[MSN LABORATORIES PVT LTD LOGO]

1. NAME OF THE MEDICINAL PRODUCT

Pulmonext 10 (Ambrisentan 10 mg film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Ambrisentan 10 mg.

For the full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Pulmonext 10 is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Treatment must be initiated by a physician experienced in the treatment of PAH.

Ambrisentan monotherapy

Ambrisentan is to be taken orally to begin at a dose of 5 mg once daily and may be increased to 10 mg daily depending upon clinical response and tolerability.

Ambrisentan in combination with tadalafil

When used in combination with tadalafil, ambrisentan should be titrated to 10 mg once daily.

In the AMBITION study, patients received 5 mg ambrisentan daily for the first 8 weeks before up titrating to 10 mg, dependent on tolerability (see section 5.1). When used in combination with tadalafil, patients were initiated with 5 mg ambrisentan and 20 mg tadalafil. Dependent on tolerability the dose of tadalafil was increased to 40 mg after 4 weeks and the dose of ambrisentan was increased to 10 mg after 8 weeks. More than 90 % of patients achieved this. Doses could also be decreased depending on tolerability.

Limited data suggest that the abrupt discontinuation of ambrisentan is not associated with rebound worsening of PAH.

When co-administered with cyclosporine A, the dose of ambrisentan should be limited to 5 mg once daily and the patient should be carefully monitored (see sections 4.5 and 5.2).

Special populations

Elderly patients

No dose adjustment is required in patients over the age of 65 (see section 5.2).

Patients with renal impairment

No dose adjustment is required in patients with renal impairment (see section 5.2). There is limited experience with ambrisentan in individuals with severe renal impairment (creatinine clearance <30 ml/min); therapy should be initiated cautiously in this subgroup and particular care taken if the dose is increased to 10 mg ambrisentan.

Patients with hepatic impairment

Ambrisentan has not been studied in individuals with hepatic impairment (with or without cirrhosis). Since the main routes of metabolism of ambrisentan are glucuronidation and oxidation with subsequent elimination in the bile, hepatic impairment might be expected to increase exposure (C_{max} and AUC) to ambrisentan. Therefore,

ambrisentan must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (>3xULN); see sections 4.3 and 4.4).

Paediatric population

The safety and efficacy of ambrisentan in children and adolescents aged below 18 years has not been established. No clinical data are available.

Method of administration

It is recommended that the tablet is swallowed whole, and it can be taken with or without food. It is recommended that the tablet should not be split, crushed or chewed.

4.3 CONTRAINDICATIONS

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

Pregnancy (see section 4.6).

Women of child-bearing potential who are not using reliable contraception (see sections 4.4 and 4.6).

Breast-feeding (see section 4.6).

Severe hepatic impairment (with or without cirrhosis) (see section 4.2).

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 secondary pulmonary hypertension (see section 5.1).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Ambrisentan has not been studied in a sufficient number of patients to establish the benefit/risk balance in WHO functional class I PAH.

The efficacy of ambrisentan as monotherapy has not been established in patients with WHO functional class IV PAH. Therapy that is recommended at the severe stage of the disease (e.g. epoprostenol) should be considered if the clinical condition deteriorates.

Liver function

Liver function abnormalities have been associated with PAH. Cases consistent with autoimmune hepatitis, including possible exacerbation of underlying autoimmune hepatitis, hepatic injury and hepatic enzyme elevations potentially related to therapy have been observed with ambrisentan (see sections 4.8 and 5.1). Therefore, hepatic aminotransferases (ALT and AST) should be evaluated prior to initiation of ambrisentan and treatment should not be initiated in patients with baseline values of ALT and/or AST >3xULN (see section 4.3).

Patients should be monitored for signs of hepatic injury and monitoring of ALT and AST as clinically indicated is recommended. If patients develop sustained, unexplained, clinically significant ALT and/or AST elevation, or if ALT and/or AST elevation is accompanied by signs or symptoms of hepatic injury (e.g. jaundice), ambrisentan therapy should be discontinued.

In patients without clinical symptoms of hepatic injury or of jaundice, re-initiation of ambrisentan may be considered following resolution of hepatic enzyme abnormalities. The advice of a hepatologist is recommended.

Haemoglobin concentration

Reductions in haemoglobin concentrations and haematocrit have been associated with endothelin receptor antagonists (ERAs) including ambrisentan. Most of these decreases were detected during the first 4 weeks of treatment and haemoglobin generally stabilised thereafter. Mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in haemoglobin concentrations persisted for up to 4 years of treatment with ambrisentan in the long-term open-label extension of the pivotal Phase 3 clinical studies. In the post- marketing period, cases of anaemia requiring blood cell transfusion have been reported (see section 4.8).

Initiation of ambrisentan is not recommended for patients with clinically significant anaemia. It is recommended that haemoglobin and/or haematocrit levels are measured during treatment with ambrisentan, for example at 1 month, 3 months and periodically thereafter in line with clinical practice. If a clinically significant decrease in haemoglobin or haematocrit is observed, and other causes have been excluded, dose reduction or discontinuation of treatment should be considered. The incidence of anaemia was increased when ambrisentan was dosed in combination with tadalafil (15 % adverse event frequency), compared to the incidence of anaemia when ambrisentan and tadalafil were given as monotherapy (7 % and 11 %, respectively).

Fluid retention

Peripheral oedema has been observed with ERAs including ambrisentan. Most cases of peripheral oedema in clinical studies with ambrisentan were mild to moderate in severity, although it may occur with greater frequency and severity in patients ≥65 years. Peripheral oedema was reported more frequently with 10 mg ambrisentan in short-term clinical studies (see section 4.8).

Post-marketing reports of fluid retention occurring within weeks after starting ambrisentan 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 ambrisentan.

If clinically significant fluid retention develops during therapy with ambrisentan, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as ambrisentan or underlying heart failure, and the possible need for specific treatment or discontinuation of ambrisentan therapy. The incidence of peripheral oedema was increased when ambrisentan was dosed in combination with tadalafil (45 % adverse event frequency), compared to the incidence of peripheral oedema when ambrisentan and tadalafil were given as monotherapy (38 % and 28 %, respectively). The occurrence of peripheral oedema was highest within the first month of treatment initiation.

Women of child-bearing potential

Pulmonext 10 treatment must not be initiated in women of child-bearing potential unless the result of a pretreatment 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).

Pulmonary veno-occlusive disease

Cases of pulmonary oedema have been reported with vasodilating medicinal products, such as ERAs, when used in patients with pulmonary veno-occlusive disease. Consequently, if PAH patients develop acute pulmonary oedema when treated with ambrisentan, the possibility of pulmonary veno-occlusive disease should be considered.

Concomitant use with other medicinal products

Patients on ambrisentan therapy should be closely monitored when starting treatment with rifampicin (see sections 4.5 and 5.2).

Excipients

Pulmonext 10 tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Ambrisentan does not inhibit or induce phase I or II drug metabolising enzymes at clinically relevant concentrations in *in vitro* and *in vivo* non-clinical studies, suggesting a low potential for ambrisentan to alter the profile of medicinal products 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.

Cyclosporine A

Steady-state co-administration of ambrisentan and cyclosporine A resulted in a 2-fold increase in ambrisentan exposure in healthy volunteers. This may be due to the inhibition by cyclosporine A of transporters and metabolic enzymes involved in the pharmacokinetics of ambrisentan. Therefore, the dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporine A (see section 4.2). Multiple doses of ambrisentan had no effect on cyclosporine A exposure, and no dose adjustment of cyclosporine A is warranted.

Rifampicin

Co-administration of rifampicin (an inhibitor of Organic Anion Transporting Polypeptide [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 8, steady state administration of rifampicin had no clinically relevant effect on ambrisentan exposure. Patients on ambrisentan therapy should be closely monitored when starting treatment with rifampicin (see sections 4.4 and 5.2).

Phosphodiesterase inhibitors

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 (see section 5.2).

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 in PAH patients (see section 5.1). No specific drug-drug interactions with soluble guanylate cyclase stimulators or prostanoids are anticipated based on the known biotransformation data (see section 5.2). However, no specific drug-drug interactions studies have been conducted with these drugs. Therefore, caution is recommended in the case of co-administration.

Oral contraceptives

In a clinical study in healthy volunteers, steady-state dosing with ambrisentan 10 mg once daily did not significantly affect the single-dose pharmacokinetics of the ethinyl estradiol and norethindrone components of a combined oral contraceptive (see section 5.2). 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 anti-coagulant activity of warfarin in a healthy volunteer study (see section 5.2). Warfarin also had no clinically significant effects on the pharmacokinetics of ambrisentan. In addition, in patients, ambrisentan had no overall effect on the weekly warfarin-type anticoagulant dose, prothrombin time (PT) and international normalised ratio (INR).

Ketoconazole

Steady-state administration of ketoconazole (a strong inhibitor of CYP3A4) did not result in a clinically significant increase in exposure to ambrisentan (see section 5.2).

Effects of ambrisentan on xenobiotic transporters

In vitro, ambrisentan has no inhibitory effect on human transporters at clinically relevant concentrations, including the P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), multi-drug resistance related protein 2 (MRP2), bile salt export pump (BSEP), organic anion transporting polypeptides (OATP1B1 and OATP1B3) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

Ambrisentan is a substrate for Pgp-mediated efflux.

In vitro studies in rat hepatocytes also showed that ambrisentan did not induce Pgp, BSEP or MRP2 protein expression.

Steady-state administration of ambrisentan in healthy volunteers had no clinically relevant effects on the single-dose pharmacokinetics of digoxin, a substrate for Pgp (see section 5.2).

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential

Ambrisentan treatment must not be initiated in women of child-bearing 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

Ambrisentan is contraindicated in pregnancy (see section 4.3). Animal studies have shown that ambrisentan is teratogenic. There is no experience in humans.

Women receiving ambrisentan must be advised of the risk of foetal harm and alternative therapy initiated if pregnancy occurs (see sections 4.3 and 4.4).

Breast-feeding

It is not known whether ambrisentan is excreted in human breast milk. The excretion of ambrisentan in milk has not been studied in animals. Therefore, breast-feeding is contraindicated in patients takingambrisentan (see section 4.3).

Male fertility

The development of testicular tubular atrophy in male animals has been linked to the chronic administration of ERAs, including ambrisentan. Although no clear evidence of a detrimental effect of ambrisentan long-term exposure on sperm count was found in ARIES-E study, chronic administration of ambrisentan was associated with changes in markers of spermatogenesis. A decrease in plasma inhibin-B concentration and an increase in plasma FSH concentration were observed. The effect on male human fertility is not known but a deterioration of spermatogenesis cannot be excluded. Chronic administration of ambrisentan was not associated with a change in plasma testosterone in clinical studies.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Ambrisentan 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 ambrisentan (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 ambrisentan before driving or using machines.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

The safety of ambrisentan has been evaluated as monotherapy and/or in combination in clinical trials of more than 1200 patients with PAH (see section 5.1). Adverse reactions identified from 12-week placebo controlled clinical trial data are included below by system organ class and frequency. Information from longer term non-placebo-controlled studies (ARIES-E and AMBITION (combination with tadalafil)) is also included below. No previously unknown adverse reactions were identified with long-term treatment or for ambrisentan in combination with tadalafil. With longer observation in uncontrolled studies (mean observation of 79 weeks), the safety profile was similar to that observed in the short-term studies. Routine pharmacovigilance data are also presented.

Peripheral oedema, fluid retention and headache (including sinus headache, migraine) were the most common 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).

Tabulated list of adverse reactions

Frequencies are 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) and not known (cannot be estimated from available data). For dose-related adverse reactions the frequency category reflects the higher dose of ambrisentan. Frequency categories do not account for other factors including varying study duration, preexisting conditions and baseline patient characteristics. Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

	Ambrisentan (ARIES-C and post marketing)	**Ambrisentan (AMBITION and ARIES-E)**	**Combination with tadalafil (AMBITION)**
Blood and lymphatic system disorders			
Anaemia (decreased haemoglobin, decreased haematocrit)	Common[1]	Very common	Very common
Immune system disorders			
Hypersensitivity reactions (e.g., angioedema, rash, pruritus)	Uncommon	Common	Common
Nervous system disorders			
Headache (including sinus headache, migraine)	Very common[2]	Very common	Very common
Dizziness	Common[3]	Very common	Very common
Eye disorders			
Blurred vision, visual impairment	Not known[4]	Common	Common
Ear and labyrinth disorders			
Tinnitus	NR	NR	Common
Sudden hearing loss	NR	NR	Uncommon
Cardiac disorders			
Cardiac failure	Common[5]	Common	Common
Palpitation	Common	Very common	Very common
Vascular disorders			
Hypotension	Common[3]	Common	Common
Flushing	Common	Common	Very common
Syncope	Uncommon[3]	Common	Common
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Common[3]	Common	Common
Dyspnoea	Common[3,6]	Very common	Very common
Upper respiratory (e.g., nasal, sinus) congestion, sinusitis, nasopharyngitis, rhinitis	Common[7]		
Nasopharyngitis		Very common	Very common
Sinusitis, rhinitis		Common	Common
Nasal congestion		Very common	Very common
Gastrointestinal disorders			
Nausea, vomiting, diarrhoea	Common[3]		
Nausea		Very common	Very common
Vomiting		Common	Very common
Diarrhoea		Very common	Very common

Abdominal pain	Common	Common	Common
Constipation	Common	Common	Common
Hepatobiliary disorders			
Hepatic injury (see section 4.4)	Uncommon[3,8]	NR	NR
Autoimmune hepatitis (see section 4.4)	Uncommon[3,8]	NR	NR
Hepatic transaminases increased	Common[3]	NR	NR
Skin and subcutaneous tissue disorders			
Rash	NR	Common[9]	Common[9]
General disorders and administration site conditions			
Peripheral oedema, fluid retention	Very common	Very common	Very common
Chest pain/ discomfort	Common	Common	Very common
Asthenia	Common[3]	Common	Common
Fatigue	Common[3]	Very common	Very common

NR – not reported

[1] See section 'Description of selected adverse reactions'.

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

[3] Data derived from routine pharmacovigilance surveillance and frequencies based on placebo-controlled clinical trial experience.

[4] Data derived from routine pharmacovigilance surveillance

[5] Most of the reported cases of cardiac failure were associated with fluid retention. Data derived from routine pharmacovigilance surveillance, frequencies based on statistical modelling of placebo-controlled clinical trial data.

[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] Cases of autoimmune hepatitis, including cases of exacerbation of autoimmune hepatitis, and hepatic injury have been reported during ambrisentan therapy.

[9] Rash includes rash erythematous, rash generalised, rash papular and rash pruritic

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. Across the 12 week placebo controlled Phase 3 clinical studies, mean haemoglobin concentrations decreased for patients in the ambrisentan groups and were detected as early as week 4 (decrease by 0.83 g/dL); mean changes from baseline appeared to stabilise over the subsequent 8 weeks. A total of 17 patients (6.5 %) in the ambrisentan treatment groups had decreases in haemoglobin of ≥15 % from baseline and which fell below the lower limit of normal.

4.9 OVERDOSAGE

There is no experience in PAH patients of ambrisentan at daily doses greater than 10 mg. 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 the mechanism of action, an overdose of ambrisentan could potentially result in hypotension. In the case of pronounced hypotension, active cardiovascular support may be required. No specific antidote is available.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anti-hypertensives, other anti-hypertensives, ATC code: C02KX02.

Mechanism of action

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

- Ambrisentan is a potent (Ki 0.016 nM) and highly selective ET_A antagonist (approximately 4000-fold more selective for ET_A as compared to ET_B).
- Ambrisentan blocks the ET_A receptor subtype, localized 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ambrisentan is absorbed rapidly in humans. After oral administration, maximum plasma concentrations (C_{max}) of ambrisentan typically occur around 1.5 hours post-dose under both fasted and fed conditions. 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.

A food-effect study involving administration of ambrisentan to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} was decreased 12 % while the AUC remained unchanged. This decrease in peak concentration is not clinically significant, and therefore ambrisentan can be taken with or without food.

Distribution

Ambrisentan is highly plasma protein bound. The in vitro plasma protein binding of ambrisentan was, on average, 98.8 % and independent of concentration over the range of 0.2 – 20 microgram/ml. Ambrisentan is primarily bound to albumin (96.5 %) and to a lesser extent to alpha1-acid glycoprotein.

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 a non-sulphonamide (propanoic acid) ERA.

Ambrisentan is glucuronidated via several UGT isoenzymes (UGT1A9S, UGT2B7S and UGT1A3S) to form ambrisentan glucuronide (13 %). Ambrisentan also undergoes oxidative metabolism mainly by CYP3A4 and to a lesser extent by CYP3A5 and CYP2C19 to form 4-hydroxymethyl ambrisentan (21 %) which is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide (5 %). The binding affinity of 4-hydroxymethyl ambrisentan for the human endothelin receptor is 65-fold less than ambrisentan. Therefore, at concentrations observed in the plasma (approximately 4 % relative to parent ambrisentan), 4-hydroxymethyl ambrisentan is not expected to contribute to pharmacological activity of ambrisentan.

In vitro data indicate that ambrisentan at 300 µM resulted in less than 50 % inhibition of UGT1A1, UGT1A6, UGT1A9, UGT2B7 (up to 30 %) or of cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 (up to 25 %). *In vitro*, ambrisentan has no inhibitory effect on human transporters at clinically relevant concentrations, including Pgp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and NTCP. Furthermore, ambrisentan did not induce MRP2, Pgp or BSEP protein expression in rat hepatocytes. Taken together, the in vitro data suggest ambrisentan at clinically relevant concentrations (plasma C_{max} up to 3.2 µM) 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, Pgp, MRP2, OATP1B1/3, or NTCP.

The effects of steady-state ambrisentan (10 mg once daily) on the pharmacokinetics and pharmacodynamics of a single dose of warfarin (25 mg), as measured by PT and INR, were investigated in 20 healthy volunteers. Ambrisentan did not have any clinically relevant effects on the pharmacokinetics or pharmacodynamics of warfarin. Similarly, co-administration with warfarin did not affect the pharmacokinetics of ambrisentan (see section 4.5).

The effect of 7-day dosing of sildenafil (20 mg three times daily) on the pharmacokinetics of a single dose of ambrisentan, and the effects of 7-day dosing of ambrisentan (10 mg once daily) on the pharmacokinetics of a single dose of sildenafil were investigated in 19 healthy volunteers. With the exception of a 13% increase in sildenafil C_{max} following co-administration with ambrisentan, there were no other changes in the pharmacokinetic parameters of sildenafil, N-desmethyl-sildenafil and ambrisentan. This slight increase in sildenafil C_{max} is not considered clinically relevant (see section 4.5).

The effects of steady-state ambrisentan (10 mg once daily) on the pharmacokinetics of a single dose of tadalafil, and the effects of steady-state tadalafil (40 mg once daily) on the pharmacokinetics of a single dose of ambrisentan were studied in 23 healthy volunteers. Ambrisentan did not have any clinically relevant effects on the pharmacokinetics of tadalafil. Similarly, co-administration with tadalafil did not affect the pharmacokinetics of ambrisentan (see section 4.5).

The effects of repeat dosing of ketoconazole (400 mg once daily) on the pharmacokinetics of a single dose of 10 mg ambrisentan were investigated in 16 healthy volunteers. Exposures of ambrisentan as measured by $AUC_{(0\text{-inf})}$ and C_{max} were increased by 35 % and 20 %, respectively. This change in exposure is unlikely to be of any clinical relevance and therefore ambrisentan may be co-administered with ketoconazole.

The effects of repeat dosing of cyclosporine A (100 – 150 mg twice daily) on the steady-state pharmacokinetics of ambrisentan (5 mg once daily), and the effects of repeat dosing of ambrisentan (5 mg once daily) on the steady-state pharmacokinetics of cyclosporine A (100 – 150 mg twice daily) were studied in healthy volunteers. The C_{max} and AUC $(0–\tau)$ of ambrisentan increased (48 % and 121 %, respectively) in the presence of multiple doses of cyclosporine A. Based on these changes, the dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporine A (see section 4.2). However, multiple doses of ambrisentan had no clinically relevant effect on cyclosporine A exposure, and no dose adjustment of cyclosporine A is warranted.

The effects of acute and repeat dosing of rifampicin (600 mg once daily) on the steady-state pharmacokinetics of ambrisentan (10 mg once daily) were studied in healthy volunteers. Following initial doses of rifampicin, a transient increase in ambrisentan AUC $(0–\tau)$ (121 % and 116 % after first and second doses of rifampicin, respectively) was observed, presumably due to a rifampicin-mediated OATP inhibition. However, there was no clinically relevant effect on ambrisentan exposure by day 8, following administration of multiple doses of rifampicin. Patients on ambrisentan therapy should be closely monitored when starting treatment with rifampicin (see sections 4.4 and 4.5).

The effects of repeat dosing of ambrisentan (10 mg) on the pharmacokinetics of single dose digoxin were studied in 15 healthy volunteers. Multiple doses of ambrisentan resulted in slight increases in digoxin $AUC_{0\text{-last}}$ and trough concentrations, and a 29 % increase in digoxin C_{max}. The increase in digoxin exposure observed in the presence of multiple doses of ambrisentan was not considered clinically relevant, and no dose adjustment of digoxin is warranted (see section 4.5).

The effects of 12 days dosing with ambrisentan (10 mg once daily) on the pharmacokinetics of a single dose of oral contraceptive containing ethinyl estradiol (35 µg) and norethindrone (1 mg) were studied in healthy female volunteers. The C_{max} and AUC $_{(0–\infty)}$ were slightly decreased for ethinyl estradiol (8 % and 4 %, respectively), and slightly increased for norethindrone (13 % and 14 %, respectively). These changes in exposure to ethinyl estradiol or norethindrone were small and are unlikely to be clinically significant (see section 4.5).

Elimination

Ambrisentan and its metabolites are eliminated primarily in the bile following hepatic and/or extrahepatic metabolism. Approximately 22 % of the administered dose is recovered in the urine following oral administration with 3.3 % being unchanged ambrisentan. Plasma elimination half-life in humans ranges from 13.6 to 16.5 hours.

Special populations

Based on the results of a population pharmacokinetic analysis in healthy volunteers and patients with PAH, the pharmacokinetics of ambrisentan were not significantly influenced by gender or age (see section 4.2).

Renal impairment

Ambrisentan does not undergo significant renal metabolism or renal clearance (excretion). In a population pharmacokinetic analysis, creatinine clearance was found to be a statistically significant covariate affecting the oral clearance of ambrisentan. The magnitude of the decrease in oral clearance is modest (20-40 %) in patients with moderate renal impairment and therefore is unlikely to be of any clinical relevance. However, caution should be used in patients with severe renal impairment (see section 4.2).

Hepatic impairment

The main routes of metabolism of ambrisentan are glucuronidation and oxidation with subsequent elimination in the bile and therefore hepatic impairment might be expected to increase exposure (C_{max} and AUC) of ambrisentan. In a population pharmacokinetic analysis, the oral clearance was shown to be decreased as a function of increasing bilirubin levels. However, the magnitude of effect of bilirubin is modest (compared to the typical patient with a bilirubin of 0.6 mg/dl, a patient with an elevated bilirubin of 4.5 mg/dl would have approximately 30 % lower oral clearance of ambrisentan). The pharmacokinetics of ambrisentan in patients with hepatic impairment (with or without cirrhosis) has not been studied. Therefore, ambrisentan should not be initiated in patients with severe hepatic impairment or clinically significant elevated hepatic aminotransferases (>3xULN) (see sections 4.3 and 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film coat

Polyvinyl alcohol (partially hydrolyzed)
Titanium dioxide (E171)
Macrogol/PEG
Talc
Iron oxide red (E172)

6.2 INCOMPATABILITIES

Not applicable.

6.3 SHELF LIFE

The expiry date is indicated on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVDC/aluminium foil blisters.

Pack size of 3 x 10’s tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements for disposal.

7. PRODUCT REGISTRATION HOLDER IN MALAYSIA

Synercam (M) Sdn. Bhd.,
A-17-7, Block A, Jaya One,
No. 72A, Jalan Professor Diraja Ungku Aziz,
Seksyen 13, 46200, Petaling Jaya,
Malaysia

8. MANUFACTURER

MSN Laboratories Pvt. Ltd.,
Formulation Division, Unit-II,
Sy. No 1277 & 1319 to 1324,
Nandigama (Village & Mandal),
Ranga Reddy District, 509228, India

9. REGISTRATION NUMBER

MALXXXXXXXAZ

10. DATE OF THE REVISION OF THE TEXT

17th September 2026