PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1.NAME OF THE MEDICINE

OPSUMIT 10 mg film-coated tablets

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg macitentan.

Excipients with known effect: Each film-coated tablet contains approximately 37 mg of lactose (as monohydrate) and approximately 0,06 mg of soya bean lecithin (E322).

For the full list of excipients, see section 6.1.

3.PHARMACEUTICAL FORM

Film-coated tablet (tablet).

5,5 mm, round, biconvex, white to off-white film-coated tablets, debossed with “10” on both sides.

4.CLINICAL PARTICULARS

4.1 Therapeutic indications

OPSUMIT, as monotherapy or in combination with approved PAH medicines, is indicated for the treatment of pulmonary arterial hypertension (PAH) to delay progression of PAH in adult patients with WHO Functional Class (FC) II to III symptoms.

4.2 Posology and method of administration

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

Posology

The recommended dose is 10 mg orally once daily.

Special populations

Elderly

No dose adjustment is required in patients over the age of 65 years (see section 5.2). There is limited clinical experience in patients over the age of 75 years. Therefore, OPSUMIT should be used with caution in this population (see section 4.4).

Hepatic impairment

Based on pharmacokinetic (PK) data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment (see sections 4.4 and 5.2). However, there is no clinical experience with the use of macitentan in PAH patients with moderate or severe hepatic impairment. OPSUMIT 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 (> 3 × ULN); see sections 4.3 and 4.4).

Renal impairment

Based on PK data, no dose adjustment is required in patients with renal impairment. There is no clinical experience with the use of macitentan in PAH patients with severe renal impairment. The use of OPSUMIT is not recommended in patients undergoing dialysis (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of macitentan in children and adolescents below 18 years have not been established. No data are available.

Method of administration

The film-coated tablets are not breakable and are to be swallowed whole, with water and must not be chewed, divided or crushed. They may be taken with or without food.

OPSUMIT should be taken every day at about the same time. If the patient misses a dose of OPSUMIT, the patient should be told to take it as soon as possible and then take the next dose at the regularly scheduled time. The patient should be told not to take two doses at the same time if a dose has been missed.

4.3 Contraindications

- Hypersensitivity to the active substance, soya or to any of the excipients listed in section 6.1.
- Pregnancy and Breastfeeding (see section 4.6).
- Women of childbearing potential who are not using reliable contraception (see sections 4.4 and 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) > 3 × ULN) (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

The benefit/risk balance of macitentan has not been established in patients with WHO class I functional status of pulmonary arterial hypertension.

Liver function

Elevations of liver aminotransferases (AST, ALT) have been associated with PAH and with endothelin receptor antagonists (ERAs including OPSUMIT). OPSUMIT is not to be initiated in patients with severe (Child-Pugh Class C) hepatic impairment or elevated aminotransferases (> 3 × ULN) (see sections 4.2 and 4.3) and is not recommended in

patients with moderate (Child-Pugh Class B) hepatic impairment. Liver enzyme tests should be obtained prior to initiation of OPSUMIT.

Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin > 2 × ULN, or by clinical symptoms of liver injury (e.g., jaundice), OPSUMIT treatment should be discontinued.

Haemoglobin concentration

Decrease in haemoglobin concentrations and anaemia has been associated with endothelin receptor antagonists (ERAs) including macitentan (see section 4.8). In placebo-controlled studies, macitentan-related decreases in haemoglobin concentration, stabilised after the first 4–12 weeks of treatment and remained stable during chronic treatment. Cases of anaemia requiring blood cell transfusion have been reported with macitentan. Initiation of OPSUMIT is not recommended in patients with severe anaemia. It is recommended that haemoglobin concentrations be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated.

Pulmonary veno-occlusive disease

Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when macitentan is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered.

Concomitant use with strong CYP3A4 inducers

In the presence of strong CYP3A4 inducers reduced efficacy of macitentan may occur. The combination of macitentan with strong CYP3A4 inducers (e.g., rifampicin, St. John's wort, carbamazepine, and phenytoin) should be avoided (see section 4.5).

Concomitant use with strong CYP3A4 inhibitors

Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) (see section 4.5).

Renal impairment

Patients with renal impairment may run a higher risk of experiencing hypotension and anaemia during treatment with macitentan. Therefore, monitoring of blood pressure and haemoglobin should be considered. There is no clinical experience with the use of macitentan in PAH patients with severe renal impairment. Caution is recommended in this population. There is no experience with the use of macitentan in patients undergoing dialysis, therefore OPSUMIT is not recommended in this population (see sections 4.2 and 5.2).

Elderly

There is limited clinical experience with macitentan in patients over the age of 75 years, therefore OPSUMIT should be used with caution in this population (see section 4.2).

Excipients

OPSUMIT contains lactose. Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take OPSUMIT.

OPSUMIT contains soya bean lecithin. If a patient is hypersensitive to soya, OPSUMIT must not be used (see section 4.3).

OPSUMIT contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies

The cytochrome P450 enzymes CYP3A4, CYP2C8, CYP2C9, and CYP2C19 are involved in the metabolism of macitentan and formation of its metabolites (see section 5.2). Macitentan and its active metabolite do not have clinically relevant inhibitory or inducing effects on cytochrome P450 enzymes.

Macitentan and its active metabolite are not inhibitors of hepatic or renal uptake transporters at clinically relevant concentrations, including the organic anion transporting polypeptides (OATP1B1 and OATP1B3). Macitentan and its active metabolite are not relevant substrates of OATP1B1 and OATP1B3 but enter the liver by passive diffusion.

Macitentan and its active metabolite are not inhibitors of hepatic or renal efflux pumps at clinically relevant concentrations, including the multi-drug resistance protein (P-gp, MDR-1) and multidrug and toxin extrusion transporters (MATE1 and MATE2-K). Macitentan inhibits the breast cancer resistance protein (BCRP) at clinically relevant intestinal concentrations. Macitentan is not a substrate for P-gp/MDR-1.

At clinically relevant concentrations, macitentan and its active metabolite do not interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

In vivo studies

Strong CYP3A4 inducers: Concomitant treatment with rifampicin 600 mg daily, a potent inducer of CYP3A4, reduced the steady-state exposure to macitentan by 79 % but did not affect the exposure to the active metabolite. Reduced efficacy of macitentan in the

presence of a potent inducer of CYP3A4 such as rifampicin should be considered. The combination of macitentan with strong CYP3A4 inducers should be avoided (see section 4.4).

Ketoconazole: In the presence of ketoconazole 400 mg once daily, a strong CYP3A4 inhibitor, exposure to macitentan increased approximately 2-fold. The predicted increase was approximately 3-fold in the presence of ketoconazole
200 mg twice daily using physiologically based pharmacokinetic (PBPK) modelling. The uncertainties of such modelling should be considered. Exposure to the active metabolite of macitentan was reduced by 26 %. Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors (see section 4.4).

Fluconazole: In the presence of fluconazole 400 mg daily, a moderate dual inhibitor of CYP3A4 and CYP2C9, exposure to OPSUMIT may increase approximately 3.8-fold based on physiologically based pharmacokinetic (PBPK) modelling. However, there was no clinically relevant change in exposure to the active metabolite of OPSUMIT. Caution should be exercised when OPSUMIT is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone).

Caution should also be exercised when OPSUMIT is administered concomitantly with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine).

Warfarin: Macitentan given as multiple doses of 10 mg once daily had no effect on exposure to S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate) after a single dose of 25 mg warfarin. The pharmacodynamic effect of warfarin on International

Normalised Ratio (INR) was not affected by macitentan. The pharmacokinetics of macitentan and its active metabolite were not affected by warfarin.

Sildenafil: At steady-state, the exposure to sildenafil 20 mg three times a day was increased by 15 % during concomitant administration of macitentan 10 mg once daily. Sildenafil, a CYP3A4 substrate, did not affect the pharmacokinetics of macitentan, while there was a 15 % reduction in the exposure to the active metabolite of macitentan. These changes are not considered clinically relevant. In a placebo-controlled trial in

patients with PAH, the efficacy and safety of macitentan in combination with sildenafil were demonstrated.

Ciclosporin A: Concomitant treatment with ciclosporin A 100 mg twice daily, a combined CYP3A4 and OATP inhibitor, did not alter the steady-state exposure to macitentan and its active metabolite to a clinically relevant extent.

Hormonal contraceptives: Macitentan 10 mg once daily did not affect the pharmacokinetics of an oral contraceptive (norethisterone 1 mg and ethinyl estradiol 35 µg).

Breast cancer resistance protein (BCRP) substrate drugs: Macitentan 10 mg once daily did not affect the pharmacokinetics of oral riociguat or rosuvastatin.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

OPSUMIT is contraindicated in pregnancy and lactation.

Use in women of childbearing potential/Contraception in males and females

OPSUMIT treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised (see sections 4.3 and 4.4). Women should not become pregnant for 1 month after discontinuation of OPSUMIT. Monthly

pregnancy tests during treatment with OPSUMIT are recommended to allow the early detection of pregnancy.

Pregnancy

There are no data from the use of macitentan in pregnant women. Studies in animals have shown teratogenicity and reproductive toxicity (see section 5.3). The potential risk for humans is still unknown. OPSUMIT is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception (see section 4.3).

Breastfeeding

It is unknown whether macitentan is excreted in human milk. In rats, macitentan and its metabolites are excreted into milk during lactation (see section 5.3). A risk to the breastfeeding child cannot be excluded. OPSUMIT is contraindicated during breastfeeding (see section 4.3).

Male fertility

The development of testicular tubular atrophy in male animals was observed after treatment with macitentan (see section 5.3). Decreases in sperm count have been observed in patients taking endothelin receptor antagonists (ERAs). OPSUMIT, may have an adverse effect on spermatogenesis in men. Males intending procreation should be counselled by their healthcare professional on the potential effects on fertility with use of OPSUMIT.

4.7 Effects on ability to drive and use machines

OPSUMIT has influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed. However,

undesirable effects may occur (e.g., headache, hypotension) that may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are nasopharyngitis (14 %), headache (13,6 %) and anaemia (13,2 %, see section 4.4).

Tabulated list of adverse reactions in Clinical Studies

The safety of macitentan has been evaluated in a long-term placebo-controlled trial of 742 patients with symptomatic PAH. The mean treatment duration was 103.9 weeks in the macitentan 10 mg group, and 85.3 weeks in the placebo group. Adverse reactions associated with macitentan obtained from this clinical study are tabulated below.

The following terms and frequencies are applied: *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 the available data).

Summary of Adverse Reactions

System organ class	**Adverse reaction**	**Frequency**
Infections and infestations	Nasopharyngitis	Very common
	Bronchitis	Very common
	Pharyngitis	Common
	Influenza	Common
	Urinary tract infection	Common
Blood and lymphatic system disorders	Anaemia, haemoglobin decrease[5]	Very common
	Leukopenia[6]	Common

	Thrombocytopenia[7]	Common
Hepatobiliary disorders	Aminotransferase elevations[4]	Common
Immune system disorders	Hypersensitivity reactions (e.g., angioedema, pruritus, rash)[1]	Uncommon
Nervous system disorders	Headache	Very common
Vascular disorders	Hypotension[2]	Common
Respiratory, thoracic and mediastinal disorders	Nasal congestion[1]	Common
General disorders and administration site conditions	Oedema, fluid retention[3]	Very common

[1]Data derived from pooled placebo-controlled studies

Description of selected adverse reactions

[2] Hypotension has been associated with the use of ERAs including OPSUMIT. In a long-term double-blind study in patients with PAH, hypotension was reported for 7,0 % and 4,4 % of patients on macitentan 10 mg and placebo, respectively. This corresponded to 3.5 events / 100 patient-years on macitentan 10 mg compared to 2.7 events / 100 patient-years on placebo.

[3] Oedema/fluid retention has been associated with the use of ERAs including macitentan. In a long-term double-blind study in patients with PAH, the incidence of oedema AEs in the macitentan 10 mg and placebo treatment groups was 21, 9 % and 20,5 %, respectively. In a double-blind study in patients with idiopathic pulmonary fibrosis, the incidence of peripheral oedema AEs in the macitentan and placebo treatment groups was 11,8 % and 6,8 %, respectively. In two double-blind

clinical studies in patients with digital ulcers associated with systemic sclerosis, the incidences of peripheral oedema AEs ranged from 13,4 % to 16,1 % in the macitentan 10 mg groups and from 6,2 % to 4,5 % in the placebo groups.

Laboratory abnormalities

[4] Liver aminotransferases

The incidence of aminotransferase elevations (ALT/AST) > 3 × ULN was 3,4 % on macitentan 10 mg and 4,5 % on placebo in a double-blind study in patients with PAH. Elevations > 5× ULN occurred in 2,5 % of patients on macitentan 1 mg versus 2 % of patients on placebo. The incidence of elevated aminotransferases of >8 x ULN was 2,1 % on OPSUMIT 10 mg versus 0,4 % in the placebo group.

[5] Haemoglobin

In a double-blind study in patients with PAH, macitentan 10 mg was associated with a mean decrease in haemoglobin versus placebo of 1 g/dL. A decrease from baseline in haemoglobin concentration to below 10 g/dL was reported in 8,7 % of patients treated with macitentan 10 mg and 3,4 % of placebo-treated patients.

[6] White blood cells

In a double-blind study in patients with PAH, macitentan 10 mg was associated with a decrease in mean leucocyte count from baseline of 0, 7 × 10^9 /L versus no change in placebo-treated patients.

[7] Platelets

In a double-blind study in patients with PAH, macitentan 10 mg was associated with a decrease in mean platelet count of 17 × 10^9 /L, versus a mean decrease of 11 × 10^9 /L in placebo-treated patients.

Paediatric population

The safety of macitentan in children and adolescents below 18 years has not been established.

Reporting of suspected adverse reactions

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

4.9 Overdose

Macitentan has been administered as a single dose of up to 600 mg to healthy subjects.

Symptoms

Adverse reactions of headache, nausea, and vomiting were observed.

Management

In the event of an overdose, standard supportive measures must be taken, as required. Due to the high degree of protein binding of macitentan, dialysis is unlikely to be effective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.7.13 Other hypotensives

Pharmacotherapeutic group: anti-hypertensives, anti-hypertensives for pulmonary arterial hypertension. ATC code: C02KX04.

Macitentan is an orally active endothelin receptor antagonist, active on both ET_A and ET_B receptors and approximately 100-fold more selective for ET_A as compared to ET_B *in*

vitro. Endothelin (ET)-1 and its receptors (ETA) and (ETs) mediate a variety of effects such as vasoconstriction. fibrosis, proliferation, hypertrophy. and inflammation. In disease conditions such as pulmonary arterial hypertension (PAH). the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage.

Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. This inhibits endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.

5.2 Pharmacokinetic properties

The pharmacokinetics of macitentan and its active metabolite have mainly been documented in healthy subjects. Exposure to macitentan in patients with PAH was approximately 1, 2-fold greater than in healthy subjects. The exposure to the active metabolite in patients, which is approximately 5-fold less potent than macitentan, was approximately 1, 3-fold higher than in healthy subjects. The pharmacokinetics of macitentan in PAH patients were not influenced by the severity of the disease.
After repeated administration, the pharmacokinetics of macitentan are dose-proportional up to and including 30 mg.

Absorption

Maximum plasma concentrations of macitentan are achieved about 8 hours after administration. Thereafter, plasma concentrations of macitentan and its active

metabolite decrease slowly, with an apparent elimination half-life of approximately 16 hours and 48 hours, respectively.

In healthy subjects, the exposure to macitentan and its active metabolite is unchanged in the presence of food and, therefore, macitentan may be taken with or without food.

Distribution

Macitentan and its active metabolite are highly bound to plasma proteins (> 99 %), primarily to albumin and to a lesser extent to alpha1-acid glycoprotein. Macitentan and its active metabolite ACT-132577 are well distributed into tissues as indicated by an apparent volume of distribution (Vss/F) of approximately 50 L and 40 L for macitentan and ACT-132577, respectively.

Biotransformation

Macitentan has four primary metabolic pathways. Oxidative depropylation of the sulfamide yields a pharmacologically active metabolite. This reaction is dependent on the cytochrome P450 system, mainly CYP3A4 (approximately 99 %) with minor contributions of CYP2C8, CYP2C9 and CYP2C19. The active metabolite circulates in human plasma and may contribute to the pharmacological effect. Other metabolic pathways yield products without pharmacological activity. Several members of the CYP2C family, namely CYP2C8, CYP2C9 and CYP2C19, as well as CYP3A4, are involved in the formation of these metabolites.

Elimination

Macitentan is only excreted after extensive metabolism. The major excretion route is via urine, accounting for about 50 % of the dose.

Special populations

There is no clinically relevant effect of age, sex or ethnic origin on the pharmacokinetics of macitentan and its active metabolite.

Renal impairment

Exposure to macitentan and its active metabolite was increased by 1, 3- and 1, 6-fold, respectively, in patients with severe renal impairment. This increase is not considered clinically relevant (see sections 4.2 and 4.4).

Hepatic impairment

Exposure to macitentan was decreased by 21 %, 34 %, and 6 % and, for the active metabolite by 20 %, 25 %, and 25 % in subjects with mild, moderate or severe hepatic impairment, respectively. This decrease is not considered clinically relevant (see sections 4.2 and 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Microcrystalline cellulose (E460i)

Sodium starch glycolate Type A

Povidone *K*-30

Magnesium stearate (E572)

Polysorbate 80 (E433)

Film coating

Poly(vinyl-alcohol) (E1203)

Titanium dioxide (E171)

Talc (E553b)

Soya bean lecithin (E322)

Xanthan gum (E415)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30 °C

6.5 Nature and contents of container

White, opaque PVC/PE/PVdC/Aluminium blisters in cartons containing 30 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (PTY) LTD

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8. REGISTRATION NUMBER(S)

49/7.1.3/0271

9. DATE OF FIRST AUTHORISATION

21 September 2021

10. DATE OF REVISION OF THE TEXT

21 September 2022