Professional Information for PULERTTAN 5 / 10

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PULERTTAN 5 film-coated tablets

PULERTTAN 10 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg or 10 mg ambrisentan.

Contains sugar:

PULERTTAN 5 contains 36,5 mg lactose monohydrate per tablet.

PULERTTAN 10 tablets contain 73 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

PULERTTAN 5: yellow coloured, capsule shaped, biconvex film-coated tablets, scored on both sides, debossed with “A” and “5” on one side, and plain on other side free from physical defects.

PULERTTAN 10: pink coloured, oval shaped, biconvex, film-coated tablets, debossed with “A” one side and “10” on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PULERTTAN is indicated for the treatment of pulmonary arterial hypertension (PAH):

- To improve exercise capacity, decrease the symptoms of PAH, and delay clinical worsening.
- In combination with tadalafil, to reduce the risk of clinical failure (a composite of death, PAH hospitalisation, disease progression, and unsatisfactory clinical response), and to increase satisfactory clinical response and exercise ability.

4.2 Posology and method of administration

Posology

Treatment should only be initiated by a medical practitioner experienced in the treatment of PAH.

Recommended adult dosage:

PULERTTAN treatment should be initiated at a dose of 5 mg once daily. Consider increasing the dose to 10 mg once daily if 5 mg is tolerated.

PULERTTAN used with tadalafil: When used in combination with tadalafil, the dose of PULERTTAN should be titrated to 10 mg once daily.

Use with ciclosporin A:

When co-administered with ciclosporin A, the dose of PULERTTAN should be limited to 5 mg once daily (see section 4.5).

Special populations

The elderly:

No dose adjustment is required in patients aged 65 years and over (see section 5.2).

Renal impairment:

Renal metabolism and excretion of ambrisentan are minimal, so dose adjustment is unlikely to be required in patients with renal impairment.

Hepatic impairment:

PULERTTAN has not been studied in subjects with severe hepatic impairment or with clinically significant elevated hepatic transaminases. However, hepatic impairment would be expected to increase exposure (C_{max} and AUC) to ambrisentan, since its main routes of metabolism are glucuronidation and, to a lesser extent, oxidation, with subsequent elimination in the bile. Therefore, PULERTTAN is not recommended in this patient population (see sections 4.4 and 5.2).

Recommended paediatric and adolescent dosage:

There are no data available on the use of PULERTTAN in patients under 18 years of age and therefore, the use of PULERTTAN in these patients is not recommended.

Method of administration

PULERTTAN is for oral administration and can be taken with or without food.

4.3 Contraindications

PULERTTAN is contraindicated in:

- Patients with hypersensitivity to ambrisentan or any of the excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6).
- Women of childbearing potential who are not using reliable contraception (see sections 4.4 and 4.6).
- Severe hepatic impairment (see section 4.4).
- Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT)) > 3xULN (see sections 4.2 and 4.4).
- Idiopathic pulmonary fibrosis (IPF) with or without pulmonary hypertension.

4.4 Special warnings and precautions for use

Hepatic impairment:

Hepatic enzyme elevations have been observed with ambrisentan as contained in PULERTTAN (see section 5.1). Therefore, hepatic function should be evaluated prior to initiation of PULERTTAN. If aminotransferases (alanine aminotransferase, ALT or aspartate aminotransferase, AST) are greater than 3 times upper limit of normal, initiation of PULERTTAN is not recommended (see section 4.3).

In addition, monthly monitoring of aminotransferases is recommended. If patients develop clinically significant aminotransferase elevations or if aminotransferase elevations are accompanied by signs or symptoms of hepatic injury (e.g. jaundice), PULERTTAN therapy should be discontinued. In patients without clinical symptoms of hepatic injury or of jaundice, re-initiation of PULERTTAN may be considered following resolution of hepatic enzyme abnormalities.

Hepatic injury and autoimmune hepatitis are known to occur in PAH patients and auto-antibodies are frequently found in IPAH. Cases consistent with autoimmune hepatitis, including possible exacerbation of underlying autoimmune hepatitis, and hepatic injury have been reported with ambrisentan therapy.

Therefore, patients should be monitored for signs of hepatic injury and caution exercised when PULERTTAN is used alone or concomitantly with other medicines known to be associated with hepatic injury as the additive effects of PULERTTAN with these medicines are not known.

Management of autoimmune hepatitis in PAH patients should be optimised prior to initiation of PULERTTAN and during PULERTTAN therapy. If patients develop signs or symptoms of hepatitis or suffer exacerbation of existing autoimmune hepatitis, PULERTTAN should be discontinued.

Haematological changes:

Reductions in haemoglobin concentrations and haematocrit have been observed with ambrisentan as contained in PULERTTAN and there have been cases where this has resulted in anaemia, sometimes requiring transfusion. In clinical trials, decreases in haemoglobin and haematocrit were observed within the first few weeks of therapy and generally stabilised thereafter.

Decreases in haemoglobin concentrations have been reported in patients taking PULERTTAN.

It is recommended that haemoglobin is measured prior to initiation of PULERTTAN, again at one month and periodically thereafter. Initiation of PULERTTAN therapy is not recommended for patients with clinically significant anaemia. If a clinically significant decrease in haemoglobin is observed during therapy and other causes have been excluded, discontinuation of PULERTTAN should be considered.

Fluid retention:

Peripheral oedema has been observed with ambrisentan as contained in PULERTTAN. Peripheral oedema may also be a clinical consequence of PAH. Most cases of peripheral oedema in clinical studies with ambrisentan were mild to moderate in severity.

Post-marketing reports of fluid retention occurring within weeks after starting ambrisentan as contained in PULERTTAN have been received and, in some cases, have required intervention with a diuretic or hospitalisation for fluid management or decompensated heart failure. If patients have pre-existing fluid overload, this should be managed as clinically appropriate prior to starting PULERTTAN.

If clinically significant fluid retention develops during therapy with PULERTTAN, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as PULERTTAN or underlying heart failure, and the possible need for specific treatment or

discontinuation of PULERTTAN therapy.

Pulmonary veno-occlusive disease:

If patients develop acute pulmonary oedema during initiation of therapy with vasodilating medicines such as PULERTTAN, the possibility of pulmonary veno-occlusive disease should be considered.

Women of childbearing potential:

Ambrisentan treatment must not be initiated in women of childbearing potential unless the result of a pre-treatment pregnancy test is negative and reliable contraception is practiced. If there is any doubt on what contraceptive advice should be given to the individual patient, consultation with a gynaecologist should be considered. Monthly pregnancy tests during treatment with ambrisentan are recommended (see sections 4.3 and 4.6).

Contains lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take PULERTTAN.

4.5 Interaction with other medicines and other forms of interaction

Ambrisentan is primarily metabolised by glucuronidation and to a lesser extent by oxidative metabolism, principally by CYP3A and to a lesser extent by CYP2C19. Ambrisentan does not inhibit or induce phase I or II medicine metabolising enzymes at clinically relevant concentrations in non-clinical studies, suggesting a low potential for ambrisentan to alter the profile of medicines metabolised by these pathways.

The potential for ambrisentan to induce CYP3A4 activity was explored in healthy volunteers, with results suggesting a lack of inductive effect of ambrisentan on the CYP3A4 isoenzyme.

- *Ciclosporin:* Steady-state co-administration of ambrisentan and ciclosporin A (an inhibitor of P-glycoprotein [P-gp] and organic anion transporting polypeptide [OATP]) resulted in a 2-

fold increase in ambrisentan exposure in healthy volunteers, therefore the dose of PULERTTAN should be limited to 5 mg once daily when co-administered with ciclosporin A (see section 4.2). No clinically relevant effect of ambrisentan on ciclosporin A exposure was observed.

- *Ketoconazole:* Steady state administration of ketoconazole (a strong inhibitor of CYP3A4) did not result in a clinically significant increase in exposure to ambrisentan.
- *Rifampicin:* Co-administration of rifampicin (an inhibitor of OATP, a strong inducer of CYP3A and 2C19, and inducer of P-gp and uridine-diphospho-glucuronosyltransferases [UGTs]) was associated with a transient (approximately 2-fold) increase in ambrisentan exposure following initial doses in healthy volunteers. However, by day 7, steady state administration of rifampicin had no clinically relevant effect on ambrisentan exposure. No dose adjustment of PULERTTAN is required when co-administered with rifampicin.
- *Omeprazole:* In PAH clinical studies, co-administration of ambrisentan and omeprazole (an inhibitor of CYP2C19) did not significantly affect the pharmacokinetics of ambrisentan.
- *Sildenafil:* Co-administration of ambrisentan with a phosphodiesterase inhibitor, either sildenafil or tadalafil (both substrates of CYP3A4) in healthy volunteers, did not significantly affect the pharmacokinetics of the phosphodiesterase inhibitor or ambrisentan.
- *Oral contraceptives:* In a clinical study in healthy subjects, steady state dosing with ambrisentan 10 mg did not significantly affect the single-dose pharmacokinetics of the ethinyl estradiol and norethindrone components of a combined oral contraceptive. Based on this pharmacokinetic study, ambrisentan would not be expected to significantly affect exposure to oestrogen- or progestogen-based contraceptives.
- *Warfarin:* Ambrisentan had no effects on the steady state pharmacokinetics and anticoagulant activity of warfarin in a healthy volunteer study. Warfarin also had no clinically significant effects on the pharmacokinetics of ambrisentan. In addition, in clinical studies of PAH patients, ambrisentan had no overall effect on the weekly warfarin-type anticoagulant dose, prothrombin time (PT) and international normalised ratio (INR).
- *Digoxin:* Steady-state administration of ambrisentan in healthy volunteers had no clinically

relevant effects on the single-dose pharmacokinetics of digoxin, a substrate for P-gp.

- *Other targeted PAH treatments:* The efficacy and safety of ambrisentan when co-administered with other treatments for PAH (e.g. prostanoids and soluble guanylate cyclase stimulators) has not been specifically studied in controlled clinical trials. No specific interactions between ambrisentan and soluble guanylate cyclase stimulators or prostanoids are anticipated based on the known biotransformation data (see section 5.2). However, no specific interaction studies have been conducted with these medicines. Therefore, caution is recommended in the case of co-administration.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Ambrisentan treatment must not be initiated in women of childbearing potential unless the result of a pre-treatment pregnancy test is negative and reliable contraception is practiced. Monthly pregnancy tests during treatment with ambrisentan are recommended.

Pregnancy

PULERTTAN is contraindicated in pregnancy (see section 4.3). Animal studies in rats and rabbits have shown that ambrisentan is teratogenic, which is a class effect of ERAs (endothelin receptor antagonists).

PULERTTAN is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals (see section 4.3). Pregnancy must therefore be excluded before the initiation of treatment with PULERTTAN and prevented thereafter by reliable methods of contraception. Pregnancy tests during treatment with PULERTTAN are recommended as clinically indicated. Women of childbearing potential should be advised to contact their medical practitioner immediately if they become pregnant or suspect they may be pregnant.

Breastfeeding

It is not known whether ambrisentan is excreted in human milk. Mothers on PULERTTAN should not breastfeed their infants (see section 4.3).

Fertility

The development of testicular tubular atrophy in male animals has been linked to the chronic administration of ambrisentan as contained in PULERTTAN. The effect on male human fertility is not known.

4.7 Effects on ability to drive and use machines

PULERTTAN has minor or moderate influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of PULERTTAN (such as hypotension, dizziness, asthenia, fatigue) should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills (see section 4.8). Patients should be aware of how they might be affected by PULERTTAN before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Peripheral oedema and headache were the most frequent adverse reactions observed with ambrisentan. The higher dose (10 mg) was associated with a higher incidence of these adverse reactions, and peripheral oedema tended to be more severe in patients > 65 years in short-term clinical studies (see section 4.4). Serious adverse reactions associated with ambrisentan use include anaemia (decreased haemoglobin, decreased haematocrit) and hepatotoxicity.

Reductions in haemoglobin concentrations and haematocrit have been associated with ERAs including ambrisentan. Most of these decreases were detected during the first 4 weeks of treatment and haemoglobin generally stabilised thereafter (see section 4.4). Hepatic enzyme elevations, hepatic injury and autoimmune hepatitis (including exacerbation of underlying disease)

have been observed with ambrisentan (see section 4.4).

Tabulated list of adverse reactions

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	*Frequent*	Anaemia (decreased haemoglobin, decreased haematocrit)[1]
Immune system disorders	*Frequent*	Hypersensitivity reactions (e.g. angioedema, rash, pruritus)
Nervous system disorders	*Frequent*	Headache (including sinus headache, migraine)[2], dizziness
Eye disorders	*Frequent*	Blurred vision, visual impairment
Ear and labyrinth disorders	*Frequent*	Tinnitus[3]
	Less frequent	Sudden hearing loss[3]
Cardiac disorders	*Frequent*	Palpitations, cardiac failure[4]
Vascular disorders	*Frequent*	Flushing[5], hypotension, syncope
Respiratory, thoracic and mediastinal disorders	*Frequent*	Dyspnoea[6], upper respiratory (e.g. nasal, sinus) congestion[7], nasopharyngitis[7], epistaxis, rhinitis[7], sinusitis[7]
Gastrointestinal disorders	*Frequent*	Nausea, diarrhoea, vomiting[5], abdominal pain, constipation
Hepatobiliary disorders	*Frequent*	Hepatic transaminases increased

	Less frequent	Hepatic injury, autoimmune hepatitis (see section 4.4)
Skin and subcutaneous tissue disorders	*Frequent*	Rash[8]
General disorders and administration site conditions	*Frequent*	Peripheral oedema, fluid retention, chest pain/discomfort[5], fatigue, asthenia

[1]See section **Description of selected adverse reactions** below.

[2]The frequency of headache appeared higher with 10 mg ambrisentan.

[3]Cases were only observed in a placebo-controlled clinical study of ambrisentan in combination with tadalafil.

[4]Most of the reported cases of cardiac failure were associated with fluid retention.

[5]Frequencies were observed in a placebo-controlled clinical study of ambrisentan in combination with tadalafil. Lower incidence was observed with ambrisentan monotherapy.

[6]Cases of worsening dyspnoea of unclear aetiology have been reported shortly after starting ambrisentan therapy.

[7]The incidence of nasal congestion was dose related during ambrisentan therapy.

[8]Rash includes rash erythematous, rash generalised, rash papular and rash pruritic.

Post-marketing experience

In addition to adverse reactions identified from clinical studies, the following adverse reactions were identified during post-approval use of PULERTTAN. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

System organ class	**Adverse reactions**
Blood and lymphatic system disorders	anaemia requiring transfusion
Cardiac disorders	heart failure (associated with fluid retention)

Vascular disorders	hypotension
Hepatobiliary disorders	hepatic transaminases, increased hepatic injury, autoimmune hepatitis (see section 4.4).

Cases of autoimmune hepatitis, including cases of exacerbation of autoimmune hepatitis, and hepatic injury of unclear aetiology have been reported during PULERTTAN therapy.

PULERTTAN used in combination with tadalafil

The adverse reactions observed were generally consistent with the safety profile of ambrisentan used alone. The following adverse reactions were seen more frequently in the combination of ambrisentan with tadalafil than with either medicine alone:

Gastrointestinal disorders

Frequent: vomiting.

In addition, the following adverse reaction was observed:

Ear and labyrinth disorders

Frequent: tinnitus.

Description of selected adverse reactions

Decreased haemoglobin:

In the post-marketing period, cases of anaemia requiring blood cell transfusion have been reported (see section 4.4). The frequency of decreased haemoglobin (anaemia) was higher with 10 mg ambrisentan.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of PULERTTAN is important. It allows continued monitoring of the benefit/risk balance of PULERTTAN. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms and signs

In healthy volunteers, single doses of 50 and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Due to its mechanism of action, an overdose of PULERTTAN could also potentially result in hypotension.

Treatment

In the case of pronounced hypotension, active cardiovascular support may be required. No specific antidote is available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Other hypotensives.

Pharmacotherapeutic group: Anti-hypertensives, other anti-hypertensives.

ATC code: C02KX02.

Mechanism of action

Ambrisentan is an orally active, propanoic acid-class, endothelin receptor A (ET_A) selective, endothelin receptor antagonist (ERA). Endothelin plays a significant role in the pathophysiology of PAH.

- Ambrisentan blocks the ET_A receptor subtype, localised predominantly on vascular smooth muscle cells and cardiac myocytes. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.
- The selectivity of ambrisentan for the ET_A over the ET_B receptor is expected to retain ET_B receptor mediated production of the vasodilators nitric oxide and prostacyclin.

Invasive haemodynamic parameters were assessed in patients with PAH. Treatment with ambrisentan resulted in a significant increase in mean cardiac index and a decrease in mean pulmonary artery pressure and mean pulmonary vascular resistance.

In patients with PAH, reductions in B-type natriuretic peptide (BNP) have been shown to parallel improvements in haemodynamics and 6-minute walk distance (6MWD). Clinical studies have demonstrated that plasma concentrations of BNP decreased in patients who received ambrisentan.

In patients with PAH who received first-line combination therapy with ambrisentan and tadalafil, a greater decrease from baseline in N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) relative to pooled monotherapy was observed. Similar results were seen with comparisons to ambrisentan monotherapy and tadalafil monotherapy. The decrease in NT-pro-BNP was observed early and was sustained through treatment.

5.2 Pharmacokinetic properties

Absorption

In patients with PAH, the maximum plasma concentrations (C_{max}) typically occur around 2 hours after oral administration. In healthy volunteers, under both fasted and fed conditions, ambrisentan exposure does not change significantly with food intake and therefore ambrisentan can be taken with or without food. C_{max} and area under the plasma concentration-time curve (AUC) increase dose proportionally over the therapeutic dose range. Steady state is generally achieved following 4 days of repeat dosing.

Distribution

The plasma protein binding of ambrisentan was 98,8 %. Ambrisentan is primarily bound to albumin (96,5 %).

The distribution of ambrisentan into red blood cells is low, with a mean blood: plasma ratio of 0,57 and 0,61 in males and females, respectively.

Biotransformation

Ambrisentan is glucuronidated by several UGT enzymes (UGT1A9S, UGT2B7S and UGT1A3S) to form ambrisentan glucuronide. Ambrisentan also undergoes oxidative metabolism, mainly by CYP3A4 and to a lesser extent by CYP3A5 and CYP2C19, to form 4-hydroxymethyl ambrisentan, which is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide.

In plasma, the AUC of 4-hydroxymethyl ambrisentan accounts for approximately 4 % relative to parent ambrisentan AUC. Furthermore, the binding affinity of 4-hydroxymethyl ambrisentan for the human ET_A receptor is more than 100-fold less than ambrisentan. Therefore, 4-hydroxymethyl ambrisentan is not expected to contribute to pharmacological activity of ambrisentan.

In vitro studies using rat and human hepatocyte cultures have demonstrated that ambrisentan is a possible substrate for the hepatic influx transporter OATP and for the efflux transporter P-gp, but not for the hepatic influx or efflux sodium-taurocholate co-transporter protein (NTCP) or bile salt export pump (BSEP), respectively.

The *in vitro* data suggest ambrisentan at clinically relevant concentrations would not be expected to have an effect on UGT1A1, UGT1A6, UGT1A9, UGT2B7 or cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 or transport via BSEP, BCRP, P-gp, MRP2, OATP1B1/3, or NTCP.

Elimination

Ambrisentan and its metabolites are eliminated primarily in the bile. In the faeces, 40 % of the dose is recovered as parent ambrisentan and 21 % as the 4-hydroxymethyl ambrisentan. Approximately 22 % of the administered dose is recovered in the urine following oral administration with 3,3 % being unchanged ambrisentan and the remainder as glucuronide metabolites. Steady-state plasma elimination half-life ranged from 13,6 to 16,5 hours in healthy volunteers and from 12,9 to 17,9

hours in patients with PAH.

Pharmacokinetics in special populations

The pharmacokinetics of ambrisentan are not influenced by gender or age.

Hepatic impairment:

The pharmacokinetics of ambrisentan have not been studied in subjects with severe hepatic impairment or with clinically significant elevated hepatic transaminases. However, hepatic impairment would be expected to increase exposure (C_{max} and AUC) to ambrisentan, since its main routes of metabolism are glucuronidation and, to a lesser extent by oxidation with subsequent elimination in the bile. The magnitude of this effect and any impact on safety and efficacy, have not been evaluated. Therefore, ambrisentan is not recommended in this patient population.

Renal impairment:

The pharmacokinetics of ambrisentan have not been studied in subjects with renal impairment. However, renal metabolism and excretion of ambrisentan is minimal, so renal impairment is unlikely to significantly increase exposure to ambrisentan.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Microcrystalline cellulose

Croscarmellose sodium

Magnesium stearate.

Film-coating:

PULERTTAN 5 contains Opadry II Yellow consisting of:

Polyvinyl alcohol (E1203)

Titanium dioxide (E171)

Macrogol 4000/PEG 3350 (E1521)

Talc (E553b)

Iron oxide yellow (E172)

Iron oxide red (E172).

PULERTTAN 10 contains Opadry II Pink consisting of:

Polyvinyl alcohol (E1203)

Titanium dioxide (E171)

Macrogol 4000/PEG 3350 (E1521)

Talc (E553b)

Iron oxide red (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Store at or below 25 °C.

6.4 Special precautions for storage

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

PVC/PVdC aluminium blister strips containing 10 tablets each.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville 7551

Tel no.: 087 551 3245

8. REGISTRATION NUMBERS

PULERTTAN 5: 59/7.1.3/0710.708

PULERTTAN 10: 59/7.1.3/0711.709

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 May 2026

10. DATE OF REVISION OF THE TEXT