Opsumit®

Composition

Active substances

Macitentan

Excipients

Tablet core:
Lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone K-30, sodium starch glycolate Type A.
Film coat:
Polyvinyl alcohol, soya lecithin, talc, titanium dioxide (E171), xanthan gum.

A 10 mg film-coated tablet contains 38.86 mg lactose monohydrate and 0.21 mg sodium.

Pharmaceutical form and active substance quantity per unit

Film coated tablets: 10 mg (white, round, biconvex, debossed «10»)

Indications/Uses

Long-term treatment of pulmonary arterial hypertension (PAH) in patients of WHO Functional Class II to III to reduce morbidity and the risk of mortality.

Dosage/Administration

Treatment should only be initiated by a physician experienced in the treatment of pulmonary arterial hypertension.
Opsumit is effective when used as monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled/oral prostanoids.
The film-coated tablets are not breakable and are to be swallowed whole.

Usual dosage

Opsumit is to be taken orally at a dose of 10 mg once daily, with or without food. The film-coated tablets must be swallowed whole, with water, and must not be chewed, divided or crushed.

Special dosage instructions

Patients with impaired hepatic function

Based on pharmacokinetic data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment *(*see section “Pharmacokinetics”).

There is no clinical experience with the use of Opsumit in patients with moderate or severe hepatic impairment. The use of Opsumit in such patients is therefore not recommended (see section “Warnings and precautions”).

Patients with impaired renal function

Based on pharmacokinetic data, no dose adjustment is required in patients with renal impairment. There is no clinical experience with the use of Opsumit in PAH patients with severe renal impairment. The use of Opsumit is therefore not recommended in patients with severe renal impairment or those undergoing dialysis.

Elderly patients

No dose adjustment is required in patients over the age of 65 years (see section “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of Opsumit in children below the age of 12 years have not yet been established. There is limited clinical experience in pediatric patients above 12 years of age. The recommended dose is 10 mg once daily.

Contraindications

- Hypersensitivity to macitentan or to any of the excipients
- Pregnancy
- Women of child bearing potential who are not using a reliable method of contraception
- Before the start of treatment, elevation of liver aminotransferases, i.e. aspartate amino-transferase (AST) and/or alanine aminotransferase (ALT) to more than three times the upper normal level (see section “Warnings and precautions”).

Warnings and precautions

Liver function

Elevations of liver aminotransferases (AST, ALT) have been associated with PAH and with endothelin receptor antagonists (ERAs).
Opsumit is not to be initiated in patients with elevated aminotransferases (> 3 × ULN) at baseline. Because of the lack of data, treatment with Opsumit cannot be recommended in patients with moderate and severe hepatic impairment.
Liver enzyme values should be determined prior to initiation of treatment and the test should be repeated as clinically indicated.
If persistent, 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, Opsumit should be discontinued. Reinitiation of treatment may be considered following the return of hepatic

enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury. The advice of a hepatologist is recommended.

Hemoglobin concentration

As with other ERAs, treatment with Opsumit may be associated with a decrease in hemoglobin concentration. In placebo-controlled studies, macitentan-related decreases in hemoglobin concentration occurred early and levels remained stable during chronic treatment.
Cases of anemia requiring blood cell transfusion have been reported with Opsumit and other ERAs. Initiation of Opsumit is not recommended in patients with severe anemia prior to treatment.
It is recommended that hemoglobin concentrations be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated.

Pulmonary veno-occlusivedisease (PVOD)

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

Renal function

Patients with moderate or severe renal impairment may run a higher risk of experiencing a drop in blood pressure and anemia during treatment with Opsumit. Therefore, monitoring of blood pressure and hemoglobin should be considered. There is no experience with the use of Opsumit in patients with severe renal impairment or those undergoing dialysis, therefore use of Opsumit is not recommended in these patients.

Pulmonary arterial hypertension in patients with HIV infection, drugs and toxins

There is limited experience of the use of OPSUMIT in patients with PAH associated with HIV infection, drugs and toxins.

Use in women of child-bearing potential

See section "Pregnancy, lactation".

Male fertility

The development of testicular tubular atrophy in male animals was observed after life long treatment with macitentan in rats. Decreases in sperm count have been observed in patients taking ERAs. Opsumit, like other ERAs, may have an adverse effect on spermatogenesis in men.

Concomitant use with other medicinal products

See section "Interactions".

Excipients

Opsumit contains

- lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose-malabsorption should not take Opsumit.
- less than 1 mmol sodium (23 mg) per film-coated tablet, i.e. it is almost "sodium-free".

Interactions

The metabolism of macitentan to its active metabolite is catalyzed mainly by CYP3A4, with minor contributions from CYP2C8, CYP2C9 and CYP2C19.
At clinically relevant concentrations, macitentan and its active metabolite are not substrates for OATP1B1 and OATP1B3 and macitentan is not a substrate for P-gp and MDR-1.
At clinically relevant concentrations, macitentan and its active metabolite do not inhibit or induce cytochrome P450 (CYP) enzymes, nor are they inhibitors of most hepatic or renal transporters of active substances, including P-gp, MDR-1, Mate1, Mate2-K, BSEP, NTCP, OATP1B3, OCT1, OCT2, OAT1 and OAT3.
At clinically relevant intestinal concentrations, macitentan inhibits BRCP *in vitro*.
Specific investigations of interactions with other medicinal products revealed the following:
Warfarin: Macitentan given as multiple doses of 10 mg once daily had no effect on exposure to S-warfarin (CYP2C9 substrate) or R-warfarin after a single dose of 25 mg warfarin. The pharmacodynamic effect of warfarin on the International Normalized Ratio (INR) was not affected by macitentan.
Corresponding data are not available for acenocoumarol and phenprocoumon.
Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. (three times daily) during concomitant administration of macitentan 10 mg once daily was increased by 15% for AUC and 26% for Cmax. The exposure to the active metabolite of sildenafil was increased by 8% for AUC and 10% for Cmax during concomitant administration of macitentan. Sildenafil, a CYP3A4 substrate, did not affect the pharmacokinetics of macitentan (increase in AUC by 6% and decrease of Cmax by 1%), while there was a 15% reduction of AUC and 18% reduction of Cmax 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.
Ketokonazole: In the presence of ketoconazole 400 mg daily, a strong CYP3A4 inhibitor, the exposure expressed as AUC of a single oral dose of 10 mg macitentan increased approximately 2-fold. Cmax increased by 28% in the presence of ketoconazole. AUC and Cmax of the active metabolite of macitentan was reduced by 26% and 51%, respectively.
Caution is required if macitentan is used simultaneously with potent inhibitors of CYP3A4 (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir).

Fluconazole: In the presence of fluconazole 400 mg daily, a moderate dual inhibitor of CYP3A4 and CYP2C9, exposure to Macitentan may increase approximately 3.8-fold based on physiologically based pharmacokinetic (PBPK) modelling.It is recommended to avoid concomitant use with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone).
It is also recommended to avoid concomitant use with both a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine).
Cyclosporin A: Concomitant treatment with cyclosporine A 100 mg b.i.d., a combined CYP3A4 and OATP inhibitor, did not alter the steady-state exposure to macitentan (increase in AUC by 10% and decrease of Cmax by 3%) or its active metabolite (decrease in AUC and Cmax by 3% and 4%, respectively) to a clinically relevant extent.
Rifampicin: Concomitant treatment with rifampicin 600 mg daily, a potent inducer of CYP3A4, reduced the steady-state exposure to macitentan expressed as AUC and Cmax by 79% and 60% but did not affect the exposure to the active metabolite (no change in AUC and increase of Cmax by 17%). Reduced efficacy of macitentan in the presence of a potent inducer of CYP3A4 such as rifampicin should be considered.

Hormonal contraceptives:

Administration of 10 mg macitentan once daily had no influence on the pharmacokinetics of an oral contraceptive (1 mg norethisterone and 35 µg ethinylestradiol).
Breast cancer resistance protein substrate drugs: Macitentan 10 mg once daily did not affect the pharmacokinetics of oral riociguat or rosuvastatin (riociguat 1 mg; rosuvastatin 10 mg).

Pregnancy, lactation

Pregnancy

PAH is, due to its high mortality risk for mother and child, a contraindication for pregnancy.
Very limited data (isolated cases) are available on the use of Opsumit during pregnancy. The potential risk for humans is still unknown. Experimental studies in animals have shown teratogenicity. Women who are treated with Opsumit should be made aware of the potential risk of damage of the child.
Opsumit is contraindicated in pregnancy (see section "Contraindications").
Opsumit treatment should only be initiated in women of child-bearing potential when the absence of pregnancy has been verified, appropriate advice on reliable methods of contraception has been provided, and reliable contraception is practiced.
Women should not become pregnant for 1 month after discontinuation of Opsumit.
Because of the possible failure of hormonal contraception during treatment with Opsumit and in view of the risk of pulmonary hypertension being severely aggravated by pregnancy, monthly pregnancy tests during treatment with Opsumit are recommended to allow the early detection of pregnancy.

Lactation

It is not known whether macitentan is excreted into human breast milk. In rats, macitentan and its metabolites were excreted into milk during lactation. Breast-feeding is not recommended during treatment with Opsumit.

Effects on ability to drive and use machines

No corresponding studies have been performed.

Undesirable effects

Experience from clinical studies

The safety of macitentan has been evaluated in a long-term placebo-controlled trial of 742 patients with symptomatic PAH, in a placebo-controlled trial with 379 essential hypertension patients, and in a placebo-controlled trial with 178 idiopathic pulmonary fibrosis patients.
Frequency determination does not account for other factors including varying study duration, pre-existing conditions, and baseline patient characteristics.
Frequency is reported according to organ class with the following definition:
Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1 000), very rare (<1/10,000)

Table 1: Undesirable effects

	Double-blind PAH (SERAPHIN)		Pooled, double-blind**		Frequency
System organ class	Macitentan 10 mg (N=242)	Placebo (N=249)	Macitentan 10 mg (N=423)	Placebo (N=370)	
Infections and Infestations					
Nasopharyngitis	14%	10%	9%	7%	Very common
Bronchitis	12%	6%	10%	6%	Very common
Pharyngitis	6%	3%	4%	2%	Common
Influenza	6%	2%	5%	2%	Common
Urinary Tract Infection	9%	6%	6%	5%	Common
Gastroenteritis	3%	1%	2%	1%	Common
Blood and Lymphatic System Disorders					
Anemia	13%	3%	11%	2%	Very common
Leukopenia	2.5%	1.6%	1.7%	1.1%	Common
Thrombocytopenia	5.0%	2.8%	3.3%	2.2%	Common
Aminotransferase elevations (ALT/AST >3xULN))	3.4%	4.5%	3.1%	3.9%	Common
Nervous System Disorders					
Headache	14%	9%	11%	10%	Very common
Vascular disorders					
Hypotension#	7.0%	4.4%	5.7%	3.8%	Common

Reproductive System and Breast Disorders*	**N=194 Female**	**N=184 Female**	**N=249 Female**	**N=230 Female**	
Menstrual disorders (primarily bleeding)	5%	1%	4%	1%	Common
Ovarian cyst	1.5%	0%	1%	0%	Common

* Incidences in female treated patients.

** Pooled double-blind studies include: AC-055-302 (SERAPHIN) in PAH, AC-055-201 in essential hypertension, and AC-055B201 in idiopathic pulmonary fibrosis.

Due to the vasodilatory effects of macitentan, effects on blood pressure may be expected. As the patients in the double-blind essential hypertension study (AC-055-201) were hypertensive at baseline (as this was the indication under study), the Pooled data did not include this study.

Undesirable effects after market launch

Immune system disorders: hypersensitivity reactions (angioedema, pruritus and rash)
Vascular disorders: flushing
Respiratory, thoracic and mediastinal disorders: nasal congestion.
Reproductive system and breast disorders: increased uterine bleeding
General disorders and administration site conditions: edema, fluid retention

Description of selected undesirable effects

Edema/fluid retention has been associated with the use of ERAs and is also a clinical manifestation of right heart failure and underlying PAH disease. In a long-term double-blind study in patients with PAH, the incidence of edema AEs in the macitentan 10 mg and placebo treatment groups was 11.0 events / 100 patient-years on macitentan 10 mg compared to 12.5 events / 100 patient-years on placebo. The incidence of edema/fluid retention in the elderly was 15.3 events / 100 patient-years on macitentan 10 mg compared to 17.7 events / 100 patient-years on placebo.

Hypotension has been associated with the use of endothelin receptor antagonists. In a long-term double-blind study in patients with PAH, hypotension as an AE was reported for 7.0% and 4.4% of patients on macitentan 10 mg and placebo, respectively. This corresponds to 3.5 events/ 100 patient-years on macitentan 10 mg compared with 2.7 events/ 100 patient-years on placebo.

Laboratory abnormalities

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 10 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.
Hemoglobin: In a double-blind study in patients with PAH, macitentan 10mg was associated with a mean decrease in hemoglobin versus placebo of 1 g/dL. A decrease from baseline in hemoglobin

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.
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 × 109/L versus no change in placebo-treated patients.
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.

Long-term safety

Of the 742 patients who participated in the pivotal SERAPHIN double-blind study, 550 patients entered a long-term open-label extension study (182 patients who continued on Opsumit 10 mg and 368 patients who received placebo or macitentan 3 mg and crossed over to Opsumit 10 mg).
Long-term follow up of patients treated with Opsumit 10 mg in the double-blind / open-label extension studies (N=242) for a median exposure of 4.6 years and a maximum exposure of 11.8 years showed a safety profile that was consistent as described above.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Signs and symptoms

Adverse events of headache, nausea, and vomiting were observed. In view of the mechanism of action, overdose could possibly also lead to hypotension.

Treatment

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.

Properties/Effects

ATC code

C02KX04

Mechanism of action

Endothelin (ET)-1 and its receptors (ETA and ETB) mediate a variety of deleterious effects such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage.
Macitentan is an orally active, dual ETA and ETB receptor antagonist that prevents the binding of ET-1 to its receptors. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells and has physicochemical properties favoring penetration into lung tissue, particularly into diseased lung tissue conditions. One of the metabolites of macitentan (ACT-132577) is also pharmacologically active at the ET receptors and is estimated to be about 20% as potent as the parent drug in vitro.
In models of pulmonary hypertension, macitentan selectively decreased mean pulmonary arterial pressure without affecting systemic blood pressure, prevented pulmonary arterial hypertrophy and right ventricular remodeling, and significantly increased survival.

Pharmacodynamics

In healthy subjects, macitentan dose-dependently increased plasma ET-1 concentrations at single and multiple doses.
In a randomized, placebo-controlled, four-way crossover study with a positive control in healthy subjects, repeated doses of 10 mg and 30 mg macitentan had no significant effect on the QTc interval.

Clinical efficacy

A multicenter, double-blind, placebo-controlled, parallel-group, event-driven, Phase 3 outcome study (SERAPHIN) was conducted in 742 patients with symptomatic PAH, who were randomized to three treatment groups (placebo [N = 250], 3 mg [N = 250] or 10 mg [N = 242] of macitentan once daily), to assess the long-term effect on morbidity and mortality. At baseline, the majority of enrolled patients (64%) were treated with a stable dose of specific therapy for PAH, either oral phosphodiesterase inhibitors (61%) and/or inhaled/oral prostanoids (6%). The primary study endpoint was the time to first occurrence of a morbidity or mortality event, up to end of treatment (EOT), defined as death, or atrial septostomy, or lung transplantation, or initiation of intravenous (i.v.) or subcutaneous (s.c.) prostanoids, or other worsening of PAH.
Other worsening of PAH was defined as the presence of all of the three following components: a sustained decrease in 6-minute walk distance of at least 15% from baseline; worsening of PAH symptoms (worsening of WHO Functional Class [FC] or right heart failure); and need for new treatment for PAH. All events were confirmed by an independent adjudication committee, blinded to treatment allocation.

The median treatment duration was 101, 116, and 118 weeks in the placebo, macitentan 3 mg, and 10 mg groups, respectively, up to a maximum of 188 weeks on macitentan. Patients who stopped treatment prior to EOS were followed up to EOS for vital status. The ascertainment rate for those patients was greater than 95%.

The mean age of all patients was 46 years (range 12–85 years of age) with the majority of subjects being Caucasian (55%) and female (77%). Approximately 52%, 46%, and 2% of patients were in WHO FC II, III, and IV, respectively.

Idiopathic or heritable PAH was the most common etiology in the study population (57%), followed by PAH due to connective tissue disorders (31%), PAH associated with congenital heart disease with shunts (8%), and PAH associated with other etiologies (drugs and toxins [3%] and HIV [1%]).

Treatment with macitentan 10 mg compared with placebo resulted in a 45% reduction in the risk of morbidity or mortality events(HR0.55; 97.5% CI 0.39–0.76; logrank $p < 0.0001$). The treatment effect was established early and sustained during the study treatment.

Consistent efficacy of macitentan 10 mg on the primary endpoint was seen across subgroups of age, sex, ethnic origin, geographical region, etiology, by monotherapy or in combination with another PAH therapy and WHO FC.

Compared with placebo, the risk of PAH related death (14/250 placebo; 7/242 macitentan) or hospitalization for PAH (82/250 placebo; 49/242 macitentan) was reduced by 50% ($p < 0.001$).

Other protocol-defined secondary endpoints were changes in 6-minute walk distance and WHO functional class, and time to death of all causes. Compared with placebo, macitentan showed positive and statistically significant effects. There were no significant differences between macitentan and placebo with respect to all-cause mortality. Hemodynamic parameters were assessed in a subset of patients (placebo [N = 67], macitentan 10 mg [N = 57]) after 6 months of treatment. Patients treated with macitentan 10 mg achieved a median reduction of 36.5% (97.5% CI: 21.7 to 49.2%) in pulmonary vascular resistance and an increase of 0.58 L/min/m^2 (97.5% CI: 0.28 to 0.93 L/min/m^2) in cardiac index compared to placebo.

Pharmacokinetics

The pharmacokinetics of macitentan and its active metabolite have mainly been documented in healthy subjects.

Exposure to macitentan in patients with PAH was for both AUC and Cmax approximately 1.3-fold higher than in healthy subjects. For the active metabolite, which is approximately 5-fold less potent than macitentan, the exposure expressed as AUC and Cmax was approximately 1.3-fold higher in patients 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 10 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 ACT-132577 show good tissue distribution, which is seen in apparent volumes of distribution (Vss/F) of approximately 50 l and 40 l, respectively.
Macitentan and its active metabolite are highly bound to plasma proteins (>99%), primarily to albumin and to a lesser extent to alpha1-acid glycoprotein.

Metabolism

Macitentan is metabolized via four primary metabolic pathways. The oxidative depropylation of the sulfamide results in a pharmacologically active metabolite. This reaction is dependent on the cytochrome P450 system, primarily on CYP3A4 with minor contributions from CYP2C8, CYP2C9 and CYP2C19. The active metabolite circulates in human plasma and may contribute to pharmacological activity.
Other metabolic pathways result in pharmacologically inactive products. For these pathways, CYP2C9 plays a predominant role with minor contributions from CYP2C8, CYP2C19 and CYP3A4.

Elimination

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

Kinetics in specific patient groups

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

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.

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.

Preclinical data

No adverse effects were observed in repeated dose toxicity studies in mice, rats, and dogs up to 39 weeks of treatment at exposures of 2- to 6-fold the human exposure at 10 mg/day.
In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

Long-term toxicity

There were no adverse liver findings in long-term studies conducted in mice, rats and dogs at exposures of 12- to 116-fold the human exposure.

Carcinogenicity

Carcinogenicity studies of 2 years' duration did not reveal a carcinogenic potential at exposures 18-fold and 116-fold the human exposure in rats and mice, respectively.
Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure.

Reproductive toxicity

Macitentan did not affect male or female fertility at exposures ranging from 18- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility and morphology in male rats. No testicular findings were noted in mice after treatment for up to 2 years.
Macitentan was shown to be teratogenic in rabbits and rats at exposures of 32-fold and 48-fold the human exposure, respectively. In both species there were cardiovascular and mandibular arch fusion abnormalities.
Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the reproductive capability of the offspring at maternal exposures 5-fold the human exposure.
Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.
Other data (local toxicity, phototoxicity, immunotoxicity)
Macitentan was not genotoxic in a standard battery of in vitro and in vivo assays.
Macitentan was not phototoxic in vivo.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.

Keep out of the reach of children.

Authorisation number

61863

Packs

Opsumit: 30 Film-Coated Tablets [B]

Marketing authorisation holder

Actelion Pharmaceuticals Ltd., 4123 Allschwil

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