Abbreviated Summary of Product Characteristics

Opsumit 10 mg film-coated tablets

Indications: Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension PAH in adult patients of WHO Functional Class FC II to III to reduce morbidity and the risk of mortality. **Posology and method of administration:** Posology: Opsumit is effective when used as monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled/oral prostanoids. Method of administration: Opsumit is to be taken orally at a dose of 10 mg once daily, with or without food. Special populations: *Hepatic impairment:* The use of Opsumit in patients with moderate or severe hepatic impairment is not recommended due to lack of clinical experience. *Renal impairment:* The use of Opsumit is not recommended in patients with severe renal impairment or those undergoing dialysis due to lack of experience. *Elderly patients:* No dose adjustment is required in patients over the age of 65 years. *Paediatric population:* The safety and efficacy of Opsumit in children below the age of 12 years have not yet been established due to limited clinical experience. **Contraindications**: Macitentan is contraindicated in cases of hypersensitivity to macitentan or its excipients, during pregnancy, in women of childbearing potential without reliable contraception, and in patients with severe hepatic impairment (with or without cirrhosis). It's contraindicated if liver aminotransferases (AST and/or ALT) are elevated to more than three times the upper normal level before treatment initiation. **Special warnings and precautions for use**: *Liver function:* Opsumit is not to be initiated in patients with severe hepatic impairment or elevated aminotransferases (> 3 × ULN) and is not recommended in patients with moderate hepatic impairment. *Hemoglobin concentration:* Initiation of Opsumit is not recommended in patients with severe anemia prior to treatment. *Pulmonary veno-occlusivedisease (PVOD)*: 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: In* patients with moderate or severe renal impairment, monitoring of blood pressure and hemoglobin should be considered with Opsumit treatment. The use of Opsumit is not recommended in patients with severe renal impairment or those undergoing dialysis. *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. *Excipients:* Opsumit contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose-malabsorption should not take Opsumit. **Interaction with other medicinal products and other forms of interaction:** 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 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. Moreover, they are not substrates for OATP1B1 and OATP1B3 and macitentan is not a substrate for P-gp and MDR-1. However, 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 or R-warfarin after a single dose of 25 mg warfarin. *Sildenafil*: Sildenafil did not affect the pharmacokinetics of macitentan These changes are not considered clinically relevant. *Ketokonazole*: 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*: 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: cyclosporine A 100 mg b.i.d., did not alter the steady-state exposure to macitentan or its active metabolite to a clinically relevant extent. *Rifampicin*: Concomitant treatment with rifampicin 600 mg daily reduced the steady-state exposure to macitentan 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. *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). **Fertility, pregnancy and lactation**: Pregnancy: The potential risk for humans is still unknown. Opsumit is contraindicated in pregnancy. Women should not become pregnant for 1 month after discontinuation of Opsumit. Breast-feeding: It is not known whether macitentan is excreted into human breast milk. Breast-feeding is not recommended during treatment with Opsumit. Male fertility:. Opsumit, like other ERAs, may have an adverse effect on spermatogenesis in men. **Effects on ability to drive and use machines**: No corresponding studies have been performed. **Undesirable effects:** The safety of macitentan has been assessed in a long-term placebo-controlled trial, with adverse events categorized by frequency as follows: Very common (≥1/10) adverse events include nasopharyngitis, bronchitis, anemia, and headache. Common (≥1/100, <1/10) adverse events include pharyngitis, influenza, urinary tract infection, gastroenteritis, leukopenia, thrombocytopenia, aminotransferase elevations (ALT/AST >3xULN), hypotension, menstrual disorders (primarily bleeding), and ovarian cysts. **Overdose:** Macitentan has been administered as a single dose of up to and including 600 mg to healthy subjects. **Storage:** Store below 30°C**.** Keep out of the reach of children.

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Date of Version: February 2023.

To report Adverse Events/Product Complaints, please contact us at
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For further information please refer to the locally approved summary of product characteristics.