# European Union Risk Management Plan

# OPSUMIT® (macitentan)

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| Data lock point for current RMP | 22 Nov 2021 | Version number | 13.1 |

**QPPV Sign-off Date:** 15 June 2022
**RMP Version Number:** 13.1
**Supersedes Version:** 12.2
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**Final for Procedure** EMEA/H/C/002697/II/0046
**Health Authority approval date (positive CHMP opinion)** 10/06/2022

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|---|---|
| QPPV Name(s): | Dr. Laurence Oster-Gozet, PharmD, PhD |
| QPPV Signature: | The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable. |

| **Details of this RMP Submission** | |
|---|---|
| Version Number | 13.1 |
| Rationale for submitting an updated RMP | Updates made to the important potential risk of testicular disorders and male infertility to align with the current Company Core Data Sheet (CCDS; Version 13, 22 November 2021). |
| Summary of significant changes in this RMP: | <u>Safety concerns</u><br>Updates made to the important potential risk of testicular disorders and male infertility to align with the current CCDS.<br><u>Annexes</u><br>Annex 7.3 has been updated to provide the Medical Dictionary for Regulatory Activities (MedDRA; Version 24.0) search terms used for the updated data in Module SVII.<br><u>Other</u><br>Update of clinical trial and postmarketing data using a data lock point of 17 October 2021 and, where needed, to align with internal company standards (data limited to approved indications only).<br>Exposure from postmarketing use has been updated using a data lock point of 30 September 2021.<br>Update of epidemiology text, where needed, to reflect recent data from published literature and the approved population for macitentan treatment. |

**Other RMP Versions Under Evaluation:**

| RMP Version Number | Submitted on | Procedure Number |
|---|---|---|
| Not applicable | Not applicable | Not applicable |

**Details of the Currently Approved RMP:**

| | |
|---|---|
| Version number of last agreed RMP: | 13.1 |
| Approved within procedure | EMEA/H/C/002697/II/0046 |
| Date of approval (Competent authority opinion date) | 10 June 2022 |

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# PART I: PRODUCT(S) OVERVIEW

| | |
|---|---|
| **Active substance(s)**<br>**(INN or common name)** | Macitentan |
| **Pharmacotherapeutic group(s) (ATC Code)** | C02KX04 |
| **Marketing Authorization Holder** | Janssen-Cilag International NV |
| **Medicinal products to which the RMP refers** | 1 (macitentan [OPSUMIT®]) |
| **Invented name(s) in the European Economic Area (EEA)** | OPSUMIT® |
| **Marketing authorization procedure** | Centralized |
| **Brief description of the product**<br>*Chemical class*<br>*Summary of mode of action*<br>*Important information about its composition* | Macitentan is an orally active potent endothelin (ET) receptor antagonist, active on both ETA and ETB receptors and approximately 100-fold more selective for ETA as compared to ETB in vitro. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. This prevents ET-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.<br>The macitentan active substance is a sulfamide substituted pyrimidine of chemical origin. |
| **Reference to the Product Information** | Mod1.3.1/SPC, Labelling and Package Leaflet |
| **Indication(s) in the EEA** | Current:<br>Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of World Health Organization (WHO) Functional Class (FC) II to III.<br>Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. |
| | Proposed:<br>Not applicable. |
| **Dosage in the EEA** | Current:<br>The recommended dose is 10 mg once daily. |
| | Proposed:<br>Not applicable. |

| | | |
|---|---|---|
| **Pharmaceutical form(s) and strengths** | Current:<br>5.5 mm, round, biconvex, white film-coated tablets, debossed with "10" on both sides. | |
| | Proposed:<br>Not applicable. | |
| **Is/will the product be subject to additional monitoring in the EU?** | ☐ **Yes** | ☑ **No** |

# PART II: SAFETY SPECIFICATION

## Module SI: Epidemiology of the Indication(s) and Target Population(s)

### Indication: Pulmonary arterial hypertension

**Incidence and Prevalence:**

Population-based estimates of PAH incidence and prevalence are not available.

*Adults*

The Orphanet 2021 report estimates the overall prevalence of PAH in Europe to be about 20 cases per million (Orphanet 2021).

A recent critical appraisal of the literature reported epidemiology estimates of approximately 5.8 adult patients per million for PAH incidence and 47.6 to 54.7 per million for PAH prevalence (Leber 2021) using recent (<5 years) national systematic registry data from centralized healthcare systems (NHS Digital 2020, Kjellström 2020).

Pulmonary arterial hypertension can be further classified into subtypes according to etiology. These are idiopathic PAH (IPAH), heritable PAH (HPAH), PAH induced by exposure to drugs and toxins, or PAH associated with other conditions (APAH), such as connective tissue disease (CTD-PAH) and congenital heart disease (CHD-PAH). For the most common PAH subtypes, incidences and prevalences per million population are reported in systematic national registries: for IPAH 2.6 to 7.6 and 9.0 to 18.3; CTD-PAH 2.8 and 10.0 to 13.0; and CHD-PAH 2.2 and 7.0 to 19.0, respectively (Peacock 2007, Skride 2018, NHS Digital 2020; Table SI.1).

The Orphanet 2021 report describes prevalences for IPAH of 11 cases per million and HPAH of 0.8 cases per million (Orphanet 2021). The prevalences of CTD-PAH and CHD-PAH were reported as 2.5 and 5.7 cases per million, respectively.

The United States (US) IPAH incidence estimate from the US multicenter Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) is 0.9 patients per million, which is lower compared with European data (McGoon 2013) (Table SI.1).

**Table SI.1: Annual Incidence and Prevalence of Pulmonary Arterial Hypertension Identified from National Systematic and Multicenter Registries in Adults**

| Publication | Country | Time period | Annual incidence (patients per million) | Prevalence (patients per million) |
|---|---|---|---|---|
| Peacock et al., 2007 (SPVU) | United Kingdom (Scotland) | 2005 | IPAH: 2.6<br>CTD-PAH: 2.8<br>CHD-PAH: 2.2 | IPAH: 9.0<br>CTD-PAH: 10.0<br>CHD-PAH: 7.0 |
| Skride et al., 2018 | Latvia | 2007-2016 | IPAH: 7.6 | IPAH: 18.3 |
| NHS Digital, 2020 | United Kingdom | 2019-2020 | - | IPAH: 16.8*<br>CTD-PAH: 13.0*<br>CHD-PAH: 19.0* |
| McGoon, 2013 (REVEAL) | United States of America | 2006-2009 | IPAH: 0.9 | - |

Note: *Numerator: number of active PAH patients on March 2020 (IPAH n = 1128; CTD-PAH n = 873; CHD-PAH n = 1273); denominator: Great Britain population 2020 mid-year (N = 87,081,000).
CHD-PAH = congenital heart disease PAH; CTD-PAH = connective tissue disease PAH; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; REVEAL = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SPVU = Scottish Pulmonary Vascular Unit.

### *Demographics of the Population in the Authorized Indication and Risk Factors for the Disease*

Demographics of Patients with PAH

*Adults*

A median or mean age of 50 to 64 years at diagnosis is commonly reported from PAH registries across European countries, with a higher proportion of females (66% to 80%) (Escribano-Subias 2012, Kopec 2020, Hoeper 2016a, Ling 2012, Hurdman 2012). In the US REVEAL registry, patients had a mean age of 50 years at diagnosis and were more likely to be females (80%) (Badesch 2010). The same observation was reported from a pulmonary hypertension (PH) expert center in Southeast Asia, where mean age was 51 years and 77% were females (Lim 2019).

Ethnicity distribution in patients with PAH is reported to be similar to the general population. REVEAL data reflect the contemporaneous US Census data with 73% of the included patients being White non-Hispanic, 12% Black, 9% Hispanic, 3% Asian, and 3% other categories (Medrek 2018, Frost 2011). Similarly, racial distribution in Southeast Asian patients with PAH was consistent with the Southeast Asia population census (Lim 2019).

Risk Factors for the Disease

Any factor or condition that is suspected to play a predisposing or facilitating role in the development of the disease is defined as a risk factor. A number of risk factors for the development

of PAH have been identified that include family history, drugs and chemicals, diseases, age, and sex (Simonneau 2019).

*Idiopathic PAH/Hereditary PAH*

Idiopathic PAH corresponds to sporadic disease in which there is neither a family history of PAH nor an identified risk factor, and represents the most frequent form of PAH. When PAH occurs in a familial context, germ-line mutations in the bone morphogenetic protein receptor type 2 gene, a member of the transforming growth factor beta signaling family, can be detected in approximately 70% to 80% of cases. Mutations of this gene can also be detected in 10% to 20% of apparently sporadic cases, thus representing the major genetic predisposing factor for PAH (Morrell 2019).

*Drug- and Toxin-induced PAH*

There are several well-known toxin and drug risk factors for PAH, including aminorex, fenfluramine derivatives, methamphetamines, dasatinib, and toxic rapeseed oil. Possible associations are suspected for cocaine, phenylpropanolamine, L tryptophan, St John's Wort, amphetamines, interferon α and β, alkylating agents, bosutinib, direct-acting antiviral agents against hepatitis C virus, leflunomide, and indirubin (Simonneau 2019).

*Pulmonary Arterial Hypertension Associated with Underlying Conditions/Diseases*

Pulmonary arterial hypertension may also occur associated with other diseases. Associated PAH includes connective tissue diseases (CTDs), CHD, portopulmonary hypertension (PoPH), human immunodeficiency virus (HIV) infection, and schistosomiasis (Galiè 2015a) Frequent causes of PAH in countries where these diseases are still endemic are schistosomiasis, HIV infection, post-streptococcal rheumatic heart disease, and sickle cell disease (Hoeper 2016b).

CTD-PAH represents about 15% to 25% of adult patients with PAH. Several CTDs are associated with PAH, such as mixed CTD and systemic lupus erythematosus (SLE) but is most commonly seen with systemic sclerosis (Mukerjee 2003, Hachulla 2005, Humbert 2006, Escribano-Subias 2012, Hoeper 2016b).

A significant proportion of patients with CHD, in particular those with relevant systemic-to-pulmonary shunts, will develop PAH if left untreated (Simonneau 2013). Eisenmenger syndrome (ES) represents the most advanced form of CHD-PAH (Simonneau 2013). CDH-PAH represents about 7% to15% of cases in the adult PAH population (Humbert 2006, Escribano-Subias 2012, Hoeper 2016b).

PoPH is a form of PAH associated with portal hypertension with or without underlying chronic liver disease. In the French PH Network registry, PoPH represented 18% of all PAH patients, the majority of whom had alcohol-related cirrhosis (58%) (Savale 2020).

Pulmonary arterial hypertension is a rare complication of HIV infection (Simonneau 2013). In France, the prevalence of this condition was estimated at 0.5% of the PAH population in 2005 (Sitbon 2008).

**Main Existing Treatment Options:**

*Supportive Therapy*

A range of conventional therapies have been shown to provide some degree of symptomatic benefit to PAH patients. However, they have a limited effect on the disease process or prognosis.

Among those conventional treatments are oxygen for patients with dyspnea associated with PAH, anticoagulants to decrease the risk for intrapulmonary thrombosis and thromboembolism, diuretics for patients with decompensated right heart failure associated with PAH, and calcium channel blockers, which may be of benefit in PAH patients with a positive vasoreactive response during right heart catherization (Simonneau 2019, Fuso 2011).

*Advanced Therapy (Also Termed PAH-specific Therapy)*

Pulmonary arterial hypertension-specific therapies target one of three major pathways known to be involved in the development of PAH: The prostacyclin and nitric oxide pathways, which are underexpressed in patients with PAH, and ET pathway, which is overexpressed. Route of administration varies between the drugs (intravenous, subcutaneous, oral, or inhaled). These PAH-specific therapies are either prescribed alone or in combination, which can be either provided as initial or subsequent therapies (Galiè 2019).

- Phosphodiesterase-5 (PDE-5) inhibitors: these oral agents act on the nitric oxide pathway to induce vasodilation. They also have antiproliferative effects on vascular smooth muscle cells. A systematic review and meta-analysis of clinical trials reported that treatment with PDE-5 inhibitors has a beneficial effect on exercise capacity, hemodynamic parameters, WHO FC, and survival in patients with PAH (Barnes 2019).
- Endothelin receptor antagonists (ERAs): ET is implicated in the pathogenesis of PAH through its actions on the pulmonary vasculature. Endothelin is elevated in patients with PAH and levels are directly related to disease severity and prognosis. Endothelin receptor antagonists are oral treatments that act by blocking the binding of ET to either one (single antagonist) or both (dual antagonist) of its receptors. Clinical trials have shown that treatment with ERAs has a beneficial effect on exercise capacity, WHO FC, hemodynamics, and time to clinical worsening in patients with PAH (Mehta 2017, Pulido 2013). Currently marketed ERA therapies are bosentan (dual antagonist), macitentan (dual antagonist), and ambrisentan (single receptor antagonist).
- Drugs targeting the prostacyclin pathway: synthetic prostacyclins (eg, epoprostenol), prostacyclin analogs (eg, treprostinil, beraprost, iloprost), and prostacyclin receptor agonists (eg, selexipag) act by correcting the deficiency of endogenous prostacyclin seen in patients with PAH. The clinical use of intravenously administered prostacyclins in patients with PAH has been extended by the synthesis of more stable analogs that can be given by subcutaneous infusion, by inhalation, or by oral administration. Clinical trials

with prostacyclin and prostacyclin analogs have shown improvement in PAH symptoms (eg, epoprostenol, iloprost, treprostinil), exercise capacity (eg, beraprost, epoprostenol, iloprost, treprostinil), hemodynamics (eg, epoprostenol, iloprost, treprostinil, selexipag), and survival (eg, epoprostenol, selexipag) (Sitbon 2015, Galié 2015a).

- Soluble guanylate cyclase (sGC) stimulator (riociguat) acts in synergy with endogenous nitric oxide and directly stimulates sGC to produce intracellular cyclic guanosine monophosphate, which influences vascular tone, proliferation, fibrosis, and inflammation. Short-term clinical trials (12 weeks) have demonstrated a statistically significant improvement in exercise capacity, WHO FC, and delay in clinical worsening with riociguat (Galiè 2015b).

**Natural History of the Indicated Condition, Including Mortality and Morbidity:**

Pulmonary arterial hypertension is a disease of the small pulmonary arteries, characterized by vascular proliferation and remodeling. These vascular changes result in a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death. There is currently no cure for PAH. Common symptoms of PAH are shortness of breath, fatigue, nonproductive cough, angina pectoris, fainting or syncope, peripheral edema, rarely hemoptysis, and other signs and symptoms of cardiovascular decompensation. With disease progression, exercise tolerance is markedly decreased, and life expectancy is reduced (Galiè 2015a).

*Survival Estimates in Adult Patients with PAH*

Published survival rates at 1, 2, 3, and 5 years range from 85% to 99%, 76% to 81%, 67% to 94%, and 57% to 86%, respectively in the French, United Kingdom, Russian, and US registries (Humbert 2010, Hurdman 2012, Benza 2012, Chazova 2019; Table SI.2). Survival with PAH is worse in men (Thenappan 2018).

**Table SI.2 Survival Estimates in Adult Patients with Pulmonary Arterial Hypertension**

| Study Name, Region, Reference | Analysis period | Popultion characteristics | Survival (years), % | | | |
|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 |
| REVEAL, United States of America (Benza 2012) | 2006-2009 | n=2,635, ≥3 m | 85 | - | 68 | 57 |
| Russian National Registry (Chazova 2019) | 2012-2017 | n=470, >18 yrs | 99 | - | 94 | 86 |
| French Pulmonary Arterial Hypertension Registry, France (Humbert 2010) | 2002-2003 | n=674, ≥18 yrs | 87* | 76* | 67* | - |
| ASPIRE, United Kingdom (Hurdman 2012) | 2001-2010 | n=598, adults | 88[1] | 81*[1] | 68[1] | 57*[1] |

| Study Name, Region, Reference | Analysis period | Popultion characteristics | Survival (years), % | | | |
|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 |

Note: *Extracted from graph; [1]Transplant-free survival.
ASPIRE = Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre; REVEAL = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management.

**Important Co-morbidities:**

The co-occurrence of PAH and co-morbidities increases the complexity of disease management for patients who may require multiple pharmacological interventions to treat both PAH and the co-morbidity. In PAH, approximately three quarters of patients have at least one co-morbidity, with patients aged 65 years and over having a greater number of co-morbidities. Current research suggests that the presence of co-morbid conditions in patients with PAH negatively affects outcomes (Lang 2019).

A variety of co-morbid conditions, not representing the principal cause of the development of PAH, have been identified in patients with PAH. The US REVEAL Registry (2006 to 2007) reported the following co-morbidities in more than 10% of all IPAH patients: systemic hypertension, obesity, sleep apnea, clinical depression, obstructive airway disease, thyroid disease, diabetes mellitus, and ischemic cardiovascular events (Lang 2019). In the US Pulmonary Hypertension Scientific Registry conducted almost 10 years later (2015 to 2018), obesity, diabetes, hypertension, hypothyroidism, and clinical depression were found to be among the most common co-morbid conditions (Badlam 2021).

Additional co-morbidities associated with PAH include anemia, chronic kidney disease, chronic liver disease, chronic pain, chronic muscle disease, frailty, peripheral vascular disease, cancer, dementia, cirrhosis, renal insufficiency, and atrial fibrillation (Lang 2019). The main causes of death reported in PAH patients are cardiovascular events, including heart failure and sudden death, which account for 44% to 89% deaths in PAH patients (Tonelli 2013, Ruiz-Cano 2009).

Patients with PAH may develop various severe liver complications (due to severe congestive hepatopathy induced by right heart failure and/or due to autoimmune disease / CTD) (Wells 2018, Nickel 2021).

# PART II: SAFETY SPECIFICATION

## Module SII: Nonclinical Part of the Safety Specification

The results from the nonclinical toxicology, carcinogenicity, reproductive toxicity, and drug-drug interaction studies are adequately reflected in the Summary of Product Characteristics (SmPC) for OPSUMIT.

| Key Safety Findings | Relevance to Human Usage |
|---|---|
| **Toxicity** | |
| Macitentan has undergone a complete program of toxicity studies in rodents and dogs. | |
| **Repeat-dose toxicity** | |
| Intimal thickening of coronary arteries in dogs was observed at 17-fold the human exposure after 4-39 weeks of treatment. | Due to the species-specific sensitivity and safety margin, this finding is considered not relevant for humans under therapeutic conditions. |
| Increased heart weight without histological changes and without consistent correlation between dose/exposure and effect size was observed in some rat toxicity studies. A safety margin of 6-7 was established in the 26-week study. | The finding of increased heart weight in rats is considered of questionable toxicological relevance and not relevant for humans. |
| A dose-related, reversible decrease in hematocrit, red blood cell count, and hemoglobin concentration without reticulocytosis was observed in different rat and dog toxicity studies. The effects were more pronounced in dogs than in rats, where the changes were minimal and mostly within the range of historical control values. Other hematological cell lineages were not affected. Available data suggest an absence of drug induced hemolysis and bone marrow toxicity. The observed effect might be secondary to increased plasma volume, as described for other ERAs and vasodilating drugs. | Similar effects were observed in humans. |
| **Reproductive toxicity** | |
| Reproductive toxicity of macitentan was assessed in fertility, embryo-fetal development, and pre- and post-natal development studies. These studies were complemented by a rat juvenile toxicity study, including exposure assessment. | |
| Macitentan was teratogenic in rabbits and rats at all doses tested. The teratogenic effects in animals are considered to be related to ET-receptor antagonism. | Macitentan is considered to be a potentially teratogenic compound.<br>Macitentan is contraindicated in pregnant women based on non-clinical findings similar to those of other ERAs. |

| Key Safety Findings | Relevance to Human Usage |
|---|---|
| Administration of macitentan to female rats from late pregnancy through lactation at maternal exposures 5-fold the human exposure caused reduced pup survival and impairment of the reproductive capability of the offspring that were exposed to macitentan during late intrauterine life and via the milk during the suckling period. | The relevance to human usage is unknown.<br>Macitentan is contraindicated in lactation. |
| Treatment of juvenile rats from post-natal 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. | There was no indication of target organ toxicity that could be considered critical for specific post-natal development phases. |
| **Developmental toxicity** | |
| Testicular tubular dilatation was observed in chronic toxicity studies with male rats and dogs with safety margins of 11.6 and 5.8, respectively. Tubular dilatation was fully reversible. After 2 years of treatment, testicular tubular atrophy was seen in rats at 4-fold the human exposure. Hypospermatogenesis was observed in the life-long carcinogenicity study in rats and in the repeat dose toxicity studies in dogs, at exposures that provide safety margins of 9.7 in rats and 23 in dogs. The no-observed-effect level (NOEL) for rat male and female fertility was 250 mg/kg/day with a safety margin of 18 for male and 44 for female animals. No testicular findings were noted in mice after treatment up to 2 years. | Although it cannot be excluded that similar effects could occur in male patients, that is, a deterioration of spermatogenesis, the type of effect, the minimal degree of severity, the reversibility as shown in all general toxicity studies, and the absence of impaired fertility in a male fertility study at ≥19-fold human exposure do not indicate a relevant risk for impaired fertility in male patients.<br>As described in Section SVII.3.1, one suspected unexpected serious adverse reaction of decreased sperm concentration has been reported to date. |
| In the uterus, an increased weight associated with increased incidence of endometrial cysts was observed in the carcinogenicity studies, in rats at doses ≥10 mg/kg/day, and in mice at the high-dose level of 100 mg/kg/day. | In mice, the no-observed-adverse-effect level (NOAEL) of 30 mg/kg/day provides a safety margin of 46.<br>In rats, the finding is interpreted as secondary to reduced body-weight gain, which leads to a decreased incidence of (prolactin-secreting) pituitary tumors in macitentan-treated groups. This results in lower prolactin levels and lower progesterone levels. The resulting higher estrogen/progesterone ratio causes endometrial stimulation in the ageing rat. As prolactin does not play a role in human progesterone production, this rat-specific finding is not considered to be clinically relevant. |

| Key Safety Findings | Relevance to Human Usage |
|---|---|
| **Genotoxicity** | |
| Macitentan was not genotoxic in a standard battery of in vitro and in vivo assays. Macitentan was not phototoxic in vivo. | No genotoxic risk has been identified. |
| **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. | No carcinogenic risk has been identified. |
| Angiomatous change, characterized by the presence of prominent blood vessels, was noted in the ovaries of few female rats after 104 weeks of treatment at the high dose of 250/50 mg/kg/day in the carcinogenicity study, corresponding to 20-fold the human exposure. The NOAEL was 50/25 mg/kg/day.<br><br>Angiomatous change was noted in the ovaries of 7/51 female rats at the high dose of 250/50 mg/kg/day in the carcinogenicity study, compared to 2/51 control females. | The finding of angiomatous change is not linked to the rat uterus findings, or to the observation of ovarian cysts in humans after treatment with macitentan, for the following reasons: Angiomatous change in rat ovaries is a change originating from blood vessels, characterized by a prominent dilation. The changes in rat endometrium are considered to be due to an increased estrogen/progesterone ratio. Since the diameter of blood vessels is not regulated by sex steroid hormones, these two findings are not mechanistically linked. If there were a link between the dilation of blood vessels and the development of ovarian cysts, then ovarian cysts would be expected in these rats.<br><br>The finding occurred only after life-long treatment at 20-fold the human exposure. The NOEL for this finding provides a safety margin of 13 and therefore it is not considered relevant for the therapeutic use of macitentan in women. |
| **Safety pharmacology:** | |
| **Cardiovascular system** | |
| In cardiovascular safety pharmacology studies in telemetered dogs, macitentan induced a decrease in mean arterial blood pressure (BP) at doses ≥0.3 mg/kg. | The relevance to humans cannot be excluded, and symptomatic hypotension was initially included as an important potential risk in Module SVII.<br><br>Based on cumulative clinical trials and postmarketing data accumulated over the first 3 years after launch, and following Pharmacovigilance Risk Assessment Committee (PRAC) recommendation, symptomatic hypotension has been upgraded as an important identified risk in Module SVII. |

| Key Safety Findings | Relevance to Human Usage |
|---|---|
| **Other** | |
| Hepatotoxicity | |
| Increased liver weight and hepatocellular hypertrophy were observed in mice, rats, and dogs after treatment with macitentan. These changes were largely reversible and considered non-adverse adaptations of the liver to increased metabolic demand. | The non-clinical profile of macitentan does not indicate a relevant risk for liver toxicity in humans. |
| Macitentan did not induce liver toxicity at high multiples of human exposure (120- to 149-fold in dogs; 60- to 152-fold in Sprague Dawley rats; 12- to 44-fold in Wistar rats; and 90- to 116-fold in B6C3F1 mice) after sub-chronic to chronic treatment. | |
| **Other toxicity-related information or data** | |
| Macitentan and the active metabolite ACT-132577 do not inhibit the major human transport proteins responsible for hepatic bile salt trafficking (ie, bile salt export pump [BSEP] and sodium-dependent taurocholate co-transporting polypeptide [NTCP]) at clinically relevant concentrations. Macitentan did not have any effect on serum bile salt concentrations in humans or in animals at very high dose levels and during chronic dosing. | None |

## Summary of Nonclinical Safety Concerns

| | |
|---|---|
| Important identified risks | Anemia, decrease in hemoglobin concentration |
| | Teratogenicity |
| | Symptomatic hypotension |
| Important potential risks | Testicular disorders and male infertility |
| Missing information | None |

# PART II: SAFETY SPECIFICATION

## Module SIII: Clinical Trial Exposure

### SIII.1. Brief Overview of Development

The overall number of subjects exposed and the duration of exposure to macitentan in the Phase 2 and Phase 3 studies are presented in the tables in Section SIII.2. In line with internal company standards, data from subjects with conditions other than PAH (PH Group 1) are not included in the RMP.

**AC-055-302 / SERAPHIN (PAH):** Double-blind, randomized, parallel-group, placebo-controlled, Phase 3 study in subjects with symptomatic PAH. Overall, 742 subjects were randomized. The safety set included 741 subjects who were treated with once-daily macitentan 3 mg (250 subjects), 10 mg (242 subjects), or matching placebo (249 subjects); the macitentan treatment duration was up to 188 weeks.

**AC-055-303 / SERAPHIN Open-label (OL) extension (PAH):** Open-label, uncontrolled, Phase 3, single-arm extension study to protocol AC-055-302 in subjects with symptomatic PAH, who either completed the double-blind treatment period (ie, up to the sponsor-declared end of study) or experienced clinical worsening of PAH in the double-blind study (AC-055-302). Of the 742 subjects randomized in AC-055-302 SERAPHIN, 550 subjects were enrolled and treated in AC-055-303 / SERAPHIN OL with once-daily 10 mg macitentan. At study completion (07 December 2020), the person-years exposure to macitentan 10 mg in the OL cohort (n=550) was 2074.7 years, ranging from 668.3 to 737 person-years across the 3 double-blind randomized groups.

**AC-055-305 / MAESTRO (ES):** Multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study to evaluate the effects of macitentan on exercise capacity in subjects with ES. A total of 226 subjects were randomized and treated with once-daily 10 mg macitentan (114 subjects) or matching placebo (112 subjects). Subjects received study treatment (macitentan 10 mg) for a median duration of 16 weeks up to a maximum of 21.3 weeks.

**AC-055-308 / MAESTRO OL extension (ES):** Long-term, single-arm, open-label extension of MAESTRO to assess the safety, tolerability, and efficacy of macitentan in subjects with ES. A total of 217 subjects were enrolled and treated with once-daily 10 mg macitentan. Subjects received study treatment (macitentan 10 mg) for a median duration of 128.7 weeks up to a maximum of 213.3 weeks.

**AC-055-404 / PORTICO and PORTICO OL:** Randomized, double-blind, placebo-controlled, prospective, multicenter, parallel-group, Phase 4 study to assess the safety and efficacy of macitentan in subjects with PoPH and its open-label extension phase. A total of 85 subjects were randomized and treated with once-daily 10 mg macitentan (43 subjects) or matching placebo (42 subjects) in the double-blind period. Eighty subjects received macitentan in the OL treatment period, with 33 subjects receiving treatment in the OL extension period. Across the overall

macitentan treatment-emergent period of PORTICO, the median duration of macitentan treatment was 24.4 weeks up to a maximum of 156.6 weeks.

**AC-055-401 / SYMPHONY, AC-055-402 / SYMPHONY extension (PAH):** Multicenter, open-label, single-arm, Phase 3b study of macitentan in subjects with PAH to psychometrically validate the PAH-SYMPACT® instrument and its open-label, single-arm extension study. A total of 284 subjects were enrolled and treated in Study AC-055-401 with once-daily 10 mg macitentan for a median duration of 16.1 weeks up to a maximum of 21.4 weeks. A total of 4 subjects entered the extension study (AC-055-402) and were treated with once-daily 10 mg macitentan for a median duration of 10.5 weeks up to 17.6 weeks in the extension study.

**AC-055-310 / ORCHESTRA, AC-055-311 / ORCHESTRA extension (PAH):** Multicenter, open-label, single-arm, Phase 3b study with an extension arm of macitentan in subjects with PAH to psychometrically validate the French, Italian, and Spanish versions of the PAH-SYMPACT®. In the main study, a total of 88 subjects were enrolled and treated with once-daily 10 mg macitentan for a median duration of 16 weeks up to a maximum of 18.7 weeks. In the extension arm, 74 subjects received macitentan for a median duration of 103.9 weeks up to a maximum of 206.1 weeks.

**AC-055-403 / REPAIR (PAH):** Prospective, multicenter, single-arm, open-label, Phase 4 study to evaluate the effects of macitentan on right ventricular remodeling in PAH, assessed by cardiac magnetic resonance imaging. A total of 89 subjects were enrolled, 87 of whom received treatment with once-daily macitentan 10 mg. The median duration of study treatment was 52.0 weeks up to a maximum of 58.3 weeks.

**AC-055-405 / OPTIMA (PAH):** Prospective, multicenter, open-label study evaluating the effects of first-line oral combination therapy of macitentan (10 mg) and tadalafil (40 mg) in subjects with newly diagnosed PAH. For tadalafil, 20 mg could be used for tolerability reasons. A total of 46 subjects were enrolled and received study treatment. The median exposure to macitentan was 86.5 weeks up to a maximum of 139.6 weeks.

**AC-055-314 / UMBRELLA (PAH):** Ongoing multicenter, single-arm, open-label Phase 3 study in which subjects with PAH or chronic thromboembolic pulmonary hypertension previously enrolled in macitentan clinical studies continued to receive macitentan 10 mg, with the aim of assessing long-term safety. As of 17 October 2021, 131 subjects have been enrolled, all of whom have been treated with macitentan.

**AC-065A308 / TRITON (PAH):** Multicenter, double-blind, placebo-controlled, Phase 3b study evaluating the efficacy and safety of initial triple (macitentan, tadalafil, and selexipag) versus initial double (macitentan, tadalafil, and placebo) oral combination therapy in subjects with newly diagnosed PAH. A total of 119 subjects in the triple therapy group and 127 subjects in the double therapy group received at least 1 dose of macitentan. Up to the end of study, the median duration of exposure (irrespective of interruptions) to macitentan was 84.9 weeks up to a maximum of

188.0 weeks in the initial triple therapy and 82.9 weeks up to a maximum of 189.6 weeks in the initial double therapy groups, respectively.

In addition, the following ongoing studies form part of the macitentan clinical trial program; however, data arising from these studies are not included in this RMP:

**AC-055-312 / TOMORROW (PAH):** Multicenter, open-label, randomized Phase 3 study with single-arm extension period to assess the pharmacokinetics (PK), safety, and efficacy of macitentan versus standard of care in children with PAH. The dose of macitentan was 1.0 or 2.5 mg for subjects <2 years of age or 3.5 to 10 mg for subjects ≥2 years of age. As of 17 October 2021, 121 subjects have been enrolled, all of whom have been treated with macitentan or standard of care.

**AC-077A301 / A DUE (PAH):** Prospective, multicenter, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 study to compare the efficacy and safety of macitentan (10 mg) and tadalafil (40 mg) monotherapies with the corresponding fixed dose combination (10/40 mg) in subjects with PAH, followed by an open-label treatment period with macitentan and tadalafil fixed dose combination therapy. As of 17 October 2021, 112 subjects have been enrolled, all of whom have received blinded study medication. Eighty-four subjects have received open-label treatment with macitentan and tadalafil fixed dose combination.

**AC-055-315 / UNISUS (PAH):** Phase 3, prospective, multicenter, double-blind, double-dummy, randomized, active-controlled, parallel-group, group-sequential, adaptive, event-driven study to compare the efficacy, safety, and tolerability of macitentan 75 mg versus macitentan 10 mg in subjects with PAH, followed by an open-label treatment period with macitentan 75 mg. As of 17 October 2021, 135 subjects have been enrolled, 62 of whom have been treated with macitentan during the run-in period. All subjects received blinded medication during the double-blind period.

## SIII.2. Clinical Trial Exposure

**Exposure in Completed Randomized Clinical Trials**

The randomized clinical trials population includes 3 trials:

- AC-055-302 / SERAPHIN double-blind
- AC-055-305 / MAESTRO double-blind
- AC-055-404 / PORTICO double-blind

Exposure to macitentan in the randomized, double-blind, completed clinical trials population is summarized in Tables SIII.1 through SIII.3 for all subjects by duration, by age group and sex, and by race/ethnicity.

**Table SIII.1: Duration of Exposure: Randomized Clinical Trials Population**

| Cumulative (person time) | | |
|---|---|---|
| **Duration of exposure** | **Patients** | **Person time (years)** |
| < 1 m | 10 | 0.3 |
| 1 to <3 m | 51 | 10.9 |
| 3 to <6 m | 130 | 41.0 |
| 6 to <12 m | 20 | 14.3 |
| 12 to <24 m | 33 | 47.9 |
| 24 to <36 m | 120 | 299.2 |
| 36 to <48 m | 35 | 112.7 |
| Total | 399 | 526.2 |

Exposure summarized from the completed RDB studies: AC-055-302 (SERAPHIN DB), AC-055-305 (MAESTRO DB) and AC-055-404 (PORTICO DB).
Exposure includes treatment interruptions.

**Table SIII.2: Exposure by Age Group and Sex: Randomized Clinical Trials Population**

| Cumulative (person time) | | | | |
|---|---|---|---|---|
| **Age group** | **Patients** | | **Person time (years)** | |
| | **M** | **F** | **M** | **F** |
| < 18 years | 3 | 16 | 3.2 | 10.9 |
| 18 to 64 years | 90 | 251 | 94.6 | 362.4 |
| 65 to 74 years | 8 | 25 | 9.1 | 36.6 |
| 75 to 84 years | 1 | 5 | 1.6 | 7.8 |
| >= 85 years | 0 | 0 | 0 | 0 |
| Total | 102 | 297 | 108.5 | 417.7 |

Exposure summarized from the completed RDB studies: AC-055-302 (SERAPHIN DB), AC-055-305 (MAESTRO DB) and AC-055-404 (PORTICO DB).
Exposure includes treatment interruptions.

**Table SIII.3: Exposure by Ethnic Origin: Randomized Clinical Trials Population**

| Cumulative (person time) | | |
|---|---|---|
| **Race/ethnicity** | **Patients** | **Person time (years)** |
| Caucasian/Hispanic | 248 | 360.3 |
| Asian | 114 | 145.9 |
| Black | 6 | 12.1 |
| Other | 12 | 3.7 |
| Total | 380 | 522.1 |
| Missing | 19 | |

Exposure summarized from the completed RDB studies: AC-055-302 (SERAPHIN DB), AC-055-305 (MAESTRO DB) and AC-055-404 (PORTICO DB).
Exposure includes treatment interruptions.
Patients in the 'Missing' category are not considered in the person time (years) exposure.

## Exposure in All Clinical Trials

The all clinical trials population includes 13 trials:

- AC-055-302 / SERAPHIN double-blind
- AC-055-303 / SERAPHIN open-label
- AC-055-305 / MAESTRO double-blind

- AC-055-308 / MAESTRO open-label
- AC-055-404 / PORTICO double-blind and PORTICO open-label
- AC-055-401/402 / SYMPHONY open-label and extension
- AC-055-310/311 / ORCHESTRA open-label and extension
- AC-055-403 / REPAIR
- AC-065A308 / TRITON
- AC-055-405 / OPTIMA
- AC-055-314 / UMBRELLA

Exposure to macitentan in the all clinical trials (double-blind and open-label) population is summarized in Tables SIII.4 through SIII.6 for all subjects by duration, by age group and sex, and by race/ethnicity.

**Table SIII.4: Duration of Exposure: All Clinical Trials Population**

| **Cumulative (person time)** | | |
|---|---|---|
| **Duration of exposure** | **Patients** | **Person time (years)** |
| < 1 m | 47 | 1.9 |
| 1 to <3 m | 83 | 14.4 |
| 3 to <6 m | 326 | 107.0 |
| 6 to <12 m | 126 | 103.3 |
| 12 to <24 m | 288 | 423.3 |
| 24 to <36 m | 235 | 577.1 |
| 36 to <48 m | 166 | 563.8 |
| 48 to <60 m | 131 | 587.1 |
| 60 to <72 m | 74 | 400.9 |
| 72 to <84 m | 71 | 458.6 |
| 84 to <96 m | 47 | 348.0 |
| >= 96 m | 73 | 698.7 |
| Total | 1667 | 4284.2 |

Based on studies: AC-055-302 (SERAPHIN DB), AC-055-303 (SERAPHIN OL), AC-055-305 (MAESTRO DB), AC-055-308 (MAESTRO OL), AC-055-404 (PORTICO DB), AC-055-404 (PORTICO OL), AC-055-401/402 (SYMPHONY OL and Extension), AC-055-310/311 (ORCHESTRA OL and Extension), AC-055-403 (REPAIR), AC-055-405 (OPTIMA), AC-055-314 (UMBRELLA), AC-065A308 (TRITON).
For ongoing study AC-055-314 (UMBRELLA) cut-off date 17OCT2021.
Exposure includes treatment interruptions.

**Table SIII.5: Age Group and Sex: All Clinical Trials Population**

| **Cumulative (person time)** | | | | |
|---|---|---|---|---|
| **Age group** | **Patients** | | **Person time (years)** | |
| | **M** | **F** | **M** | **F** |
| < 18 years | 7 | 24 | 22.9 | 85.6 |
| 18 to 64 years | 336 | 971 | 795.3 | 2826.5 |
| 65 to 74 years | 65 | 195 | 109.8 | 361.6 |
| 75 to 84 years | 16 | 51 | 17.9 | 61.4 |
| >= 85 years | 2 | 0 | 3.2 | 0 |
| Total | 426 | 1241 | 949.1 | 3335.1 |

**Table SIII.5: Age Group and Sex: All Clinical Trials Population**

| Cumulative (person time) | | |
|---|---|---|
| **Age group** | **Patients** | **Person time (years)** |
| Exposure summarized from the studies: AC-055-302 (SERAPHIN DB), AC-055-303 (SERAPHIN OL), AC-055-305 (MAESTRO DB), AC-055-308 (MAESTRO OL), AC-055-404 (PORTICO DB), AC-055-404 (PORTICO OL), AC-055-401/402 (SYMPHONY OL and Extension), AC-055-310/311 (ORCHESTRA OL and Extension), AC-055-403 (REPAIR), AC-055-405 (OPTIMA), AC-055-314 (UMBRELLA), AC-065A308 (TRITON).<br>For ongoing study AC-055-314 (UMBRELLA) cut-off date 17OCT2021.<br>Exposure includes treatment interruptions. | | |

**Table SIII.6: Exposure by Ethnic Origin: All Clinical Trials Population**

| Cumulative (person time) | | |
|---|---|---|
| **Race/ethnicity** | **Patients** | **Person time (years)** |
| Caucasian/Hispanic | 1135 | 2611.4 |
| Asian | 317 | 1132.2 |
| Black | 60 | 75.5 |
| Other | 45 | 67.5 |
| Total | 1557 | 3886.5 |
| Missing | 110 | - |
| Exposure summarized from the studies: AC-055-302 (SERAPHIN DB), AC-055-303 (SERAPHIN OL), AC-055-305 (MAESTRO DB), AC-055-308 (MAESTRO OL), AC-055-404 (PORTICO DB), AC-055-404 (PORTICO OL), AC-055-401/402 (SYMPHONY OL and Extension), AC-055-310/311 (ORCHESTRA OL and Extension), AC-055-403 (REPAIR), AC-055-405 (OPTIMA), AC-055-314 (UMBRELLA), AC-065A308 (TRITON).<br>For ongoing study AC-055-314 (UMBRELLA) cut-off date 17OCT2021.<br>Exposure includes treatment interruptions.<br>Patients in the 'Missing' category are not considered in the Total Patient-years exposure. | | |

# PART II: SAFETY SPECIFICATION

## Module SIV: Populations Not Studied in Clinical Trials

The safety profile of macitentan has been investigated in adequate, placebo-controlled trials.

The limitations regarding lack of experience in special populations (pregnancy and lactating women, patients with moderate or severe hepatic impairment, patients on dialysis) are reflected in the SmPC for OPSUMIT.

The efficacy and safety in pediatric subjects with PAH is being assessed as part of the agreed Pediatric Investigation Plan (PIP) for macitentan in PAH. To that effect, a study (AC-055-312/TOMORROW) is currently ongoing. AC-055-312 (TOMORROW) is a multicenter, open-label, randomized, event-driven study to assess the efficacy, safety, and PK of macitentan versus standard of care in children with PAH.

### SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

**Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program**

| **Criterion 1** | **Patients with moderate to severe hepatic impairment, ie, Child-Pugh Class B or C** |
|---|---|
| Reason for being an exclusion criterion | PAH subjects with moderate or severe hepatic impairment were excluded from the clinical studies in the pre-authorization phase as a precautionary measure due to the absence of data on the PK of macitentan in subjects with hepatic impairment at that time. |
| Considered to be included as missing information: Yes/No | No. |
| Rationale (if not included as missing information) | OPSUMIT is contraindicated in patients with severe hepatic impairment with or without cirrhosis (SmPC Section 4.3 [contraindications]). Based on PK data, no dose adjustment is required in patients with hepatic impairment (SmPC section 4.3 [Contraindications]). OPSUMIT should not be initiated in patients with elevated aminotransferases (>3×upper limit of normal [ULN]) and it is not recommended in patients with moderate hepatic impairment (SmPC sections 4.2 [Posology and method of administration], 4.3 [Contraindications] and 4.4 [Special warnings and precautions for use]). The need for periodically monitoring liver function before and during treatment with OPSUMIT is also described in the SmPC (section 4.4 [Special warnings and precautions for use]). No additional pharmacovigilance activities are planned to further characterize the use of OPSUMIT in patients with |

**Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program**

| | |
|---|---|
| | moderate to severe hepatic impairment.<br>Per PRAC feedback on the macitentan Periodic Benefit Risk Evaluation Report (PBRER) covering the period 18 October 2018 to 17 October 2020, and in line with GVP Module V Revision 2, patients with moderate to severe hepatic impairment are no longer considered to be missing information in the summary of safety concerns for the purposes of risk management planning. |
| **Criterion 2** | **Patients with an estimated creatinine clearance <30 mL/min** |
| Reason for being an exclusion criterion | PAH subjects with estimated creatinine clearance <30 mL/min were not studied in the pre-authorization phase for PAH as a precautionary measure due to the absence of data on the PK of macitentan in subjects with severe renal impairment. |
| Considered to be included as missing information: Yes/No | No. |
| Rationale (if not included as missing information) | Sections 4.2 (Posology and method of administration) and 4.4 (Special warnings and precautions for use) of the SmPC describe relevant information regarding the use of OPSUMIT in patients with severe renal impairment. No additional pharmacovigilance activities are planned to further characterize the use in patients with severe renal impairment and/or undergoing dialysis.<br>Per PRAC feedback on the macitentan PBRER covering the period 18 October 2018 to 17 October 2020, and in line with GVP Module V Revision 2, patients with severe renal impairment and/or undergoing dialysis are no longer considered to be missing information in the summary of safety concerns for the purposes of risk management planning. |
| **Criterion 3** | **Children** |
| Reason for being an exclusion criterion | Children under 12 years of age were excluded from clinical development. However, a PIP for macitentan in PAH is ongoing. |
| Considered to be included as missing information: Yes/No | Yes. |
| Rationale (if not included as missing information) | Not applicable |

**Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program**

| **Criterion 4** | **Elderly subjects older than 75 years of age** |
|---|---|
| Reason for being an exclusion criterion | Elderly subjects were not formally excluded from clinical trials. However, there is limited clinical experience with macitentan in subjects over the age of 75. |
| Considered to be included as missing information: Yes/No | No. |
| Rationale (if not included as missing information) | In light of all postmarketing data available to date, the safety profile of OPSUMIT in the elderly population ≥75 years of age is in line with the expected and, in general terms, does not differ greatly from that observed in patients 18 to <75 years. No additional pharmacovigilance activities are planned to further characterize use in elderly patients (≥75 years of age).<br>Per PRAC feedback on the macitentan PBRER covering the period 18 October 2018 to 17 October 2020, elderly patients older than 75 years of age are no longer considered to be missing information in the summary of safety concerns for the purposes of risk management planning. |
| **Criterion 5** | **Pregnant subjects** |
| Reason for being an exclusion criterion | Animal studies have shown teratogenicity, similarly to what was observed with other ERAs. The potential risk for humans is still unknown. |
| Considered to be included as missing information: Yes/No | No. |
| Rationale (if not included as missing information) | OPSUMIT is contraindicated in pregnancy, women of childbearing potential not using reliable contraception, and during lactation (SmPC section 4.3 [Contraindications]). |
| **Criterion 6** | **Breastfeeding subjects** |
| Reason for being an exclusion criterion | In rats, macitentan and its metabolites were excreted into milk during lactation. There are no clinical data available regarding the use of macitentan during lactation. |
| Considered to be included as missing information: Yes/No | No. |
| Rationale (if not included as missing information) | OPSUMIT is contraindicated during lactation (SmPC section 4.3 [Contraindications]). |

## SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

## SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

**Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs**

| Type of Special Population | Exposure |
|---|---|
| Pregnant women | The data from the use of macitentan in pregnant women comprise 119 reports pertaining to maternal exposure during pregnancy, including 25 cases from interventional clinical trials and 94 cases observed in the postmarketing setting (cut-off 17 October 2021). |
| Breastfeeding women | Not included in the clinical development program. |
| Population with relevant different ethnic origin | Not applicable. |
| Subpopulations carrying relevant genetic polymorphisms | Not applicable. |
| Other:<br>• Children<br>• Elderly patients older than 75 years of age | In Study AC-055-302 (SERAPHIN), 2.7% of subjects enrolled (n=20) were <18 years of age at enrolment, and 3.4% of subjects enrolled (n=25) were ≥75 years of age at enrolment.<br>Study AC-055-312 (TOMORROW) is ongoing and will help to characterize the safety profile of macitentan in children.<br>Per PRAC feedback on the macitentan PBRER covering the period 18 October 2018 to 17 October 2020, elderly patients older than 75 years of age are no longer considered to be missing information in the summary of safety concerns as the safety profile in these patients is in line with that expected and, in general terms, does not differ greatly from that observed in patients aged 18 to <75 years. As of 17 October 2021, almost 8,000 patients aged ≥75 years have received macitentan, including around 1,100 aged ≥85 years. |
| **Patients with relevant co-morbidities:** | |
| Patients with hepatic impairment | There is no clinical experience with the use of macitentan in PAH subjects with moderate or severe hepatic impairment. There were 24 subjects with hepatic impairment (Child Pugh classes A-C) |

| | |
|---|---|
| | in Phase 1 studies. Per PRAC feedback on the macitentan PBRER covering the period 18 October 2018 to 17 October 2020, and in line with GVP Module V Revision 2, patients with moderate to severe hepatic impairment are no longer considered to be missing information in the summary of safety concerns for the purposes of risk management planning. |
| Patients with renal impairment | There is no clinical experience with the use of macitentan in PAH subjects with severe renal impairment or those undergoing dialysis. There were 8 subjects with severe impairment in Phase 1 studies. Per PRAC feedback on the macitentan PBRER covering the period 18 October 2018 to 17 October 2020, and in line with GVP Module V Revision 2, patients with severe renal impairment and/or undergoing dialysis are no longer considered to be missing information in the summary of safety concerns for the purposes of risk management planning. |

## Summary of Missing Information Due to Limitations of the Clinical Trial Program

| |
|---|
| Pediatric patients |

# PART II: SAFETY SPECIFICATION

## Module SV: Postauthorization Experience

## SV.1. Postauthorization Exposure

### SV.1.1. Method used to Calculate Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient.

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. The number of patients exposed to macitentan during the postmarketing period is estimated via controlled distribution systems or from the number of packages sold. Data are collected on a monthly basis, therefore the cut-off date used for the purpose of this report is 30 September 2021.

### SV.1.2. Exposure

Cumulatively, between International Birth Date (IBD) and 30 September 2021, an estimated 106,691 patients have been exposed to commercial macitentan worldwide.

- **By age group and sex (US data)**

Data on exposure (number of patients and patient years) by age group and sex are available for the US. According to cumulative exposure data from the US, 70.8% of the [redacted] exposed patients were females and 29.2% were males (Table SV.1).

The distribution by age group was as follows: 50.5% were adults, 48.7% were elderly (21.3%; ≥75 years), 0.3% of exposed patients were below the age of 12 years, and 0.5% were between 12 and 18 years.

The estimated cumulative exposure in the US corresponds to [redacted] patient-years. Table SV.2 shows the cumulative US exposure in patient-years by age group and sex.

**Table SV.1 Postmarketing Macitentan Cumulative US Exposure – Number of Patients by Age Group and Sex (Launch to 30 September 2021)**

| Patient age groups | Age (years) | Females | | Males | | Total | |
|---|---|---|---|---|---|---|---|
| **Pediatric** | <12 | 53 | 0.2% | 51 | 0.1% | 104 | 0.3% |
| | ≥12 to <18 | 112 | 0.3% | 86 | 0.2% | 198 | 0.5% |
| **Adult** | ≥18 to <65 | 13,025 | 35.9% | 5,317 | 14.6% | 18,342 | 50.5% |
| **Elderly** | ≥65 to <75 | 7,051 | 19.4% | 2,913 | 8.0% | 9,964 | 27.4% |
| | ≥75 to <85 | 4,588 | 12.6% | 1,949 | 5.4% | 6,537 | 18.0% |
| | ≥85 | 889 | 2.4% | 305 | 0.9% | 1,194 | 3.3% |
| **Total** | | **25,718** | **70.8%** | **10,621** | **29.2%** | **36,339** | **100%** |

Cumulative data: 06 September 2004 to 30 September 2021.
US=United States (of America).

**Table SV.2 Postmarketing Macitentan Cumulative US Exposure – Patient-years by Age Group and Sex (Launch to 30 September 2021)**

| Patient age groups | Age (years) | Females | Males | Total |
|---|---|---|---|---|
| **Pediatric** | <12 | 125.6 | 100.2 | 225.8 |
| | ≥12 to <18 | 250.5 | 215.2 | 465.7 |
| **Adult** | ≥18 to <65 | 27,092.2 | 9,805.7 | 36,897.9 |
| **Elderly** | ≥65 to <75 | 12,635.8 | 4,225.5 | 16,891.3 |
| | ≥75 to <85 | 6,890.2 | 2,296.3 | 9,186.5 |
| | ≥85 | 1,020.6 | 273.5 | 1,294.1 |
| **Total** | | **48,014.9** | **16,946.4** | **64,961.3** |

Note: The method regarding patient age calculation is based on patient age at the time of first product shipment.
Cumulative data: 06 September 2004 to 30 September 2021.
US=United States (of America).

### By indication

Not applicable as macitentan (Opsumit) is only indicated in PAH.

### By route of administration

Not applicable as macitentan (Opsumit) is only registered as film-coated tablets for oral use.

### By dose

Not applicable as macitentan (Opsumit) is only available in one dose strength (10 mg tablets).

### By country

**Table SV.3 Estimated Cumulative Exposure by Region (Launch to 30 September 2021)**

| Region | Estimated patient exposure* |
|---|---|
| European Economic Area | [redacted] |
| United States | |
| Rest of the World | 37,072 |
| **Total** | **106,691** |

* 06 September 2004 to 30 September 2021.

# PART II: SAFETY SPECIFICATION

## Module SVI: Additional EU Requirements for the Safety Specification

### Potential for Misuse for Illegal Purposes

There are no specific comments of relevance.

# PART II: SAFETY SPECIFICATION

## Module SVII: Identified and Potential Risks

### SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

### SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

**Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:**

Not applicable.

### SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

### SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

**Removal of Safety Concerns**

Not applicable.

### SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

### SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

**Important Identified Risk: Anemia, decrease in hemoglobin concentration**

Potential Mechanisms:

Macitentan therapy is associated with a dose-related decrease in hemoglobin concentration. Hemoglobin decrease is a known reaction to treatment with ERAs, although the mechanism has not been fully elucidated. It has been hypothesized to be related to plasma volume expansion.

The magnitude of hemoglobin decrease observed during chronic treatment with macitentan is similar to that with ambrisentan and bosentan, according to the prescribing information for these products.

There is no evidence of hemolysis or bone marrow depression associated with treatment with ERAs, including macitentan.

Evidence Source(s) and Strength of Evidence:

Macitentan and medicines of the same chemical class may reduce the blood hemoglobin level. Blood transfusion may be required in some cases. In the pivotal Phase 3 study of macitentan in PAH (SERAPHIN), a clinically relevant decrease in hemoglobin concentration was reported in 8.7% of macitentan-treated subjects and 3.4% of placebo-treated subjects.

Characterization of the Risk:

*Randomized, double-blind studies*

**Table SVII.1: Important Identified Risk (Anemia/decrease in hemoglobin concentration): Treatment-emergent Adverse Event of Special Interest in RDB Studies; RDB Safety Set**

| | All RDB studies | |
|---|---|---|
| | Macitentan 10 mg | Placebo |
| Analysis set: RDB Safety Set | 399 | 403 |
| Anemia/decrease in hemoglobin concentration | | |
| Patients with at least one AESI | 60 (15.0%) | 21 (5.2%) |
| Relative Risk | 2.886 | |
| 95% confidence interval | (1.791 - 4.651) | |
| Patients at least one AESI with: | | |
| Serious | 8 (2.0%) | 3 (0.7%) |
| Leading to discontinuation of trt. | 2 (0.5%) | 2 (0.5%) |
| Fatal outcome | 0 | 0 |
| Number of recurrent AESIs | 84 | 27 |
| Patient-years exposure | 526.16 | 451.11 |
| Average annualized event rate | 0.1596 | 0.0599 |
| Severity (worst)* | | |
| Mild | 36 (9.0%) | 9 (2.2%) |
| Moderate | 21 (5.3%) | 10 (2.5%) |
| Severe | 3 (0.8%) | 2 (0.5%) |

Based on the completed RDB studies: AC-055-302 (SERAPHIN DB), AC-055-305 (MAESTRO DB) and AC-055-404 (PORTICO DB).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.

*Relevant laboratory data from RBD studies*

- Pivotal Phase 3 study in PAH (SERAPHIN): In the macitentan 10 mg group, there was a mean±SD decrease in hemoglobin of 1.1±2.2 g/dL up to end of study plus 28 days from a mean baseline value of 15.6 g/dL. In the placebo group, there was a mean±SD decrease of 0.1±1.67 g/dL from a mean baseline value of 15.6 g/dL. The proportion of subjects with marked hemoglobin decreases (values <11 g/dL and a decrease of 15% from baseline) was 13.9% in the macitentan 10 mg group, compared with 3.8% in the placebo group. The proportion of subjects with decreases in hemoglobin to between >8 g/dL and ≤10 g/dL during the study period plus 28 days after treatment discontinuation was 4.3% in the macitentan 10 mg group compared with 3.0% in the placebo group. For the vast majority of subjects who had decreases in hemoglobin to ≤8 g/dL or had a transfusion, these occurred in the context of hemorrage (particularly gynecology bleeds), a medical history of anemia, or other

confounding factors such as hypothyroidism and chronic renal failure. In 19 of 30 subjects, a recovery of hemoglobin levels to at least 10 g/dL was reported, or the investigator indicated resolution of hemoglobin decrease. The remaining subjects did not show recovery due to death, showed a partial recovery, or did not have values documenting recovery.

- Phase 3 study in ES (MAESTRO): Hemoglobin decreases from baseline ≥20 g/L and <50 g/L were reported for 50 subjects (22.1%), 40 (35.1%) in the macitentan group, and 10 (8.9%) in the placebo group. Of these cases, 7 (6 in the macitentan group and 1 in the placebo group) were reported as adverse events (AEs). In 1 subject in the macitentan group who had a decrease from baseline hemoglobin of ≥50 g/dL, the subject's baseline value was 237 g/L, which fell to 177 g/L on Day 50. There was no bleeding diathesis. The subject remained asymptomatic, and no AEs were reported. Hemoglobin rebounded by Week 16 to 85% of baseline value without treatment interruption. A marked abnormality in hemoglobin values <100 g/L was reported for 1 subject in the macitentan group with a medical history of anemia, iron deficiency and gastrointestinal bleeding (this subject had a baseline hemoglobin value that was abnormally low for a subject with ES [111 g/L]). No subjects had a market decrease in hemoglobin values to <80 g/L.
- Phase 3 study in PoPH (PORTICO): Hemoglobin decreases from baseline ≥20 g/L were reported for 12 subjects (27.9%) in the macitentan group, and 2 subjects (4.9%) in the placebo group. In the macitentan group, one of the decreases was ≥50 g/L. In 3 subjects in the macitentan group and 2 in the placebo group, there were decreases in hemoglobin concentration to ≤100 g/L, but none was ≤80 g/L. Of these cases, anemia AEs were reported for 6 subjects (14.0% in the macitentan group versus 1 subject (2.4%) in the placebo group.

*All studies*

**Table SVII.2: Important Identified Risk (Anemia/decrease in hemoglobin concentration): Treatment-emergent Adverse Event of Special Interest in Macitentan-treated Patients; Macitentan Treated Set**

| | All macitentan |
|---|---|
| Analysis set: Macitentan Treated Set | 1667 |
| Anemia/decrease in hemoglobin concentration | |
| Patients with at least one AESI | 334 (20.0%) |
| Patients at least one AESI with: | |
| Serious | 63 (3.8%) |
| Leading to discontinuation of trt. | 11 (0.7%) |
| Fatal outcome | 0 |
| Number of recurrent AESIs | 514 |
| Patient-years exposure | 4284.16 |
| Average annualized event rate | 0.1200 |
| Severity (worst)* | |
| Mild | 166 (10.0%) |
| Moderate | 126 (7.6%) |
| Severe | 41 (2.5%) |
| Missing | 1 (0.1%) |

**Table SVII.2: Important Identified Risk (Anemia/decrease in hemoglobin concentration): Treatment-emergent Adverse Event of Special Interest in Macitentan-treated Patients; Macitentan Treated Set**

| | All macitentan |
|---|---|
| Based on the completed and on-going studies<br>Completed studies: AC-055-302 (SERAPHIN DB), AC-055-303 (SERAPHIN OL), AC-055-305 (MAESTRO DB), AC-055-308 (MAESTRO OL), AC-055-404 (PORTICO DB), AC-055-404 (PORTICO OL), AC-055-401/402 (SYMPHONY OL and Extension), AC-055-310/311 (ORCHESTRA OL and Extension), AC-055-403 (REPAIR), AC-055-405 (OPTIMA), AC-065A308 (TRITON).<br>On-going study: AC-055-314 (UMBRELLA, cut-off date: 17OCT2021).<br>* The event experienced by the patient with the worst severity is used.<br>Adverse events are coded using MedDRA Version 24.0. | |

*Postmarketing data (from IBD to 17 October 2021)*

Cumulatively, 3,776 cases containing events of anemia and/or decreased hemoglobin have been received from postmarketing data sources as of 17 October 2021. Taking into account the estimated exposure of 106,691 patients, the estimated cumulative reporting rate is 3.5%. The most frequently reported event was anemia, in 2,485 of the 3,776 cases (65.8%). Events of anemia reported in the postmarketing setting have increased proportionally with the accumulating number of exposed patients and the increasing duration of exposure. Transfusion was reported in 775 of the anemia cases. Alternative explanations, such as underlying conditions, bleeding events (eg, gastrointestinal hemorrhage), or underlying diseases (eg, CTD) were present in most cases.

The nature of the events of anemia reported via postmarketing data sources is consistent with observations from clinical trials.

MedDRA terms used in database search: Refer to Annex 7.3 for the list of MedDRA preferred terms (PTs) for the risk of Anemia, decrease in hemoglobin concentration.

Risk Factors and Risk Groups:

General risk factors for anemia are, eg, iron deficiency, history of anemia, concomitant use of platelet inhibitors, anticoagulants, steroids, and pre-existing or concurrent bleeding.

Preventability:

Anemia is measurable, monitorable, and treatable.

The following warning is included in section 4.4 of the OPSUMIT SmPC:

"Decrease in haemoglobin concentrations has been associated with endothelin receptor antagonists (ERAs) including macitentan (see section 4.8). In placebo-controlled studies, macitentan-related decreases in haemoglobin concentration were not progressive, 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 and other ERAs. 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."

Impact on the Risk-Benefit Balance of the Product:

Anemia is measurable, monitorable, and treatable. Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Anemia may require blood transfusion.

Annex 1 MedDRA Term:

Standardized MedDRA Query (SMQ): Haematopoietic erythropenia (broad).

**Important Identified Risk: Hepatotoxicity**

Potential Mechanisms:

The mechanisms of liver toxicity with other ERAs are not fully elucidated. For bosentan, BSEP blockage and/or direct hepatotoxic effect have been implicated.

Macitentan is an alkyl-sulfamide with a pyrimidine scaffold containing three aromatic rings. It contains no substructures considered to be toxicophores for liver toxicity. The chemical nature of human metabolites and the cytochrome P450 enzymes involved in its metabolism do not indicate any liver liability. The two macitentan metabolites circulating in human plasma, ACT-132577 and ACT-373898, were fully characterized in the non-clinical safety program.

Macitentan and the pharmacologically active metabolite ACT-132577 do not inhibit the major human transport proteins responsible for hepatic bile salt transport, ie, BSEP and NTCP, at clinically relevant concentrations. Macitentan has no effect on serum bile salt concentrations in animals up to very high dose levels and during chronic dosing, or in healthy human subjects at high single doses or supratherapeutic doses for up to 10 days.

The non-clinical profile of macitentan does not indicate a relevant risk for liver toxicity in humans.

Evidence Source(s) and Strength of Evidence:

Macitentan, like other medicines of the same chemical class, may affect the liver.

The mechanism of this adverse effect is unclear. Interruption or stopping treatment may be necessary.

## Characterization of the Risk:

### *Randomized, double-blind studies*

**Table SVII.3: Important Identified Risk (Hepatotoxicity): Treatment-emergent Adverse Event of Special Interest in RDB Studies; RDB Safety Set**

| | All RDB studies | |
|---|---|---|
| | Macitentan 10 mg | Placebo |
| Analysis set: RDB Safety Set | 399 | 403 |
| Hepatotoxicity | | |
| Patients with at least one AESI | 34 (8.5%) | 52 (12.9%) |
| Relative Risk | 0.660 | |
| 95% confidence interval | (0.438 - 0.995) | |
| Patients at least one AESI with: | | |
| Serious | 8 (2.0%) | 7 (1.7%) |
| Leading to discontinuation of trt. | 8 (2.0%) | 4 (1.0%) |
| Fatal outcome | 0 | 1 (0.2%) |
| Number of recurrent AESIs | 56 | 85 |
| Patient-years exposure | 526.16 | 451.11 |
| Average annualized event rate | 0.1064 | 0.1884 |
| Severity (worst)* | | |
| Mild | 20 (5.0%) | 28 (6.9%) |
| Moderate | 10 (2.5%) | 19 (4.7%) |
| Severe | 4 (1.0%) | 5 (1.2%) |

Based on the completed RDB studies: AC-055-302 (SERAPHIN DB), AC-055-305 (MAESTRO DB) and AC-055-404 (PORTICO DB).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.

### *Relevant laboratory data from RBD studies*

- Pivotal Phase 3 study in PAH (SERAPHIN): The proportion of subjects who had alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >3×upper limit of normal (ULN) was 3.4% in the macitentan 10 mg group compared with 4.5% in the placebo group. ALT and/or AST elevations >8×ULN were observed in 2.1% of macitentan-treated subjects compared with 0.4% in the placebo-treated subjects. Four subjects in the 10 mg macitentan group had ALT and/or AST >3×ULN and an elevation of total bilirubin >2×ULN. These cases were observed in the setting of worsening of the underlying concomitant disease or had other confounding factors.
- Phase 3 study in ES (MAESTRO): AEs of increased AST and/or ALT were reported in a total of 4 subjects (2 macitentan [1.7%], 2 [1.7%] placebo). For 2 additional subjects, elevated bilirubin was reported (1 macitentan [0.8%], 1 placebo [0.9%]). One subject in each group had an ALT or AST elevation ≥3×ULN. No subjects had ALT or AST elevations ≥3×ULN with a concomitant increase in total bilirubin to ≥2×ULN.
- Phase 3 study in PoPH (PORTICO): There was 1 macitentan-treated subject in the double-blind phase who had Hy's Law range liver test abnormalities; however, this occurred in the context of a liver condition considered unrelated to macitentan treatment.

*All studies*

**Table SVII.4: Important Identified Risk (Hepatotoxicity): Treatment-emergent Adverse Event of Special Interest in Macitentan-treated Patients; Macitentan Treated Set**

| | All macitentan |
|---|---|
| Analysis set: Macitentan Treated Set | 1667 |
| Hepatotoxicity | |
| Patients with at least one AESI | 229 (13.7%) |
| Patients at least one AESI with: | |
| Serious | 32 (1.9%) |
| Leading to discontinuation of trt. | 30 (1.8%) |
| Fatal outcome | 0 |
| Number of recurrent AESIs | 418 |
| Patient-years exposure | 4284.16 |
| Average annualized event rate | 0.0976 |
| Severity (worst)* | |
| Mild | 113 (6.8%) |
| Moderate | 79 (4.7%) |
| Severe | 30 (1.8%) |
| Missing | 7 (0.4%) |

Based on the completed and on-going studies
Completed studies: AC-055-302 (SERAPHIN DB), AC-055-303 (SERAPHIN OL), AC-055-305 (MAESTRO DB), AC-055-308 (MAESTRO OL), AC-055-404 (PORTICO DB), AC-055-404 (PORTICO OL), AC-055-401/402 (SYMPHONY OL and Extension), AC-055-310/311 (ORCHESTRA OL and Extension), AC-055-403 (REPAIR), AC-055-405 (OPTIMA), AC-065A308 (TRITON).
On-going study: AC-055-314 (UMBRELLA, cut-off date: 17OCT2021).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.

*Postmarketing data (from IBD to 17 October 2021)*

Cumulatively, from IBD up to 17 October 2021, 1,865 postmarketing cases with hepatic AEs have been reported for 106,691 patients receiving macitentan, corresponding to an estimated reporting rate of 1.7%. The most frequently reported event was aspartate aminotransferase increased, in 412 of the 1,865 cases (22.1%).

The nature of the hepatic events of reported via postmarketing data sources is consistent with observations from clinical trials. In cases with sufficient information provided, the underlying PAH disease and associated co-morbidities were assessed as the more likely cause of the hepatic events in the majority of cases. A few isolated cases with transient and reversible transaminase elevations, with no confounding factors identified, were reported.

MedDRA terms used in database search: Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Hepatotoxicity.

Risk Factors and Risk Groups:

Unknown in patients with ALT/AST >3×ULN at baseline or patients with moderate or severe liver impairment, as they were excluded from clinical trials with macitentan.

Preventability:

The following statements are included in the SmPC:

Section 4.2 – Posology and method of administration

"*Hepatic impairment*

Based on pharmacokinetic (PK) data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment. 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)."

Section 4.3 – Contraindications:

"• Patients with 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)."

Section 4.4 – Special warnings and precautions for use

"*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 severe hepatic impairment or elevated aminotransferases (> 3 × ULN) (see sections 4.2 and 4.3), and is not recommended in patients with moderate 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 (eg, jaundice), Opsumit treatment should be discontinued.

Reinitiation of Opsumit 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."

The following additional risk minimization activity is in place: patient card (Part V.2).

Impact on the Risk-Benefit Balance of the Product:

Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Hepatic enzyme levels are measurable and monitorable. In severe cases, elevations of liver aminotransferases or other liver impairment events may require hospitalization.

Annex 1 MedDRA Term:

SMQ: Hepatic disorders (broad).

**Important Identified Risk: Teratogenicity**

Potential Mechanisms:

The ET-A receptor pathway is critical to normal induction, migration, and maintenance of neural crest cells during early embryonic development. Disruption of this pathway, such as by ERA therapy, can lead to severe defects in neural crest derivatives and physical malformation (de Raaf 2015).

Evidence Source(s) and Strength of Evidence:

According to results from animal studies, macitentan and medicines of the same chemical class may harm unborn babies conceived before starting or during treatment. Based on a limited number of pregnancies observed in women exposed to macitentan, no translation of this risk to humans has been observed.

Characterization of the Risk:

| | |
|---|---|
| Frequency | Unknown. Pregnancy was an exclusion criterion in macitentan clinical trials.<br>Up to 17 October 2021 cumulatively, 119 reports pertaining to maternal exposure during pregnancy have been received, including 25 mother cases from interventional clinical trials on macitentan, and 94 mother cases from postmarketing data sources. A further 4 reports described pregnancy in female partners of male patients treated with macitentan.<br>Of the 27 live births (3 from clinical trials, 6 from solicited programs, and 18 spontaneous reports), 1 clinical trial case described a premature baby born at 24 weeks' gestation, who suffered complications of extreme prematurity (neonatal respiratory distress syndrome, sepsis, intracranial hemorrhage, skin atrophy) and died 3 days after birth due to persistent hypotension.<br>No cases of congenital abnormalities were reported during the macitentan clinical development program. No fetal malformations were reported in cases where the pregnancy outcome was induced or spontaneous abortion.<br>Cumulatively, 2 cases describing congenital anomalies have been received from |

| | |
|---|---|
| | all data sources:<br>• 1 case, referring to a premature baby with [redacted] diagnosed as chondrodysplasia, was confounded by the mother's underlying SLE disease and concomitant medications.<br>• 1 case referred to a premature baby with [redacted] |
| Seriousness/outcomes | Based on the medical assessment of both cases, there was no evidence of a contributory role of macitentan, and neither anomaly corresponded to the pattern of malformations that may be expected from ERAs based on nonclinical findings (ie, defects in neural crest derivatives).<br>Both babies with congenital anomalies described above experienced respiratory distress syndrome at birth (in context of their prematurity), requiring admission to a neonatal intensive care unit.<br>Overall, no indication of teratogenicity arose from review of these cases. |
| Severity and nature of risk | Unknown in humans, due to limited data. Pregnant women and women of childbearing potential not using reliable contraception were excluded from clinical trials.<br>In animal studies, macitentan was shown to be teratogenic: cardiovascular and craniofacial abnormalities were observed in rabbits and rats at exposures 32- to 48-fold the human exposure, respectively. |

MedDRA terms used in database search: Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Teratogenicity.

Risk Factors and Risk Groups:

All women of childbearing potential on macitentan therapy who are not using a reliable method of contraception.

Preventability:

As outlined in section 4.3 of the SmPC, OPSUMIT is contraindicated in women who are or may become pregnant.

The following warning is included in section 4.4 of the OPSUMIT SmPC:

"Use in women of childbearing potential

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 practiced (see sections 4.3 and 4.6). 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."

Section 4.6 of the SmPC contains the following information:

"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 practiced (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 on the use of macitentan in pregnant women. Animal studies have shown 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)."

The SmPC, Package Leaflet (PL), and patient card will provide information regarding the contraindication in pregnancy and in women of childbearing potential who are not using a reliable method of contraception, and the need to report immediately any pregnancy that may occur on treatment with macitentan. This will ensure awareness of the prescribers/patients regarding necessary contraceptive precautions.

All reported pregnancies will be followed up to final outcome, to identify potential congenital disorders.

The following additional risk minimization activity is in place: patient card (Part V.2).

Impact on the Risk-Benefit Balance of the Product:

Pregnancy is strongly contra-indicated for women with PAH, regardless of the medications used. The additional risk of teratogenicity from macitentan does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Potential congenital anomalies.

Annex 1 MedDRA Term:

SMQ: Congenital, familial, and genetic disorders (broad).

## Important Identified Risk: Symptomatic Hypotension

Potential Mechanisms:

As with other ERAs, treatment with macitentan may be associated with a reduction in BP due to its vasodilatory effects.

Evidence Source(s) and Strength of Evidence:

Macitentan, like other medicines of the same chemical class, widens blood vessels, and BP decrease has been reported.

In a long-term double-blind study (SERAPHIN), decrease of BP was reported in 7.0% of macitentan-treated subjects and 4.4% of placebo-treated subjects.

Among patients who receive prescribed macitentan, 1–2 in 100 report symptomatic hypotension. The most frequent clinical sign of hypotension is dizziness.

Macitentan may lead to more reduction of BP in patients with kidney problems.

Characterization of the Risk:

*Randomized, double-blind studies*

**Table SVII.5: Important Identified Risk (Symptomatic hypotension): Treatment-emergent Adverse Event of Special Interest in RDB Studies; RDB Safety Set**

| | All RDB studies | |
|---|---|---|
| | Macitentan 10 mg | Placebo |
| Analysis set: RDB Safety Set | 399 | 403 |
| Symptomatic hypotension | | |
| Patients with at least one AESI | 3 (0.8%) | 3 (0.7%) |
| Relative Risk | 1.010 | |
| 95% confidence interval | (0.205 - 4.974) | |
| Patients at least one AESI with: | | |
| Serious | 0 | 1 (0.2%) |
| Leading to discontinuation of trt. | 0 | 0 |
| Fatal outcome | 0 | 0 |
| Number of recurrent AESIs | 6 | 6 |
| Patient-years exposure | 526.16 | 451.11 |
| Average annualized event rate | 0.0114 | 0.0133 |
| Severity (worst)* | | |
| Mild | 1 (0.3%) | 1 (0.2%) |
| Moderate | 2 (0.5%) | 1 (0.2%) |
| Severe | 0 | 1 (0.2%) |

**Table SVII.5: Important Identified Risk (Symptomatic hypotension): Treatment-emergent Adverse Event of Special Interest in RDB Studies; RDB Safety Set**

| | All RDB studies | |
|---|---|---|
| | Macitentan 10 mg | Placebo |

Based on the completed RDB studies: AC-055-302 (SERAPHIN DB), AC-055-305 (MAESTRO DB) and AC-055-404 (PORTICO DB).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.

*Relevant laboratory data from RBD studies*

- Pivotal Phase 3 study in PAH (SERAPHIN): In the double-blind PAH population, there was no meaningful difference between macitentan and placebo regarding mean and median change from baseline to EOT for systolic BP (SBP) or diastolic BP (DBP). A decrease in SBP (>20 mmHg and to ≤90 mmHg) was observed in 11.9% of subjects on macitentan 10 mg versus 9.9% in those on placebo. Evaluation by subgroup in the double-blind PAH population showed that most hypotension AEs were reported in female subjects. The incidence of hypotension showed little indication of any correlation with the age of the subject. There was a slightly increased incidence of hypotension in subjects with moderate to severe renal function impairment, which is mentioned in section 4.4 of the SmPC. The incidence of hypotension did not show any clear pattern associated with the use of concomitant PAH therapy, mainly PDE-5 inhibitors.
- Phase 3 study in ES (MAESTRO): Mean±SD changes from baseline up to 30 days after study treatment discontinuation in SBP and DBP were -2.2±12.5 mmHg and -3.1±10.7 mmHg, respectively, compared with -1.2±11.8 mmHg and -0.5±9.3 mmHg for placebo. These differences were not considered clinically relevant.
- Phase 3 study in PoPH (PORTICO): Mean±SD changes in SBP from baseline to the end of the double-blind phase (Week 12) were -3.0±14.1 mmHg for macitentan and -0.9±14.6 mmHg for placebo. For DBP, the corresponding values were -3.3±10.6 and 0±12.5, respectively.

*All studies*

**Table SVII.6: Important Identified Risk (Symptomatic hypotension): Treatment-emergent Adverse Event of Special Interest in Macitentan-treated Patients; Macitentan Treated Set**

| | All macitentan |
|---|---|
| Analysis set: Macitentan Treated Set | 1667 |
| Symptomatic hypotension | |
| Patients with at least one AESI | 22 (1.3%) |
| Patients at least one AESI with: | |
| Serious | 6 (0.4%) |
| Leading to discontinuation of trt. | 0 |
| Fatal outcome | 1 (0.1%) |
| Number of recurrent AESIs | 44 |
| Patient-years exposure | 4284.16 |
| Average annualized event rate | 0.0103 |
| Severity (worst)* | |
| Mild | 8 (0.5%) |
| Moderate | 10 (0.6%) |
| Severe | 4 (0.2%) |

**Table SVII.6: Important Identified Risk (Symptomatic hypotension): Treatment-emergent Adverse Event of Special Interest in Macitentan-treated Patients; Macitentan Treated Set**

| | All macitentan |
|---|---|
| Based on the completed and on-going studies<br>Completed studies: AC-055-302 (SERAPHIN DB), AC-055-303 (SERAPHIN OL), AC-055-305 (MAESTRO DB), AC-055-308 (MAESTRO OL), AC-055-404 (PORTICO DB), AC-055-404 (PORTICO OL), AC-055-401/402 (SYMPHONY OL and Extension), AC-055-310/311 (ORCHESTRA OL and Extension), AC-055-403 (REPAIR), AC-055-405 (OPTIMA), AC-065A308 (TRITON).<br>On-going study: AC-055-314 (UMBRELLA, cut-off date: 17OCT2021).<br>* The event experienced by the patient with the worst severity is used.<br>Adverse events are coded using MedDRA Version 24.0. | |

*Postmarketing data (from IBD to 17 October 2021)*

Cumulatively, 1,573 postmarketing cases (regardless of causality) retrieved by the search criteria for symptomatic hypotension have been received as of 17 October 2021. Taking into account the estimated exposure of 106,691 patients, the estimated cumulative reporting rate is 1.5%. The most frequently reported event indicating symptomatic hypotension was dizziness, in 1,034 of the 1,573 cases (65.7%).

The nature of the events of hypotension reported via postmarketing data sources is consistent with observations from clinical trials.

MedDRA terms used in database search: Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Symptomatic hypotension.

Risk Factors and Risk Groups:

Patients with moderate or severe renal impairment.

Preventability:

In case of clinically significant BP reduction, appropriate measures should be taken as per usual clinical practice.

The following information is included in the SmPC:

Section 4.4 – Special warnings and precautions for use

"Renal impairment

Patients with renal impairment may run a higher risk of experiencing hypotension and anemia during treatment with macitentan. Therefore, monitoring of blood pressure and hemoglobin 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 clinical 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).

Section 4.8 – Undesirable effects

"Description of selected adverse reactions

Hypotension has been associated with the use of ERAs including macitentan. 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."

Impact on the Risk-Benefit Balance of the Product:

BP is monitorable, and symptomatic hypotension can typically be managed, eg, by adjusting other medications. Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Severe hypotension in the high morbidity PAH population may require hospitalization.

Annex 1 MedDRA Term:

PT: Blood pressure ambulatory decreased.

**Important Potential Risk: Menstrual Disorders (Primarily Bleeding)**

Potential Mechanisms:

Unknown.

Evidence Source(s) and Strength of Evidence:

Among female PAH subjects participating in the pivotal clinical study (AC-055-302, SERAPHIN), menstrual disorders (primarily bleeding) occurred in 5.1% of the macitentan 10 mg-treated subjects compared to 1.1% of the placebo-treated subjects. Most of the subjects were receiving anticoagulants and/or other medications with known side effects of bleeding at the same time. At present, a causal relationship between macitentan and menstrual disorders, primarily bleeding, is difficult to establish.

Characterization of the Risk:

*Randomized, double-blind studies*

**Table SVII.7: Important Potential Risk (Menstrual disorders (primarily bleeding)): Treatment-emergent Adverse Event of Special Interest in RDB studies; RDB Safety Set**

| | All RDB studies | |
|---|---|---|
| | Macitentan 10 mg | Placebo |
| Analysis set: RDB Safety Set - female patients | 297 | 272 |

**Table SVII.7: Important Potential Risk (Menstrual disorders (primarily bleeding)): Treatment-emergent Adverse Event of Special Interest in RDB studies; RDB Safety Set**

| | All RDB studies | |
|---|---|---|
| | Macitentan 10 mg | Placebo |
| Menstrual disorders (primarily bleeding) | | |
| Patients with at least one AESI | 16 (5.4%) | 7 (2.6%) |
| Relative Risk | 2.093 | |
| 95% confidence interval | (0.875 - 5.011) | |
| Patients at least one AESI with: | | |
| Serious | 3 (1.0%) | 1 (0.4%) |
| Leading to discontinuation of trt. | 0 | 0 |
| Fatal outcome | 0 | 0 |
| Number of recurrent AESIs | 20 | 9 |
| Patient-years exposure | 417.65 | 328.16 |
| Average annualized event rate | 0.0479 | 0.0274 |
| Severity (worst)* | | |
| Mild | 9 (3.0%) | 5 (1.8%) |
| Moderate | 5 (1.7%) | 2 (0.7%) |
| Severe | 2 (0.7%) | 0 |

Based on the completed RDB studies: AC-055-302 (SERAPHIN DB), AC-055-305 (MAESTRO DB) and AC-055-404 (PORTICO DB).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.

*All studies*

**Table SVII.8: Important Potential Risk (Menstrual disorders (primarily bleeding)): Treatment-emergent Adverse Event of Special Interest in Macitentan-treated Female Patients; Macitentan Treated Set**

| | All macitentan |
|---|---|
| Analysis set: Macitentan Treated Set - female patients | 1241 |
| Menstrual disorders (primarily bleeding) | |
| Patients with at least one AESI | 74 (6.0%) |
| Patients at least one AESI with: | |
| Serious | 12 (1.0%) |
| Leading to discontinuation of trt. | 0 |
| Fatal outcome | 1 (0.1%) |
| Number of recurrent AESIs | 106 |
| Patient-years exposure | 3335.10 |
| Average annualized event rate | 0.0318 |
| Severity (worst)* | |
| Mild | 37 (3.0%) |
| Moderate | 28 (2.3%) |
| Severe | 9 (0.7%) |

Based on the completed and on-going studies
Completed studies: AC-055-302 (SERAPHIN DB), AC-055-303 (SERAPHIN OL), AC-055-305 (MAESTRO DB), AC-055-308 (MAESTRO OL), AC-055-404 (PORTICO DB), AC-055-404 (PORTICO OL), AC-055-401/402 (SYMPHONY OL and Extension), AC-055-310/311 (ORCHESTRA OL and Extension), AC-055-403 (REPAIR), AC-055-405 (OPTIMA), AC-065A308 (TRITON).
On-going study: AC-055-314 (UMBRELLA, cut-off date: 17OCT2021).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.

*Postmarketing data (from IBD to 17 October 2021)*

Cumulatively, 276 cases (regardless of causality) related to menstrual disorders have been received as of 17 October 2021. Taking into account the estimated exposure of 77,564 female patients, the estimated cumulative reporting rate is 0.4%. Neither the incidence or prevalence of abnormal uterine bleeding has been well established, but it has been estimated that 9% to 14% of reproductive age women have blood loss exceeding 80 mL per cycle, and that 20% of women will report excessive bleeding during their reproductive life (Goldman 2000). The most frequently reported event was heavy menstrual bleeding, in 97 of the 276 cases (35.1%).

MedDRA terms used in database search: Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Menstrual disorders (primarily bleeding).

Risk Factors and Risk Groups:

Risk factors include a previous history of menstrual disorders / bleeding or concomitant treatment with drugs known to cause bleeding.

Endocrine causes of menorrhagia include thyroid and adrenal gland dysfunction, pituitary tumors, anovulatory cycles, polycystic ovarian syndrome, obesity, and vasculature imbalance (Shaw 2018).

Preventability:

Not applicable.

Impact on the Risk-Benefit Balance of the Product:

Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Severe menstrual bleeding may require hospitalization and/or blood transfusion.

Annex 1 MedDRA Term:

High Level Group Term: Menstrual cycle and uterine bleeding disorders.

**Important Potential Risk: Ovarian Cysts**

Potential Mechanisms:

Unknown.

Evidence Source(s) and Strength of Evidence:

Among female PAH subjects participating in the pivotal clinical study (AC-055-302, SERAPHIN), ovarian cysts were reported in few macitentan-treated subjects. Most of these subjects had other diseases known to be risk factors for ovarian cysts, as documented in their medical history. At present, a causal relationship between macitentan and ovarian cyst is difficult to establish.

Characterization of the Risk:

*Randomized, double-blind studies*

**Table SVII.9: Important Potential Risk (Ovarian cysts): Treatment-emergent Adverse Event of Special Interest in RDB Studies; RDB Safety Set**

| | All RDB studies | |
|---|---|---|
| | Macitentan 10 mg | Placebo |
| Analysis set: RDB Safety Set - female patients | 297 | 272 |
| Ovarian cysts | | |
| Patients with at least one AESI | 4 (1.3%) | 1 (0.4%) |
| Relative Risk<br>95% confidence interval | 3.663<br>(0.412 - 32.574) | |
| Patients at least one AESI with: | | |
| Serious | 2 (0.7%) | 1 (0.4%) |
| Leading to discontinuation of trt. | 0 | 0 |

**Table SVII.9: Important Potential Risk (Ovarian cysts): Treatment-emergent Adverse Event of Special Interest in RDB Studies; RDB Safety Set**

| | All RDB studies | |
|---|---|---|
| | Macitentan 10 mg | Placebo |
| Fatal outcome | 0 | 0 |
| Number of recurrent AESIs | 4 | 1 |
| Patient-years exposure | 417.65 | 328.16 |
| Average annualized event rate | 0.0096 | 0.0030 |
| Severity (worst)* | | |
| Mild | 2 (0.7%) | 0 |
| Moderate | 1 (0.3%) | 1 (0.4%) |
| Severe | 0 | 0 |
| Missing | 1 (0.3%) | 0 |

Based on the completed RDB studies: AC-055-302 (SERAPHIN DB), AC-055-305 (MAESTRO DB) and AC-055-404 (PORTICO DB).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.

*All studies*

**Table SVII.10: Important Potential Risk (Ovarian cysts): Treatment-emergent Adverse Event of Special Interest in Macitentan-treated Female Patients; Macitentan Treated Set**

| | All macitentan |
|---|---|
| Analysis set: Macitentan Treated Set - female patients | 1241 |
| Ovarian cysts | |
| Patients with at least one AESI | 25 (2.0%) |
| Patients at least one AESI with: | |
| Serious | 13 (1.0%) |
| Leading to discontinuation of trt. | 0 |
| Fatal outcome | 1 (0.1%) |
| Number of recurrent AESIs | 27 |
| Patient-years exposure | 3335.10 |
| Average annualized event rate | 0.0081 |
| Severity (worst)* | |
| Mild | 6 (0.5%) |
| Moderate | 10 (0.8%) |
| Severe | 8 (0.6%) |
| Missing | 1 (0.1%) |

Based on the completed and on-going studies
Completed studies: AC-055-302 (SERAPHIN DB), AC-055-303 (SERAPHIN OL), AC-055-305 (MAESTRO DB), AC-055-308 (MAESTRO OL), AC-055-404 (PORTICO DB), AC-055-404 (PORTICO OL), AC-055-401/402 (SYMPHONY OL and Extension), AC-055-310/311 (ORCHESTRA OL and Extension), AC-055-403 (REPAIR), AC-055-405 (OPTIMA), AC-065A308 (TRITON).
On-going study: AC-055-314 (UMBRELLA, cut-off date: 17OCT2021).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.

*Postmarketing data (from IBD to 17 October 2021)*

Cumulatively, 59 cases with events related to ovarian cysts have been received as of 17 October 2021. Taking into account the estimated exposure of 77,564 female patients, the

estimated cumulative reporting rate is 0.08%. Worldwide, about 7% of women have an ovarian cyst at some point in their lives. (Farghaly 2014). The most frequently reported event was ovarian cyst, in 27 of the 59 cases (45.8%).

MedDRA terms used in database search: Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Ovarian cysts.

Risk Factors and Risk Groups:

Ovarian cysts can occur at any age but are more common in reproductive years and have an increased occurrence in menarchal females due to endogenous hormone production (Mobeen 2021).

Simple ovarian cysts are common incidental findings in women ≥55 years of age because of the frequent use of high-resolution transvaginal ultrasound for ovarian cancer screening (Greenlee 2010). Hypo- and hyperthyroidism (autoimmune or not, as ovarian cyst is not considered a CTD) are risk factors, as well as obesity.

Other risk factors include infertility treatment, tamoxifen, pregnancy, maternal gonadotropins, cigarette smoking, and tubal ligation. Patients treated with gonadotropins or other ovulation induction agents may develop cysts as part of ovarian hyperstimulation syndrome (Mobeen 2021).

Preventability:

Not applicable.

Impact on the Risk-Benefit Balance of the Product:

Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Complications of ovarian cyst include cyst rupture, cyst hemorrhage and cyst torsion. Ovarian neoplasms are usually benign in premenopausal women. In postmenopausal patients with unilocular cysts, malignancy may develop in 0.3% of cases.

Annex 1 MedDRA Term:

SMQ: Ovarian neoplasms, malignant, and unspecified (broad).

**Important Potential Risk: Pulmonary edema associated with pulmonary veno-occlusive disease (PVOD)**

Potential Mechanisms:

Specific PAH therapies may be associated with a risk of pulmonary edema at any time during the therapy.

Evidence Source(s) and Strength of Evidence:

Pulmonary edema following administration of pulmonary vasodilators used for the treatment of PAH could be due to previously unrecognized secondary angioproliferative processes caused by post-capillary obstruction, eg, PVOD, and/or due to combined pre-capillary and post-capillary pulmonary hypertension (Galiè 2015c, Galiè 2016, Opitz 2016).

Pulmonary edema has been seen during clinical experience with other pulmonary vasodilators (ERAs, PDE-5 inhibitors, riociguat, prostacyclin and its analogs).

Fluid accumulation in the lungs has been reported with medicines that dilate blood vessels when used in patients with previously undiagnosed PVOD, which may be associated with PAH. There are no indications that macitentan is specifically implicated in this respect. However, should signs of fluid accumulation in the lungs occur when macitentan is administered in patients with PAH, the possibility of associated veno-occlusive disease should be considered.

## Characterization of the Risk:

### *Randomized, double-blind studies*

**Table SVII.11: Important Potential Risk (Pulmonary edema associated with PVOD): Treatment-emergent Adverse Event of Special Interest in RDB Studies; RDB Safety Set**

| | All RDB studies | |
|---|---|---|
| | Macitentan 10 mg | Placebo |
| Analysis set: RDB Safety Set | 399 | 403 |
| Pulmonary edema associated with PVOD | | |
| Patients with at least one AESI | 2 (0.5%) | 0 |
| Relative Risk | NE | |
| 95% confidence interval | | |
| Patients at least one AESI with: | | |
| Serious | 1 (0.3%) | 0 |
| Leading to discontinuation of trt. | 1 (0.3%) | 0 |
| Fatal outcome | 0 | 0 |
| Number of recurrent AESIs | 2 | 0 |
| Patient-years exposure | 526.16 | 451.11 |
| Average annualized event rate | 0.0038 | 0.0000 |
| Severity (worst)* | | |
| Mild | 0 | 0 |
| Moderate | 2 (0.5%) | 0 |
| Severe | 0 | 0 |

Based on the completed RDB studies: AC-055-302 (SERAPHIN DB), AC-055-305 (MAESTRO DB) and AC-055-404 (PORTICO DB).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.
NE = Non-Estimable

*All studies*

**Table SVII.12: Important Potential Risk (Pulmonary edema associated with PVOD): Treatment-emergent Adverse Event of Special Interest in Macitentan-treated Patients; Macitentan Treated Set**

| | |
|---|---|
| Analysis set: Macitentan Treated Set | 1667 |
| Pulmonary edema associated with PVOD | |
| Patients with at least one AESI | 14 (0.8%) |
| Patients at least one AESI with: | |
| Serious | 8 (0.5%) |
| Leading to discontinuation of trt. | 2 (0.1%) |
| Fatal outcome | 3 (0.2%) |
| Number of recurrent AESIs | 15 |
| Patient-years exposure | 4284.16 |
| Average annualized event rate | 0.0035 |
| Severity (worst)* | |
| Mild | 1 (0.1%) |
| Moderate | 8 (0.5%) |
| Severe | 4 (0.2%) |
| Missing | 1 (0.1%) |

Based on the completed and on-going studies
Completed studies: AC-055-302 (SERAPHIN DB), AC-055-303 (SERAPHIN OL), AC-055-305 (MAESTRO DB), AC-055-308 (MAESTRO OL), AC-055-404 (PORTICO DB), AC-055-404 (PORTICO OL), AC-055-401/402 (SYMPHONY OL and Extension), AC-055-310/311 (ORCHESTRA OL and Extension), AC-055-403 (REPAIR), AC-055-405 (OPTIMA), AC-065A308 (TRITON).
On-going study: AC-055-314 (UMBRELLA, cut-off date: 17OCT2021).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.

*Postmarketing data (from IBD to 17 October 2021)*

In the postmarketing setting up to 17 October 2021, 30 cases were reported related to pulmonary edema in patients with a history or an event of PVOD.

In 15 cases, pulmonary edema was reported for a patient with a known history of PVOD; in the other 11 cases, a suspicion of PVOD was raised, or PVOD was diagnosed, when the patients experienced pulmonary edema. Macitentan was discontinued in 21 cases, action taken was not reported in 4 cases, and macitentan remained ongoing in 5 cases.

MedDRA terms used in database search: Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Pulmonary edema associated with PVOD.

Risk Factors and Risk Groups:

Patients with previously undiagnosed PVOD and on concurrent medications leading to pulmonary vasodilation.

Preventability:

Undiagnosed pre-existing PVOD or post-capillary pulmonary arterial disease may unmask itself with administration of PAH-specific therapies that are pulmonary vasodilators. The use of any PAH-specific therapies in patients with PVOD may therefore lead to pulmonary edema.

The following information is included in the SmPC:

Section 4.4 – Special warnings and precautions for use

"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."

Impact on the Risk-Benefit Balance of the Product:

Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Might require hospitalization.

Annex 1 MedDRA Term:

PT: Pulmonary veno-occlusive disease.

**Important Potential Risk: Testicular Disorders and Male Infertility**

Potential Mechanisms:

The main morphological change after treatment with macitentan was dilation of seminiferous tubules. The mechanism is probably related to pharmacodynamics of ERAs. For more information, see Module SII.

Evidence Source(s) and Strength of Evidence:

In animal studies, macitentan had small effects on the testicular function of male rats. The fertility of the animals was not affected. Decreases in sperm count have been observed in patients taking ERAs. Macitentan, like other ERAs, may have an adverse effect on spermatogenesis in men.

## Characterization of the Risk:

### *Randomized, double-blind studies*

**Table SVII.13: Important Potential Risk (Testicular disorders and male infertility): Treatment-emergent Adverse Event of Special Interest in RDB Studies; RDB Safety Set**

| | Macitentan 10 mg | Placebo |
|---|---|---|
| Analysis set: RDB Safety Set - male patients | 102 | 131 |
| Testicular disorders and male infertility | | |
| Patients with at least one AESI | 0 | 0 |
| Relative Risk | NE | |
| 95% confidence interval | | |
| Patients at least one AESI with: | | |
| Serious | 0 | 0 |
| Leading to discontinuation of trt. | 0 | 0 |
| Fatal outcome | 0 | 0 |
| Number of recurrent AESIs | 0 | 0 |
| Patient-years exposure | 108.51 | 122.95 |
| Average annualized event rate | 0.0000 | 0.0000 |
| Severity (worst)* | | |
| Mild | 0 | 0 |
| Moderate | 0 | 0 |
| Severe | 0 | 0 |

Based on the completed RDB studies: AC-055-302 (SERAPHIN DB), AC-055-305 (MAESTRO DB) and AC-055-404 (PORTICO DB).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.
NE = Non-Estimable

*All studies*

**Table SVII.14: Important Potential Risk (Testicular disorders and male infertility): Treatment-emergent Adverse Event of Special Interest in Macitentan-treated Male Patients; Macitentan Treated Set**

| | All macitentan |
|---|---|
| Analysis set: Macitentan Treated Set - male patients | 426 |
| Testicular disorders and male infertility | |
| Patients with at least one AESI | 1 (0.2%) |
| Patients at least one AESI with: | |
| Serious | 0 |
| Leading to discontinuation of trt. | 0 |
| Fatal outcome | 0 |
| Number of recurrent AESIs | 1 |
| Patient-years exposure | 949.06 |
| Average annualized event rate | 0.0011 |
| Severity (worst)* | |
| Mild | 0 |
| Moderate | 1 (0.2%) |
| Severe | 0 |

Based on the completed and on-going studies
Completed studies: AC-055-302 (SERAPHIN DB), AC-055-303 (SERAPHIN OL), AC-055-305 (MAESTRO DB), AC-055-308 (MAESTRO OL), AC-055-404 (PORTICO DB), AC-055-404 (PORTICO OL), AC-055-401/402 (SYMPHONY OL and Extension), AC-055-310/311 (ORCHESTRA OL and Extension), AC-055-403 (REPAIR), AC-055-405 (OPTIMA), AC-065A308 (TRITON).
On-going study: AC-055-314 (UMBRELLA, cut-off date: 17OCT2021).
* The event experienced by the patient with the worst severity is used.
Adverse events are coded using MedDRA Version 24.0.

One suspected unexpected serious adverse reaction related to the important potential risk of testicular disorders and male infertility has been reported from AC-055H302 (RUBATO open-label), a prospective, multicenter, single-arm, open-label, long-term study assessing the safety, tolerability, and effectiveness of macitentan in Fontan-palliated adult and adolescent subjects following treatment in the double-blind study (AC-055H301).[1] In the double-blind study, this subject was randomized to and received placebo. This subject was found to have a decrease in sperm concentration 1 year after initiation of macitentan in the open-label study. Although the assessment of this event is confounded by the subject's pre-existing history of fertility issues (the subject was trying to have a child approximately 1 year before enrollment into the double-blind phase and for approximately 2 years before initiation of macitentan), based on the known nonclinical findings and class effects, a causal association between macitentan and the event of sperm count decrease could not be excluded.

*Postmarketing data (from IBD to 17 October 2021)*

[1] Study AC-055H301 (RUBATO) was a prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group study assessing the efficacy and safety of macitentan in Fontan-palliated adult and adolescent subjects. Following 52 weeks of treatment in this study, eligible subjects were allowed to take part in Study AC-055H302 (RUBATO open-label).

Cumulatively, from IBD to 17 October 2021, 9 cases were received from postmarketing sources.

The reported events were infertility (2), sperm concentration decreased (2), varicocele (2), blood testosterone abnormal (1), semen discolouration (1), and testicular disorder (1). Of these 9 cases, 3 cases, reporting sperm concentration decreased (2) and infertility (1), reported confounding factors, including advanced age and history of dialysis. Two cases, reporting varicocele, reported latency of approximately 5 months and 9 months, respectively. The remaining 4 cases, reporting blood testosterone abnormal, infertility, semen discolouration, and testicular disorder, reported insufficient information for assessment. Taking into account the estimated exposure of 31,153 male patients, the estimated cumulative reporting rate is 0.03%.

Infertility is defined as the inability to conceive after 12 months of regular, unprotected intercourse (WHO 2020). It is thought not currently possible to determine an unbiased prevalence of male infertility in the general population, due to the very low quality of evidence (Barratt 2017); however, it has been estimated that infertility affects 8% to 12% of couples globally, with a male factor being a primary cause in 20% to 30% of couples and a contributing cause in a further 20% (Agarwal 2021).

MedDRA terms used in database search: Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Testicular disorders and male infertility.

Risk Factors and Risk Groups:

Male patients.

Preventability:

Not applicable.

Impact on the Risk-Benefit Balance of the Product:

Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

None.

Annex 1 MedDRA Term:

SMQ: Fertility disorders (broad).

## SVII.3.2. Presentation of the Missing Information

| |
|---|
| Missing information: Pediatric patients |
| Evidence source: Only a small number of adolescent subjects (aged between 12-17 years) and children below 12 years have participated in clinical studies. Postmarketing reports are the main source of information on this population. Study AC-055-312 (TOMORROW) is ongoing and will help to characterize the safety profile of macitentan in children.<br><br>As of the cut-off date for the PBRER/ Periodic Safety Update Report (PSUR) (17 October 2021), case reports had been received for 54 pediatric study participants (3 neonates, 19 children, 32 adolescents), as well as for 930 pediatric patients treated with commercial macitentan. These included 454 adolescents, 321 children aged 2-11 years, and 155 infants below 2 years.<br><br>Information regarding doses of macitentan administered and the body weight/height of the pediatric patients treated was unavailable in the majority of cases reported with AEs. A poster presentation at a local Austrian workshop (Baumgartner 2017) showed data for 47 pediatric patients (6 below 1 year of age, 15 aged 1-10 years, and 26 aged >10 years) from 3 centers in Austria, and mentioned starting/maintenance doses of 1 mg/5 mg for babies <1 year, 3-5 mg/5-10 mg for children aged up to 10 years, and 10 mg/10 mg for patients >10 years of age, respectively. The authors specified that severe arterial hypotension, anemia, and significant elevation of liver enzymes were not observed.<br><br>Case reports for pediatric patients exposed to commercial macitentan (930 cases) included 165 cases only referring to off-label use without AE, and 6 cases of accidental exposure by a child without AE. Among the remaining 757 cases, the overall safety profile in pediatric patients appeared to be no different than that observed in adult/elderly patients. The nature of the reported events in pediatric patients was similar to other age groups, and consistent with expected events in patients with PAH and its associated co-morbidities.<br><br>There is no evidence that the safety profile is expected to be different than that in the general (adult) target population. |
| Population in need of further characterization: Pediatric patients under the age of 18 years. |

# PART II: SAFETY SPECIFICATION

## Module SVIII: Summary of the Safety Concerns

**Table SVIII.1: Summary of Safety Concerns**

| | |
|---|---|
| **Important Identified Risks** | Anemia, decrease in hemoglobin concentration |
| | Hepatotoxicity |
| | Teratogenicity |
| | Symptomatic hypotension |
| **Important Potential Risks** | Menstrual disorders (primarily bleeding) |
| | Ovarian cysts |
| | Pulmonary edema associated with PVOD |
| | Testicular disorders and male infertility |
| **Missing Information** | Pediatric patients |

# PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

## III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

**Specific Follow-up Questionnaires for Safety Concerns**

| Safety Concern | Purpose/Description |
|---|---|
| Teratogenicity | Each pregnancy is followed up to final outcome. Pregnancy information (including maternal and baby information) is collected using the Macitentan Pregnancy and Outcome Follow-Up Questionnaire (TV-eFRM-11818).<br>Closely monitor compliance with the labelling pregnancy contraindication and further characterize the risk if reported. |
| Menstrual disorders (primarily bleeding) | Topic of interest questionnaire (TOIQ) TV-TFUQ-00169 to collect information on menstrual disorders in order to closely monitor and further characterize the risk and assess causal relationship. |
| Ovarian cysts | Topic of interest questionnaire TV-TFUQ-00170 to collect information on ovarian cysts in order to closely monitor and further characterize the risk and assess causal relationship. |

**Other Forms of Routine Pharmacovigilance Activities**

| Activity | Objective/Description | Milestones |
|---|---|---|
| Not applicable | Not applicable | Not applicable |

## III.2. Additional Pharmacovigilance Activities

Not applicable.

## III.3. Summary Table of Additional Pharmacovigilance Activities

Not applicable.

# PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no ongoing or planned imposed postauthorization efficacy studies included in the macitentan pharmacovigilance plan.

# PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

## Risk Minimization Plan

## V.1. Routine Risk Minimization Measures

**Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern**

| Safety Concern | Routine Risk Minimization Activities |
|---|---|
| Anemia, decrease in hemoglobin concentration | **Routine risk communication:**<br>SmPC section 4.4 'Special warnings and precautions for use'<br>SmPC section 4.8 'Undesirable effects'<br>Package Leaflet (PL) section 2 'What you need to know before you take Opsumit – Warnings and precautions – Take special care with Opsumit'<br>PL section 4 'Possible side effects'<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>"Initiation of Opsumit is not recommended in patients with severe anemia. It is recommended that hemoglobin concentrations be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated." (SmPC section 4.4)<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Medicinal product subject to restricted medical prescription. |
| Hepatotoxicity | **Routine risk communication:**<br>SmPC section 4.3 'Contraindication' and PL section 2, 'What you need to know before you take Opsumit'<br>SmPC section 4.4 'Special Warnings and Precautions for Use and PL section 2, 'What you need to know before you take Opsumit'<br>SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects'<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>"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 (eg, jaundice), Opsumit treatment should be discontinued.<br>Reinitiation of Opsumit 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." (SmPC section 4.4)<br>**Other routine risk minimization measures beyond the Product Information:** |

| | |
|---|---|
| | Legal status: Medicinal product subject to restricted medical prescription. |
| Teratogenicity | **Routine risk communication:**<br>SmPC section 4.3 'Contraindication' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Opsumit'<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>"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 4.6). 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." (SmPC section 4.4)<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Medicinal product subject to restricted medical prescription. |
| Symptomatic hypotension | **Routine risk communication:**<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects'<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>"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)." (SmPC section 4.4)<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Medicinal product subject to restricted medical prescription. |
| Menstrual disorders (primarily bleeding) | **Routine risk communication:**<br>None.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other routine risk minimization measures beyond the Product Information:** |

| | |
|---|---|
| | Legal status: Medicinal product subject to restricted medical prescription. |
| Ovarian cysts | **Routine risk communication:**<br>None.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Medicinal product subject to restricted medical prescription. |
| Pulmonary edema associated with PVOD | **Routine risk communication:**<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Medicinal product subject to restricted medical prescription. |
| Testicular disorders and male infertility | **Routine risk communication:**<br>SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Opsumit'<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Medicinal product subject to restricted medical prescription. |
| Pediatric patients | **Routine risk communication:**<br>SmPC sections 4.2 'Posology and method of administration' and PL section 2 'What you need to know before you take Opsumit'<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None.<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Medicinal product subject to restricted medical prescription. |

## V.2. Additional Risk Minimization Measures

### Educational tools (patient card)

| **Educational tools (patient card)** | |
|---|---|
| **Objective(s):** | This additional risk minimization activity aims:<br>• To educate patients about the risks associated with OPSUMIT, with an emphasis on teratogenicity and hepatotoxicity.<br>• To inform patients where to obtain more information about their treatment.<br>• To educate patients on the need to report immediately to their prescribing physician any pregnancy that may occur, as well as symptoms and signs of any potential ADR. |
| **Rationale for the additional risk minimization activity:** | These efforts reinforce patient knowledge regarding the safe use of OPSUMIT, thereby mitigating the risks associated with OPSUMIT treatment. |
| **Target audience and planned distribution path:** | The patient card is provided as part of the product packaging. |
| **Plans to evaluate the effectiveness of the interventions and criteria for success:** | Plans to evaluate the effectiveness of the intervention:<br>• Reporting trend analyses from postmarketing data are to be monitored in the PSUR. Assessments are to be done at the end of the PSUR reporting interval.<br>Criteria for success:<br>• Stable reporting trend analysis from postmarketing safety data is the criterion for success. |

## V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

## V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

**Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern**

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Anemia, decrease in hemoglobin concentration | **Routine risk minimization measures:**<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects'<br>Recommendation to not use Opsumit in patients with severe anemia and recommendation for monitoring of hemoglobin concentration are included in SmPC Section 4.4<br>Legal status: medicinal product subject to restricted medical prescription<br>**Additional risk minimization measures:**<br>None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None.<br>**Additional pharmacovigilance activities:**<br>None. |
| Hepatotoxicity | **Routine risk minimization measures:**<br>SmPC section 4.3 'Contraindication' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects'<br>Instructions for liver function monitoring and actions to be taken in case of elevated hepatic enzymes are provided in SmPC Section 4.4<br>Legal status: medicinal product subject to restricted medical prescription | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None.<br>**Additional pharmacovigilance activities:**<br>None. |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | **Additional risk minimization measures:**<br>Risk minimization tools (patient card) | |
| Teratogenicity | **Routine risk minimization measures:**<br>SmPC section 4.3 'Contraindication' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Opsumit'<br>Instructions for the use of Opsumit in women of childbearing potential and recommendation for monthly pregnancy tests during treatment are provided in SmPC section 4.4<br>Legal status: medicinal product subject to restricted medical prescription<br>**Additional risk minimization measures:**<br>Risk minimization tools (patient card) | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Macitentan Pregnancy and Outcome Follow-Up Questionnaire (TV-eFRM-11818).<br>**Additional pharmacovigilance activities:**<br>None. |
| Symptomatic hypotension | **Routine risk minimization measures:**<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects'<br>Advice on the use of Opsumit in patients with renal impairment who are at risk of experiencing hypotension and recommendation for monitoring blood pressure are provided in SmPC Section 4.4<br>Legal status: medicinal product | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None.<br>**Additional pharmacovigilance activities:**<br>None. |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | subject to restricted medical prescription<br><br>**Additional risk minimization measures:**<br>None. | |
| Menstrual disorders (primarily bleeding) | **Routine risk minimization measures:**<br>Legal status: medicinal product subject to restricted medical prescription<br>**Additional risk minimization measures:**<br>None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>TOIQ.<br>**Additional pharmacovigilance activities:**<br>None. |
| Ovarian cysts | **Routine risk minimization measures:**<br>Legal status: medicinal product subject to restricted medical prescription<br>**Additional risk minimization measures:**<br>None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>TOIQ.<br>**Additional pharmacovigilance activities:**<br>None. |
| Pulmonary edema associated with PVOD | **Routine risk minimization measures:**<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>Legal status: medicinal product subject to restricted medical prescription<br>**Additional risk minimization measures:**<br>None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None.<br>**Additional pharmacovigilance activities:**<br>None. |
| Testicular disorders and male infertility | **Routine risk minimization measures:**<br>SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Opsumit'<br>Legal status: medicinal product subject to restricted medical prescription | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None.<br>**Additional pharmacovigilance activities:**<br>None. |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | **Additional risk minimization measures:**<br>None. | |
| Pediatric patients | **Routine risk minimization measures:**<br>SmPC sections 4.2 'Posology and method of administration' and PL section 2 'What you need to know before you take Opsumit'<br>Legal status: medicinal product subject to restricted medical prescription<br>**Additional risk minimization measures:**<br>None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None.<br>**Additional pharmacovigilance activities:**<br>None. |

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## Summary of Risk Management Plan for OPSUMIT (macitentan)

This is a summary of the risk management plan (RMP) for OPSUMIT. The RMP details important risks of OPSUMIT, how these risks can be minimized, and how more information will be obtained about OPSUMIT's risks and uncertainties (missing information).

OPSUMIT's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how OPSUMIT should be used.

This summary of the RMP for OPSUMIT should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of OPSUMIT's RMP.

## I. The Medicine and What it is Used For

OPSUMIT is authorized for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of World Health Organization Functional Class II to III (see SmPC for the full indication). It contains macitentan as the active substance and it is given orally once daily.

Further information about the evaluation of OPSUMIT's benefits can be found in OPSUMIT's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002697/human_med_001717.jsp&mid=WC0b01ac058001d124

## II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of OPSUMIT, together with measures to minimize such risks and the proposed studies for learning more about OPSUMIT's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;

Important advice on the medicine's packaging;

The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of OPSUMIT, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of OPSUMIT is not yet available, it is listed under 'missing information' below.

## II.A. List of Important Risks and Missing Information

Important risks of OPSUMIT are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of OPSUMIT. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

| **List of Important Risks and Missing Information** | |
|---|---|
| Important identified risks | Anemia, decrease in hemoglobin concentration<br>Hepatotoxicity<br>Teratogenicity<br>Symptomatic hypotension |
| Important potential risks | Menstrual disorders (primarily bleeding)<br>Ovarian cysts<br>Pulmonary edema associated with pulmonary veno-occlusive disease (PVOD)<br>Testicular disorders and male infertility |
| Missing information | Pediatric patients |

## II.B. Summary of Important Risks

| **Important Identified Risk: Anemia, decrease in hemoglobin concentration** | |
|---|---|
| Evidence for linking the risk to the medicine | Macitentan and medicines of the same chemical class may reduce the blood hemoglobin level. Blood transfusion may be required in some cases. In the pivotal Phase 3 study of macitentan in PAH (SERAPHIN), a clinically relevant decrease in hemoglobin concentration was reported in 8.7% of macitentan-treated subjects and 3.4% of placebo-treated subjects. |
| Risk factors and risk groups | General risk factors for anemia are, eg, iron deficiency, history of anemia, concomitant use of platelet inhibitors, anticoagulants, steroids, and pre-existing or concurrent bleeding. |
| Risk minimization measures | Routine risk minimization measures:<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects'<br>Recommendation to not use Opsumit in patients with severe anemia and recommendation for monitoring of hemoglobin concentration are included in SmPC Section 4.4<br>Legal status: medicinal product subject to restricted medical prescription<br>Additional risk minimization measures:<br>None. |

| **Important Identified Risk: Hepatotoxicity** | |
|---|---|
| Evidence for linking the risk to the medicine | Macitentan, like other medicines of the same chemical class, may affect the liver.<br>The mechanism of this adverse effect is unclear. Interruption or stopping treatment may be necessary. |
| Risk factors and risk groups | Unknown in patients with alanine aminotransferase/aspartate aminotransferase >3×upper limit of normal at baseline or patients with moderate or severe liver impairment, as they were excluded from clinical trials with macitentan. |
| Risk minimization measures | Routine risk minimization measures:<br>SmPC section 4.3 'Contraindication' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects'<br>Instructions for liver function monitoring and actions to be taken in |

| | |
|---|---|
| | case of elevated hepatic enzymes are provided in SmPC Section 4.4<br>Legal status: medicinal product subject to restricted medical prescription<br>Additional risk minimization measures:<br>Risk minimization tools (patient card) |

| **Important Identified Risk: Teratogenicity** | |
|---|---|
| Evidence for linking the risk to the medicine | According to results from animal studies, macitentan and medicines of the same chemical class may harm unborn babies conceived before starting or during treatment. Based on a limited number of pregnancies observed in women exposed to macitentan, no translation of this risk to humans has been observed. |
| Risk factors and risk groups | All women of childbearing potential on macitentan therapy who are not using a reliable method of contraception. |
| Risk minimization measures | Routine risk minimization measures:<br>SmPC section 4.3 'Contraindication' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Opsumit'<br>Instructions for the use of Opsumit in women of childbearing potential and recommendation for monthly pregnancy tests during treatment are provided in SmPC section 4.4<br>Legal status: medicinal product subject to restricted medical prescription<br>Additional risk minimization measures:<br>Risk minimization tools (patient card) |

| **Important Identified Risk: Symptomatic hypotension** | |
|---|---|
| Evidence for linking the risk to the medicine | Macitentan, like other medicines of the same chemical class, widens blood vessels, and blood pressure (BP) decrease has been reported.<br>In a long-term double-blind study (SERAPHIN), decrease of BP was reported in 7.0% of macitentan-treated subjects and 4.4% of placebo-treated subjects.<br>Among patients who receive prescribed macitentan, 1–2 in 100 report symptomatic hypotension. The most frequent clinical sign of hypotension is dizziness.<br>Macitentan may lead to more reduction of BP in patients with kidney problems. |

| | |
|---|---|
| Risk factors and risk groups | Patients with moderate or severe renal impairment. |
| Risk minimization measures | Routine risk minimization measures:<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects'<br>Advice on the use of Opsumit in patients with renal impairment who are at risk of experiencing hypotension and recommendation for monitoring blood pressure are provided in SmPC Section 4.4<br>Legal status: medicinal product subject to restricted medical prescription<br>Additional risk minimization measures:<br>None. |

| **Important Potential Risk: Menstrual disorders (primarily bleeding)** | |
|---|---|
| Evidence for linking the risk to the medicine | Among female PAH subjects participating in the pivotal clinical study (AC-055-302, SERAPHIN), menstrual disorders (primarily bleeding) occurred in 5.1% of the macitentan 10 mg-treated subjects compared to 1.1% of the placebo-treated subjects. Most of the subjects were receiving anticoagulants and/or other medications with known side effects of bleeding at the same time. At present, a causal relationship between macitentan and menstrual disorders, primary bleeding, is difficult to establish. |
| Risk factors and risk groups | Risk factors include a previous history of menstrual disorders / bleeding or concomitant treatment with drugs known to cause bleeding.<br>Endocrine causes of menorrhagia include thyroid and adrenal gland dysfunction, pituitary tumors, anovulatory cycles, polycystic ovarian syndrome, obesity, and vasculature imbalance (Shaw 2018). |
| Risk minimization measures | Routine risk minimization measures:<br>Legal status: medicinal product subject to restricted medical prescription<br>Additional risk minimization measures:<br>None. |

| **Important Potential Risk: Ovarian cysts** | |
|---|---|
| Evidence for linking the risk to the medicine | Among female PAH subjects participating in the pivotal clinical study (AC-055-302, SERAPHIN), ovarian cysts were reported in few macitentan-treated subjects. Most of these subjects had other diseases known to be risk factors for ovarian cysts, as documented |

| | |
|---|---|
| | in their medical history. At present, a causal relationship between macitentan and ovarian cyst is difficult to establish. |
| Risk factors and risk groups | Ovarian cysts can occur at any age but are more common in reproductive years and have an increased occurrence in menarchal females due to endogenous hormone production (Mobeen 2021).<br><br>Simple ovarian cysts are common incidental findings in women ≥55 years of age because of the frequent use of high-resolution transvaginal ultrasound for ovarian cancer screening (Greenlee 2010). Hypo- and hyperthyroidism (autoimmune or not, as ovarian cyst is not considered a connective tissue disease) are risk factors, as well as obesity.<br><br>Other risk factors include infertility treatment, tamoxifen, pregnancy, maternal gonadotropins, cigarette smoking, and tubal ligation. Patients treated with gonadotropins or other ovulation induction agents may develop cysts as part of ovarian hyperstimulation syndrome (Mobeen 2021). |
| Risk minimization measures | Routine risk minimization measures:<br>Legal status: medicinal product subject to restricted medical prescription<br>Additional risk minimization measures:<br>None. |

| **Important Potential Risk: Pulmonary edema associated with PVOD** | |
|---|---|
| Evidence for linking the risk to the medicine | Pulmonary edema following administration of pulmonary vasodilators used for the treatment of PAH could be due to previously unrecognized secondary angioproliferative processes caused by post-capillary obstruction, eg, PVOD, and/or due to combined pre-capillary and post-capillary pulmonary hypertension (Galiè 2015c, Galiè 2016, Opitz 2016).<br><br>Pulmonary edema has been seen during clinical experience with other pulmonary vasodilators (endothelin receptor antagonists [ERAs], phosphodiesterase-5 inhibitors, riociguat, prostacyclin and its analogs).<br><br>Fluid accumulation in the lungs has been reported with medicines that dilate blood vessels when used in patients with previously undiagnosed PVOD, which may be associated with PAH. There are no indications that macitentan is specifically implicated in this respect. However, should signs of fluid accumulation in the lungs occur when macitentan is administered in patients with PAH, the |

| | |
|---|---|
| | possibility of associated veno-occlusive disease should be considered. |
| Risk factors and risk groups | Patients with PVOD. |
| Risk minimization measures | Routine risk minimization measures:<br>SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit'<br>Legal status: medicinal product subject to restricted medical prescription<br>Additional risk minimization measures:<br>None. |

| **Important Potential Risk: Testicular disorders and male infertility** | |
|---|---|
| Evidence for linking the risk to the medicine | In animal studies, macitentan had small effects on the testicular function of male rats. The fertility of the animals was not affected.<br>Decreases in sperm count have been observed in patients taking ERAs. Macitentan, like other ERAs, may have an adverse effect on spermatogenesis in men. |
| Risk factors and risk groups | Male patients. |
| Risk minimization measures | Routine risk minimization measures:<br>SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Opsumit'<br>Legal status: medicinal product subject to restricted medical prescription<br>Additional risk minimization measures:<br>None. |

| **Missing Information: Pediatric patients** | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>SmPC sections 4.2 'Posology and method of administration' and PL section 2 'What you need to know before you take Opsumit'<br>Legal status: medicinal product subject to restricted medical prescription<br>Additional risk minimization measures:<br>None. |

## II.C. Postauthorization Development Plan

### II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of OPSUMIT.

### II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for OPSUMIT.

# PART VII: ANNEXES

## Table of Contents

# Annex 4: Specific Adverse Drug Reaction Follow-up Forms

## Table of Contents

Macitentan Pregnancy and Outcome Follow-Up Questionnaire (TV-eFRM-11818)

Topic of Interest Questionnaire (TOIQ) for Menstrual Disorders (Heavy Menstrual Bleeding) (TV-TFUQ-00169)

Topic of Interest Questionnaire (TOIQ) for Ovarian Cyst (TV-TFUQ-00170)

## Follow-up Forms

Macitentan Pregnancy and Outcome Follow-Up Questionnaire

**INSTRUCTIONS:**

If you are receiving this form and the mother is currently pregnant, please complete Part I. This form will be sent again post-delivery date to obtain pregnancy outcome (Part II). If further additional space is needed, attach a blank continuation page, and enter the information on the continuation page. If a continuation page is needed ensure the local reference number is entered at the top of the continuation page.

If you are receiving this form and the mother has delivered the baby or is no longer pregnant (e.g., spontaneous abortion, elective abortion, etc.), please complete Part II. Please also provide Part I details if not previously completed.

| **(COMPANY USE ONLY** - complete prior to sending to health care professional**):** | |
|---|---|
| Operating Company: | J&J Product: |
| Local Report Number: | Date Received by J&J: (dd/mmm/yyyy) |
| Originating Country: | MFR # (if available): [MFR #] |
| Exposure: ☐ Maternal ☐ Paternal | |
| Protocol number:<br>Double Blind (code not broken): ☐ | |
| Study medication/product: | |
| Subject number:<br>Site #: | |

## Part I:

| **A. MATERNAL INFORMATION** | | | |
|---|---|---|---|
| Initials*:<br>Date of birth*: (dd/mmm/yyyy)<br>*This field not to be used for clinical trial reports<br>Age at time of exposure:<br>or Age Group: ☐ <14 years ☐14 years – 18 years ☐19 years+<br>Weight: ☐ Kg ☐ Lbs Height: ☐ Cm ☐ Inches | | | |
| Methods of Contraception: Please provide Serial/Model # and expiration date if applicable.<br>1.<br>2. | | | |
| Were there any relevant maternal risk factors in the home/work environment (such as chemical exposure, x-rays, history of miscarriages, etc.)? | No ☐ | Yes ☐ | If yes, describe: |

| **B. PRESENT PREGNANCY** | | | |
|---|---|---|---|
| 1. Date of mother's last menstrual period: (dd/mmm/yyyy) | | | |
| 2. Pregnancy confirmed on: (dd/mmm/yyyy) ☐ Beta Hcg ☐ Urine Test | | | |
| 3. Was the pregnancy test negative at the time of starting Macitentan? ☐ No ☐ Yes | | | |
| 4. Date of mother's first prenatal exam: (dd/mmm/yyyy) | | | |
| 5. Expected date of delivery: (dd/mmm/yyyy) | | | |
| 6. Is the mother experiencing any medical disorder/problems during this pregnancy? | No ☐ | Yes ☐ | If yes, describe: |

**MFR #** [MFR #]

**B. PRESENT PREGNANCY**

7. Is the mother continuing with Macitentan? ☐ No ☐ Yes ☐ N/A ☐ Unknown
Was the product taken correctly at the time of gestation? ☐ No ☐ Yes If **No**, explain:

8. Tick the explanation(s) for why the patient became pregnant during the use of Macitentan:
☐ Patient wished to become pregnant
☐ Failure of contraceptive method(s)
☐ Patient unwilling to use adequate contraceptive methods
☐ Risk of pregnancy may not have been fully understood
☐ Unknown
☐ Other (Specify):

9. List all medications mother used since date of last menstrual period (include J&J products and non-J&J products, prescription, over-the-counter, vitamins, and herbal preparations - list below).

| Medication (preferably generic name) | Route | Formulation | Dosing regimen | | | Start date | End Date or Ongoing | Exposure time in gestational weeks | Indication |
|---|---|---|---|---|---|---|---|---|---|
| | | | Amount | Unit | Freq. | | | | |
| **Macitentan:** | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| **Lot #:**<br>**Exp. Date:** (dd/mmm/yyyy) | | | | | | | | | |
| **Other Medications:** | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |

10. Was an ultrasound performed? ☐ No ☐ Yes
If yes, provide date and results of each ultrasound: (dd/mm/yyyy)

11. Were any other investigations/diagnostics performed, such as amniocentesis, blood test, urine test, etc.? ☐ No ☐ Yes
If yes, provide date test performed and results of each test.
(dd/mmm/yyyy) and Result

12. What is the clinical condition of the foetus(es)?

| Unknown | Normal | Abnormal | If abnormal, describe: |
|---|---|---|---|
| ☐ | ☐ | ☐ | |

13. What is the status of the current pregnancy?
☐ Continuing
☐ Spontaneous abortion Date of abortion: (dd/mmm/yyyy)
☐ Elective abortion Date of procedure: (dd/mmm/yyyy)

**C. MATERNAL HISTORY**

1. Describe pertinent medical/obstetrical history (including but not limited to endocrine disorders, medical disorders or recent infections requiring treatment, infertility or use of fertility methods):

| 2. **Substance History** | **No** | **Yes** | **Select all that apply:** |
|---|---|---|---|
| Alcohol | ☐ | ☐ | Drinks per day: |
| Tobacco | ☐ | ☐ | Cigarettes per day: |
| Recreational drugs | ☐ | ☐ | Type of drug(s) and frequency: |

| 3. Is there any **family history** of congenital anomalies, significant obstetrical outcomes or hereditary disorders? | No ☐ | Yes ☐ | If yes, describe: |
|---|---|---|---|

**MFR #** [MFR #]

| D. PREVIOUS PREGNANCIES | | | |
|---|---|---|---|
| Has mother been pregnant before? No ☐ Yes ☐ | Gravida (include present pregnancy): | Para: | Abortions:<br>Induced: Spontaneous:<br>Gestational age: weeks days |
| | # Of normal outcomes: | # Of abnormal outcomes: | # Of unknown outcomes: |
| Describe any abnormal outcomes (include spontaneous abortion, ectopics, congenital anomalies, hereditary disorders, stillbirths or intrauterine death, etc.): | | | |
| In case of a previous abnormal pregnancy outcome, list all known medications used during the pregnancy: | | | |

| E. PATERNAL HISTORY | | | |
|---|---|---|---|
| **Substance History** | **No** | **Yes** | **Select all that apply:** |
| Alcohol | ☐ | ☐ | Drinks per day: |
| Tobacco | ☐ | ☐ | Cigarettes per day: |
| Recreational drugs | ☐ | ☐ | Type of drug(s) and frequency: |
| Was Macitentan used by father? | | | No ☐ Yes ☐ |

**Health Care Professional Information:**

Name: _____

Address: _____

Phone number: _____

Fax number: _____

_____ Signature

Date: (dd/mmm/yyyy)

**Person Completing Report:**

Name: _____

Address: _____

Phone number: _____

Fax number: _____

_____ Signature

Date: (dd/mmm/yyyy)

**MFR #** [MFR #]

## Part II:

| A. COURSE AND OUTCOME OF PREGNANCY | | | |
|---|---|---|---|
| 1. Did the mother experience any medical problems during the pregnancy? | No ☐ | Yes ☐ | If yes, describe: |

Complete the below question if there were changes since completion of corresponding section in Part I. ☐ **No Changes**

2. List all medications the mother has used since last menses, until day of delivery. (Include J&J product and non-J&J products, prescription, over-the counter, vitamins and herbal preparations, but exclude medication used during labor and delivery.)

| Medication (preferably generic name) | Route | Formulation | Dosing regimen | | | Start date | End date or ongoing | Exposure time in gestational weeks | Indication |
|---|---|---|---|---|---|---|---|---|---|
| | | | Amt | Unit | Freq | | | | |
| **Macitentan:** | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| **Lot #:** **Exp. Date:** (dd/mmm/yyyy) | | | | | | | | | |
| **Other Medications:** | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | | |

3. Did the mother receive any **medication during labor and delivery**? (Include anesthesia, analgesia, labor induction meds.)

| Medication (preferably generic name) | Route | Formulation | Dosing regimen | | | Start date | End date or ongoing | Indication |
|---|---|---|---|---|---|---|---|---|
| | | | Amt | Unit | Freq | | | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | |
| | | | | | | (dd/mmm/yyyy) | (dd/mmm/yyyy) | |

| 4. Specify the outcome of pregnancy and complete the rest of the form as applicable: | | |
|---|---|---|
| a) Interrupted pregnancy No ☐ Yes ☐ | ☐ Spontaneous Abortion | (dd/mm/yyyy) |
| | ☐ Elective Abortion | (dd/mm/yyyy) |
| | ☐ Intrauterine Death (≥20 Gestational Weeks) | Interruption date: (dd/mm/yyyy) Gestational age: Weeks Days |
| Specify suspected cause for intrauterine death or spontaneous abortion (autopsy report if done) | | |
| Describe the developmental status of the fetus (include anomalies) | | |
| b) Uninterrupted pregnancy: | Delivery date: (dd/mm/yyyy) | |
| | Gestational age: Weeks Days | |
| What was the method of delivery? | ☐ Spontaneous ☐ Forceps ☐ Vacuum Extraction ☐ Caesarean Section ☐ Other, specify: | |

**MFR #** [MFR #]

| B. CHARACTERISTICS OF THE BABY | | | | |
|---|---|---|---|---|
| 1. General appearance: ☐ Mature | | | ☐ Premature | ☐ Postmature |
| 2. Sex: ☐ Male ☐ Female | Weight: lbs/kg oz/g | | Length: in/cm | Head circumference: cm |
| Apgar score: 1min: | 5min: | 10min: | | |
| 3. Clinical condition of the baby: | | | | |
| ☐ Normal newborn | | | | |
| ☐ Congenital anomaly* | | | | |
| ☐ Neonatal problem* | | | | |
| ☐ Neonatal death* ☐ Stillbirth* | Date of death: (dd/mm/yyyy) | | | |
| *Describe the details and the probable cause for the abnormal outcome: | | | | |

| | No | Yes | |
|---|---|---|---|
| 4. Was the baby's hospitalization prolonged? | ☐ | ☐ | If yes, describe: |
| 5. Did the baby receive any medical therapy different from normal newborn care? | ☐ | ☐ | If yes, describe: |
| 6. Is the baby being breastfed? | ☐ | ☐ | |

| | | |
|---|---|---|
| 7. Was any relationship suspected between the abnormal pregnancy outcome and the use of the macitentan? | ☐ Not related | ☐ Related |
| 8. Was any relationship suspected between the abnormal pregnancy outcome and the use of concomitant medications? ☐ No ☐ Yes (if yes, describe) | Describe: | |

**Topic of Interest Questionnaire (TOIQ) for Menstrual Disorders (Heavy Menstrual Bleeding)**

To the Health Care Provider: Complete this form as a supplement to the provided Health Care Professional Adverse Event Follow-Up Form.

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]

**1. Bleeding Event Details**

Any recent changes in pattern of menstrual bleeding? ☐ Yes ☐ No ☐ Unknown
If yes, provide details:
Regularly experienced heavy menstrual bleeding? ☐ Yes ☐ No ☐ Unknown
Experienced bleeding lasting seven (7) or more days per cycle? ☐ Yes ☐ No ☐ Unknown
Needed to change sanitary protection during the night? ☐ Yes ☐ No ☐ Unknown
Limited her daily activities due to heavy periods? ☐ Yes ☐ No ☐ Unknown
Causing the patient to miss school, work or family events? ☐ Yes ☐ No ☐ Unknown
Required medication (e.g., hormone therapy)? ☐ Yes ☐ No ☐ Unknown
If yes, provide details:
Has such medication improved the event? ☐ Yes ☐ No ☐ Unknown

**2. Additional Information Related to the Event**

Gynecologist's evaluation? ☐ Yes ☐ No ☐ Unknown
If yes, provide the date: [dd-MMM-yyyy]
Results:

Were any imaging studies relevant to the event performed (e.g., CT, MRI, abdominal/transvaginal ultrasound)?
☐ Yes ☐ No ☐ Unknown
If yes, specify and provide results:

Were other diagnostic procedures relevant to the event performed (e.g., uterine/cervical biopsy)?
☐ Yes ☐ No ☐ Unknown
If yes, specify and provide results:

Diagnosis of anemia? ☐ Yes ☐ No ☐ Unknown
If yes, provide the following (at the time of the event):

| | | | |
|---|---|---|---|
| RBC count: | $\times 10^{12}$/L | Date: | [dd-MMM-yyyy] |
| Hb: | g/dL | Date: | [dd-MMM-yyyy] |
| Hct: | % | Date: | [dd-MMM-yyyy] |
| Platelets: | $10^9$/L | Date: | [dd-MMM-yyyy] |

Did the patient receive blood transfusion? ☐ Yes ☐ No ☐ Unknown
If yes, provide details:
Type of transfusions:
Number of transfusions:
Date: [dd-MMM-yyyy]
Date: [dd-MMM-yyyy]

Attach additional pages as needed.

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TOIQ for Menstrual Disorders (Heavy Menstrual Bleeding)

**Topic of Interest Questionnaire (TOIQ) for Ovarian Cyst**

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form.

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]

**1. Event of Ovarian Cyst**

(a) How was it diagnosed? Specify details:

(b) Since product initiation, has the patient:

(i) Experienced irregularity of menstrual cycle? ☐ Yes ☐ No ☐ Unknown
If yes, provide details:

(ii) Experienced absence of her period? ☐ Yes ☐ No ☐ Unknown

(iii) Observed recent changes in the pattern of menstrual bleeding? ☐ Yes ☐ No ☐ Unknown
If yes, provide details:

(iv) Regularly experienced heavy menstrual bleeding? ☐ Yes ☐ No ☐ Unknown

**2. Additional Information Related to the Event**

a) Gynecologist's evaluation? ☐ Yes ☐ No ☐ Unknown
If yes, provide the date and results:
Date: [dd-MMM-yyyy]
Results:

b) Were any imaging studies relevant to the event performed (e.g., CT, MRI, abdominal/ transvaginal ultrasound)? ☐ Yes ☐ No ☐ Unknown
If yes, specify results:

c) Were other diagnostic procedures relevant to the event performed (e.g., uterine/cervical biopsy)? ☐ Yes ☐ No ☐ Unknown
If yes, specify and provide results:

**3. Patient's Medical History (prior to product initiation)**

Ovarian cyst ☐ Yes ☐ No ☐ Unknown
Polyps of the uterus or cervix ☐ Yes ☐ No ☐ Unknown
Polycystic ovarian syndrome ☐ Yes ☐ No ☐ Unknown
Intrauterine device ☐ Yes ☐ No ☐ Unknown
Gynecological surgery ☐ Yes ☐ No ☐ Unknown
If yes, specify:
Other pelvic or abdominal surgery ☐ Yes ☐ No ☐ Unknown
If yes, specify:
Number of pregnancies:
Number of children:
Infertility ☐ Yes ☐ No ☐ Unknown
Thyroid disorder ☐ Yes ☐ No ☐ Unknown
If yes, specify:
Cancer (within the past five [5] years) ☐ Yes ☐ No ☐ Unknown
If yes, specify:

MCN:

Family history ☐ Yes ☐ No ☐ Unknown
If yes, specify:
Other diseases (specify):

**4. Medication Details**

a) Treatment with product Start date:
Stop date:

b) Concomitant medication information
(i) Method of contraception (specify):

| **Method of Contraception** | **Start Date** (dd-MMM-yyyy) | **Stop Date** (dd-MMM-yyyy) |
|---|---|---|
| | | |
| | | |
| | | |

Attach additional pages as needed.

# Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

## Approved Key Messages of the Additional Risk Minimization Measures

1. Patient card:

The patient card includes the following key elements:

- That OPSUMIT is teratogenic in animals;
- That pregnant women must not take OPSUMIT;
- That women of childbearing potential must use reliable contraception;
- The need for monthly pregnancy tests;
- The need for regular monitoring of liver function because OPSUMIT has hepatotoxic potential.