17p deletion	9.5	8.9	9
11q deletion	17.3	17.3	18.6
TP53 mutation	11.7	10.6	11.9
Unmutated IGHV	57.5	66.5	65.5
Complex karyotype (≥ 3 abnormalities)	16.2	17.3	18.1
Rai stage; %			
0	1.7	0	0.6
I	30.2	26.8	28.2
II	20.1	24.6	27.1
III	26.8	27.9	22.6
IV	21.2	20.7	21.5

The primary endpoint was progression-free survival (PFS) of Acalabrutinib +G arm versus GClb arm as assessed by an Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 28.3 months, PFS by IRC indicated a 90% statistically significant reduction in the risk of disease progression or death for previously untreated CLL patients in the Acalabrutinib +G arm compared to the GClb arm. Efficacy results are presented in Table 6.

A/s 350 X 650_ACABRUNAT_PIL _04/02/2026_ Font: Times New Roman_Size: 7pt_Material code : XXXXXXXX

Table 6. Efficacy results per IRC Assessments in (ELEVATE-TN) patients with CLL

	Acalabrutinib plus obinutuzumab N=179	Acalabrutinib monotherapy N=179	Obinutuzumab plus chlorambucil N=177
Progression-free survival*			
Number of events (%)	14 (7.8)	26 (14.5)	93 (52.5)
PD, n (%)	9 (5)	20 (11.2)	82 (46.3)
Death events (%)	5 (2.8)	6 (3.4)	11 (6.2)
Median (95% CI), months	NR	NR (34.2, NR)	22.6 (20.2, 27.6)
HR† (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-
P-value	< 0.0001	< 0.0001	-
24 months estimate, % (95% CI)	92.7 (87.4, 95.8)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
Overall Survival[a]			
Death events (%)	9 (5)	11 (6.1)	17 (9.6)
Hazard Ratio (95% CI) †	0.47 (0.21, 1.06)	0.60 (0.28, 1.27)	-
Best overall response rate* (CR + CRi + nPR + PR)			
ORR, n (%) (95% CI)	168 (93.9) (89.3, 96.5)	153 (85.5) (79.6, 89.9)	139 (78.5) (71.9, 83.9)
P-value	< 0.0001	0.0763	-
CR, n (%)	23 (12.8)	1 (0.6)	8 (4.5)
CRi, n (%)	1 (0.6)	0	0
nPR, n (%)	1 (0.6)	2 (1.1)	3 (1.7)
PR, n (%)	143 (79.9)	150 (83.8)	128 (72.3)

CI=confidence interval; HR=hazard ratio; NR=not reached; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response;
*Per IRC assessment
†Based on stratified Cox-Proportional-Hazards model
[a] Median OS not reached for both arms.

PFS results for Acalabrutinib with or without obinutuzumab were consistent across subgroups, including high risk features.In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation or unmutated IGHV), the PFS HRs of Acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil was 0.08 [95% CI (0.04, 0.15)] and0.13 [95% CI (0.08, 0.21)], respectively

Table 7. Subgroup analysis of PFS (Study ELEVATE-TN)

	Acalabrutinib monotherapy			Acalabrutinib +G		
	N	Hazard Ratio	95% CI	N	Hazard Ratio	95% CI
All subjects	179	0.20	(0.13, 0.30)	179	0.10	(0.06, 0.17)
Del 17P Yes No	 19 160	 0.20 0.20	 (0.06, 0.64) (0.12, 0.31)	 21 158	 0.13 0.09	 (0.04, 0.46) (0.05, 0.17)
TP53 mutation Yes No	 19 160	 0.15 0.20	 (0.05, 0.46) (0.12, 0.32)	 21 158	 0.04 0.11	 (0.01, 0.22) (0.06, 0.20)
Del 17P or/and TP53 mutation Yes No	 23 156	 0.23 0.19	 (0.09, 0.61) (0.11, 0.31)	 25 154	 0.10 0.10	 (0.03, 0.34) (0.05, 0.18)
IGHV mutation Mutated Unmutated	 58 119	 0.69 0.11	 (0.31, 1.56) (0.07, 0.19)	 74 103	 0.15 0.08	 (0.04, 0.52) (0.04, 0.16)
Del 11q Yes No	 31 148	 0.07 0.26	 (0.02, 0.22) (0.16, 0.41)	 31 148	 0.09 0.10	 (0.03, 0.26) (0.05, 0.20)
Complex Karyotype Yes No	 31 117	 0.10 0.27	 (0.03, 0.33) (0.16, 0.46)	 29 126	 0.09 0.11	 (0.03, 0.29) (0.05, 0.21)

With long term data, the median follow-up was 58.2 months for Acalabrutinib +G arm, 58.1 months for Acalabrutinib arm and58.2 months for the GClb arm. The median investigator assessed PFS for Acalabrutinib +G and Acalabrutinib mono therapywas not reached; and was 27.8 months in GClb arm. At the time of most recent data cut off, a total of 72 patients(40.7%) originally randomised to the GClb arm crossed over to Acalabrutinib monotherapy. The median overall survival had not been reached in any arm with a total of 76 deaths: 18 (10.1%) in the Acalabrutinib +G arm, 30 (16.8%) in the Acalabrutinib monotherapy arm, and 28 (15.8%) in the GClb arm.

Table 8. Efficacy Results per INV assessment in (ELEVATE-TN) Patients with CLL

	Acalabrutinib plus obinutuzumab N=179	Acalabrutinib monotherapy N=179	Obinutuzumab plus chlorambucil N=177
Progression-free survival*			
Number of events (%)	27 (15.1)	50 (27.9)	124 (70.1)
PD, n (%)	14 (7.8)	30 (16.8)	112 (63.3)
Death events (%)	13 (7.3)	20 (11.2)	12 (6.8)
Median (95% CI), months	NR	NR (66.5, NR)	27.8 (22.6, 33.2)
HR† (95% CI)	0.11 (0.07, 0.16)	0.21 (0.15, 0.30)	-
Overall Survival[a]			
Death events (%)	18 (10.1)	30 (16.8)	28 (15.8)
Hazard Ratio (95% CI) †	0.55 (0.30, 0.99)	0.98 (0.58, 1.64)	-

CI=confidence interval; HR=hazard ratio; NR=not reached
* 95% confidence interval based on Kaplan-Meier estimation.
† Estimate based on stratified Cox-Proportional-Hazards model for Hazard Ratio (95% CI) stratified by 17p deletionstatus (yes vs no)

The safety and efficacy of Acalabrutinib in relapsed or refractory CLL were evaluated in a randomised, multi-centre, open-label phase 3 study (ASCEND) of 310 patients who received at least one prior therapy not including BCL-2 inhibitors or B-cell receptor inhibitors. Patients received Acalabrutinib monotherapy or investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab. The study allowed patients to receive antithrombotic agents. Patients who required anticoagulation with warfarin or equivalent vitamin K antagonists were excluded.
Patients were randomised 1:1 to receive either:
• Acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity, or
• Investigator's choice:
o Idelalisib 150 mg twice daily in combination with rituximab 375 mg/m2 IV on Day 1 of the first cycle, followed by 500 mg/m2 IV every 2 weeks for 4 doses, then every 4 weeks for 3 doses for a total of 8 infusions
o Bendamustine 70 mg/m^2 (Day 1 and 2 of each 28-day cycle) in combination with rituximab (375 mg/m^2/500 mg/m^2) on Day 1 of each 28-day cycle for up to 6 cycles
Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2) and number of prior therapies (1 to 3 versus ≥ 4). After confirmed disease progression, 35 patients randomised on investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab crossed over to Acalabrutinib. Table 9 summarizes the baseline demographics and disease characteristics of the study population.

Table 9. Baseline patient characteristics in (ASCEND) patients with CLL

Characteristic	Acalabrutinib monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155
Age, years; median (range)	68 (32-89)	67 (34-90)
Male; %	69.7	64.5
Caucasian; %	93.5	91.0
ECOG performance status; %		
0	37.4	35.5
1	50.3	51.0
2	12.3	13.5
Median time from diagnosis (months)	85.3	79.0
Bulky disease with nodes ≥ 5 cm; %	49.0	48.4
Median number of prior CLL therapies (range)	1 (1-8)	2 (1-10)
Number of Prior CLL Therapies; %		
1	52.9	43.2
2	25.8	29.7
3	11.0	15.5
≥ 4	10.3	11.6
Cytogenetics/FISH Category; %		
17p deletion	18.1	13.5
11q deletion	25.2	28.4
TP53 mutation	25.2	21.9
Unmutated IGHV	76.1	80.6
Complex karyotype (≥3 abnormalities)	32.3	29.7
Rai Stage; %		
0	1.3	2.6
I	25.2	20.6
II	31.6	34.8
III	13.5	11.6
IV	28.4	29.7

The primary endpoint was PFS as assessed by IRC IWCLL 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 16.1months, PFS indicated a 69% statistically significant reduction in the risk of death or progression for patients in the Acalabrutinib arm. Efficacy results are presented in Table 9.

Table 10. Efficacy results per IRC Assessments in (ASCEND) patients with CLL

	Acalabrutinib monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155
Progression-free survival*		
Number of events (%)	27 (17.4)	68 (43.9)
PD, n (%)	19 (12.3)	59 (38.1)
Death events (%)	8 (5.2)	9 (5.8)
Median (95% CI), months	NR	16.5 (14.0, 17.1)
HR† (95% CI)	0.31 (0.20, 0.49)	
P-value	< 0.0001	
15 months estimate, % (95% CI)	82.6 (75.0, 88.1)	54.9 (45.4, 63.5)
Overall survival[a]		
Death events (%)	15 (9.7)	18(11.6)
Hazard Ratio (95% CI) †	0.84 (0.42, 1.66)	-
Best overall response rate* (CR + CRi + nPR + PR)**		
ORR, n (%) (95% CI)	126 (81.3) (74.4, 86.6)	117 (75.5) (68.1, 81.6)
P-value	0.2248	-
CR, n (%)	0	2 (1.3)
PR, n (%)	126 (81.3)	115 (74.2)
Duration of Response (DoR)		
Median (95% CI), months	NR	13.6 (11.9,NR)

CI=confidence interval; HR=hazard ratio; NR=not reached; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response; PD=progressive disease
*Per IRC assessment
[a] Median OS not reached for both arms. P<0.6089 for OS.
**CRi and nPR have values of 0.
†Based on stratified Cox-Proportional-Hazards model

PFS results for Acalabrutinib were consistent across subgroups, including high risk features. In the high risk CLLpopulation (17p deletion, 11q deletion, TP53 mutation and unmutated IGHV), the PFS HR was 0.27 [95% CI (0.17,0.44)].

Table 11. Subgroup analysis of PFS (Study ASCEND)

	Acalabrutinib monotherapy		
	N	Hazard Ratio	95% CI
All subjects	155	0.30	(0.19, 0.48)
Del 17P Yes No	 28 127	 0.21 0.33	 (0.07, 0.68) (0.21, 0.54)
TP53 mutation Yes No	 39 113	 0.24 0.33	 (0.11, 0.56) (0.20, 0.57)
Del 17P or TP53 mutation Yes No	 45 108	 0.21 0.36	 (0.09, 0.48) (0.21, 0.61)
IGHV mutation Mutated Unmutated	 33 118	 0.32 0.32	 (0.11, 0.94) (0.19, 0.52)
Del 11q Yes No	 39 116	 0.28 0.31	 (0.11, 0.70) (0.19, 0.53)
Complex Karyotype Yes No	 50 97	 0.32 0.23	 (0.16, 0.63) (0.12, 0.44)

At final analysis, with a median follow-up of 46.5 months for Acalabrutinib and 45.3 months for the IR/BR, a 72% reduction in risk of investigator-assessed disease progression or death was observed for patients in the Acalabrutinib arm. The median investigator assessed PFS was not reached in Acalabrutinib and was 16.8 months in IR/BR. Efficacy results per Investigator Assessments (INV) are presented in Table 12.

Table 12. Efficacy results at final analysis per INV assessments in (ASCEND) patients with CLL

	Acalabrutinib monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155
Progression-free survival*		
Number of events (%)	62 (40.0)	119 (76.8)
PD, n (%)	43 (27.7)	102 (65.8)
Death events (%)	19 (12.3)	17 (11.0)
Median (95% CI), months	NR	16.8 (14.1, 22.5)
HR† (95% CI)	0.28 (0.20, 0.38)	
Overall survival[a]		
Death events (%)	41 (26.5)	54 (34.8)
Hazard Ratio (95% CI) †	0.69 (0.46, 1.04)	-

CI=confidence interval; HR=hazard ratio; NR=not reached; PD=progressive disease
*Per INV assessment
a Median OS not reached for both arms P=0.0783 for OS.
† Based on stratified Cox-Proportional-Hazards model

Investigator assessed PFS results at final analysis for Acalabrutinib were consistent across subgroups, including high riskfeatures and were consistent with the primary analysis.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of acalabrutinib and its active metabolite, ACP-5862, were studied in healthy subjects and in patients with B-cell malignancies. Acalabrutinib exhibits dose-proportionality, and both acalabrutinib and 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 is similar across patients with different B-cell malignancies. At the recommended dose of 100 mg twice daily in patients with B-cell malignancies (including, CLL), the geometric mean steady state daily area under the plasma concentration over time curve (AUC_{24h}) and maximum plasma concentration (C_{max}) for acalabrutinib were 1679 ng•h/mL and 438 ng/mL, respectively, and for ACP-5862 were 4166 ng•h/mL and 446 ng/mL, respectively.

<u>Absorption</u>
The time to peak plasma concentrations (T_{max}) was 0.5-1.5 hours for acalabrutinib, and 1.0 hour for ACP-5862. The absolute bioavailability of Acalabrutinib was 25%.

<u>Effect of food on acalabrutinib</u>
In healthy subjects, administration of a single 75 mg dose of acalabrutinib 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 69% and T_{max} was delayed 1-2 hours.

<u>Distribution</u>
Reversible binding to human plasma protein was 99.4% for acalabrutinib and 98.8% for ACP-5862. The *in vitro* mean blood-to-plasma ratio was 0.8 for acalabrutinib and 0.7 for ACP-5862. The mean steady state volume of distribution (V_{ss}) was approximately 34 L for acalabrutinib.

<u>Biotransformation/Metabolism</u>
In vitro, acalabrutinib is predominantly metabolised by CYP3A enzymes, and to a minor extent by glutathione conjugation and amide hydrolysis. ACP-5862 was identified as the major metabolite in plasma, that was further metabolized primarily by CYP3A-mediated oxidation, 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 studies indicate that acalabrutinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1 or UGT2B7 at clinically relevant concentrations and is unlikely to affect clearance of substrates of these CYPs.

<u>Interactions with transport proteins</u>
In vitro studies indicate that acalabrutinib and ACP-5862 are P-gp and BCRP substrates. Co-administration with BCRP inhibitors is however unlikely to result in clinically relevant drug interactions. Co-administration with an OATP1B1/1B3 inhibitor (600 mg rifampin, single dose) resulted in an increase in acalabrutinib C_{max} and AUC by 1.2-fold and 1.4-fold (N=24, healthy subjects), respectively, which is not clinically relevant.
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, while ACP-5862 may inhibit MATE1 at clinically relevant concentrations (see section 4.5). Acalabrutinib does not inhibit MATE1, while ACP-5862 does not inhibit BCRP at clinically relevant concentrations.

<u>Elimination</u>
Following a single oral dose of 100 mg acalabrutinib, the terminal elimination half-life ($t_{1/2}$) of acalabrutinib was 1 to 2 hours. The $t_{1/2}$ of the active metabolite, ACP-5862, was approximately 7 hours.
The mean apparent oral clearance (CL/F) was 134 L/hr for acalabrutinib and 22 L/hr for ACP-5862 in patients with B-cell malignancies.
Following administration of a single 100 mg radiolabelled [^{14}C]-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.

<u>Special populations</u>
Based on population PK analysis, age (>18 years of age), sex, race (Caucasian, African American) and body weight did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862.

Paediatric population
No pharmacokinetic studies were performed with Acalabrutinib in patients under 18 years of age.

Renal Impairment
Acalabrutinib undergoes minimal renal elimination. A pharmacokinetic study in patients with renal impairment has not been conducted.
Based on population PK analysis, no clinically relevant PK difference was observed in 408 subjects with mild renal impairment (eGFR between 60 and 89 mL/min/1.73m^2 as estimated by MDRD), 109 subjects with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73m^2) relative to 192 subjects with normal renal function (eGFR greater than or equal to 90 mL/min/1.73m^2). The pharmacokinetics of acalabrutinib has not been characterised in patients with severe renal impairment (eGFR less than 29 mL/min/1.73m^2) or renal impairment requiring dialysis. Patients with creatinine levels greater than 2.5 times the institutional ULN were not included in the clinical studies (see section 4.2).

Hepatic impairment
Acalabrutinib is metabolised in the liver. In dedicated hepatic impairment (HI) studies, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by 1.9-fold, 1.5-fold and 5.3-fold in subjects with mild (n=6) (Child-Pugh A), moderate (n=6) (Child-Pugh B) and severe (n=8) (Child-Pugh C) hepatic impairment, respectively. Subjects in the moderate HI group were however not significantly affected in markers relevant for the elimination capacity of drugs, so the effect of moderate hepatic impairment was likely underestimated in this study. Based on a population PK analysis, no clinically relevant difference was observed between subjects 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=613) hepatic function (total bilirubin and AST within ULN) (see section 4.2).

5.3 Preclinical safety data

<u>Carcinogenicity</u>
Carcinogenicity studies have not been conducted with acalabrutinib.

<u>Genotoxicity/Mutagenicity/Phototoxicity</u>
Acalabrutinib was not mutagenic in a bacterial reverse mutation assay, in an *in vitro* chromosome aberration assay or in an *in vivo* mouse bone marrow micronucleus assay.
Based on phototoxicity assays using 3T3 cell line in vitro, acalabrutinib is considered to have a low risk for phototoxicity in humans.

<u>Repeat-dose toxicity</u>
In rats, microscopic findings of minimal to mild severity were observed in the pancreas (haemorrhage/pigment/inflammation/fibrosis in islets) at all dose levels. Non-adverse findings of minimal to mild severity in the kidneys (tubular basophilia, tubular regeneration, and inflammation) were observed in studies of up to 6-month duration with a No Observed Adverse Effect level (NOAEL) of 30 mg/kg/day in rats. The mean exposures (AUC) at the NOAEL in male and female rats correspond to 0.6x and 1x, respectively, the clinical exposure at the recommended dose of 100 mg twice daily, respectively. The Lowest Adverse Observed Effect Level (LOAEL) at which reversible renal (moderate tubular degeneration) and liver (individual hepatocyte necrosis) findings were observed in the chronic rat study was 100 mg/kg/day and provided an exposure margin 4.2-times greater than the clinical exposure at the recommended dose of 100 mg twice daily. In studies of 9 months duration in dogs, the NOAEL was 10-mg/kg/day corresponding to an exposure 3 times the clinical AUC at the recommended clinical dose. Minimal tubular degeneration in kidney, slight decreases in spleen weights and transient minimal to mild decreases in red cell mass and increases in ALT and ALP were observed at 30 mg/kg/day (9 times the clinical AUC) in dogs. Cardiac toxicities in rats (myocardial haemorrhage, inflammation, necrosis) and dogs (perivascular/vascular inflammation) were observed only in animals that died during studies at doses above the maximum tolerated dose (MTD). The exposures in rats and dogs with cardiac findings was at least 6.8-times and 25-times the clinical AUC, respectively. Reversibility for the heart findings could not be assessed as these findings were only observed at doses above the MTD.

<u>Reproductive toxicology</u>
No effects on fertility were observed in male or female rats at exposures 10 or 9 times the clinical AUC at the recommended dose, respectively.
No effects on embryofoetal development and survival were observed in pregnant rats, at exposures approximately 9-times the AUC in patients at the recommended dose of 100 mg twice daily. In two rat reproductive studies, dystocia (prolonged/difficult labour) was observed at exposures >2.3-times the clinical exposure at 100 mg twice daily. The presence of acalabrutinib and its active metabolite were confirmed in foetal rat plasma. Acalabrutinib and its active metabolite were present in the milk of lactating rats. In an embryofoetal study in pregnant rabbits, decreased foetal body weight and delayed ossification were observed at exposure levels that produced maternal toxicity which were 2.4 times greater than the human AUC at the recommended dose.

6. Pharmaceutical particulars

6.1 List of excipients

<u>Capsule content</u>
Mannitol
Croscarmellose sodium
Colloidal silicon dioxide
Sodium stearyl fumarate

<u>Capsule shell</u>
Gelatin
Titanium dioxide (E 171)
FD & C Blue 2 (E 132)
Iron oxide yellow (E 172)
Purified Water

<u>Printing ink</u>
Shellac (E904)
Dehydrated Alcohol (E1510)
Isopropyl Alcohol
Butyl Alcohol
Propylene glycol (E1520)
Strong Ammonia Solution (E527)
Black Iron Oxide (E172)
Potassium Hydroxide (E525)
Purified Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Refer outer carton

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Capsules are supplied as:
Alu-Alu Blister pack of 10 Capsules (6 x 10's Blisters will be packed in a mono-carton)

6.6 Special precautions for disposal and other handling
This medicinal product does not require any special storage conditions.

7. Manufactured by
Natco Pharma limited
Kothur – 509228
Rangareddy District
Telangana, India.

8. Marketing authorisation holder
Unimed Sdn.Bhd.
No. 53, Jalan Tembaga SD 5/2 B,
Bandar Sri Damansara, 52200,
Kuala Lumpur, Malaysia.

9.Date of revision of the text
February 2026

XXXXXXX