Opsumit® 10 mg
macitentan

Frequently Asked Questions Brochure for Healthcare Professionals

ACTELION
A JANSSEN PHARMACEUTICAL COMPANY OF Johnson & Johnson

Contents

1. What is the purpose of this brochure?

These frequently asked questions (FAQs) are provided by Actelion Pharmaceuticals for prescribers and other healthcare professionals (HCPs) who are involved in the treatment of patients on Opsumit.

Treatment with Opsumit should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension (PAH).

This document will enable you to:

- **Understand what Opsumit is used for and how it should be used,**
- **Learn about identified risks associated with Opsumit, and how they should be prevented and managed,**
- **Understand potential side effects of Opsumit and how they should be prevented,**
- **Provide important safety information to patients**

This document summarises the most important information about Opsumit. Please also familiarize yourself with the complete Summary of Product Characteristics (SmPC) before prescribing or dispensing Opsumit.

2. What is Opsumit?

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

Macitentan is an orally active potent endothelin 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 endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.

3. What is Opsumit indicated for?

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class II to III.

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.

4. What dose of Opsumit should be used?

Opsumit should be taken orally at a dose of 10 mg once daily with or without food. Tablets are not breakable and should be taken whole, with water.

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

5. Should the dose of Opsumit be adjusted for patients with hepatic or renal impairment or the elderly?

Based on pharmacokinetic (PK) data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment.
There is no clinical experience with the use of Opsumit in PAH patients with moderate or severe hepatic impairment. Macitentan 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 x ULN); see sections 4.3 and 4.4).

Based on PK data, no dose adjustment is required in patients with renal impairment. There is no clinical experience with the use of Opsumit in PAH patients with severe renal impairment. Caution is recommended in this population. The use of Opsumit is not recommended in patients undergoing dialysis.

6. When is Opsumit contra-indicated?

Opsumit is contra-indicated in:

- **Patients with hypersensitivity to the active substance, soya or to any of the excipients listed in section 6.1 of the SmPC. Please note that the tablets contain lactose.**
- **Pregnant women**
- **Women of child-bearing potential who are not using reliable contraception**
- **Breastfeeding women**
- **Patients with severe hepatic impairment**
- **Patients with baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT) > 3 × ULN)**

7. What are the main risks associated with the use of Opsumit?

As with other ERAs, treatment with Opsumit is associated with a risk of anaemia, teratogenicity and hepatotoxicity.

8. How can the risk of anaemia be prevented and managed?

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 Opsumit 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.

If tests show a clinically significant decrease in haemoglobin or haematocrit, other causes should be excluded.

Please report clinically significant decreases in haemoglobin or haematocrit and adverse events to Actelion Drug Safety. Reporting can be done via the Actelion standard Adverse Drug Reaction, or by telephone (phone number: +356 23976333) or email (email address: pv@ammangion.com). Copies of the forms are provided within your prescriber kit.

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form available online at http://www.medicinesauthority.gov.mt/adrportal and sent to Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN or sent by email to: postlicensing.medicinesauthority@gov.mt.

9. What should I know about the risk of teratogenicity associated with Opsumit, and how can it be prevented?

There is no specific data or relevant clinical experience with respect to the teratogenic potential of Opsumit in the human foetus. However, developmental and reproductive toxicity studies in rabbits and rats showed that Opsumit is teratogenic at all doses tested in these animal species. In both species there were cardiovascular and mandibular arch fusion abnormalities.

The risk for humans remains unknown but appropriate precautions must be taken for women of childbearing potential. Opsumit is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception.

Monthly pregnancy tests in women of childbearing potential being treated with Opsumit are recommended to allow early detection of pregnancy. Ideally, pregnancy testing, prescription and dispensing of Opsumit should occur on the same day.

Women should not become pregnant for 1 month after discontinuation of Opsumit.

10. What is meant by women of childbearing potential?

"Woman of childbearing potential" means any woman who does not meet at least one of the following criteria:

- **Aged at least 50 years and naturally amenorrhoeic for at least 1 year (amenorrhoea following cancer therapy does not rule out child-bearing potential)**
- **Premature ovarian failure, confirmed by a specialist gynaecologist**
- **Other documented impairment of oviductal or uterine function that would cause sterility**
- **Previous bilateral salpingo-oophorectomy, or hysterectomy**
- **XY genotype, Turner syndrome, or uterine agenesis**

Women with oligomenorrhea, women who are peri-menopausal and young females who have begun to menstruate are considered to be of child-bearing potential.

11. What should I consider before prescribing Opsumit to a woman of childbearing potential?

Women of childbearing potential should not start treatment with Opsumit unless:

- **The absence of pregnancy has been verified**
- **Advice on contraception has been provided**
- **They are using a reliable method of contraception**
- **They continue to use reliable contraception while taking Opsumit and for one month after treatment discontinuation**

Monthly pregnancy tests are recommended. Ideally, pregnancy testing, prescription and dispensing of Opsumit should occur on the same day.

12. What is considered a reliable method of contraception?

The following are considered reliable methods of contraception:

- **Oral contraceptive, either combined or progestogen alone**
- **Injectable progestogen**
- **Implants of levonorgestrel**
- **Oestrogenic vaginal ring**
- **Percutaneous contraceptive patches**
- **Intrauterine device (IUD) or intraiterine system (IUS)**
- **Male partner sterilization (vasectomy with documentation of azoospermia)**
- **Tubal ligation**
- **Double barrier method: condom and occlusive cap (diaphragm or cervical/ vault caps) plus vaginal spermicidal agent (foam, gel, film, cream or suppository)**
- **No male partner**

13. What should I do in case a patient taking Opsumit becomes pregnant?

If a pregnancy occurs during Opsumit therapy, the risks to the foetus should be discussed with the patient and a decision taken whether to discontinue treatment, taking into account also the risk to the mother due to PAH.

If a pregnancy occurs during Opsumit therapy, please inform Actelion Drug Safety using a pregnancy reporting form available in your prescriber kit, or by telephone (phone number: +356 23976333) or email (email address: pv@ammangion.com).
All cases of pregnancy should be reported to Actelion.

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form available online at http://www.medicinesauthority.gov.mt/adrportal and sent to Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN or sent by email to: postlicensing.medicinesauthority@gov.mt.

14. What should I know about the risk of hepatotoxicity associated with Opsumit?

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) 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 (e.g., 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.

Please report clinically significant elevations of ALT and/or AST, or any other liver related adverse events to Actelion Drug Safety.
Reporting can be done via the Actelion standard Adverse Drug Reaction, or by telephone (phone number: +356 23976333) or email (email address: pv@ammangion.com).
Contact person: Mr Nigel Cauchi at A.M. Mangion Ltd.
Copies of the forms are provided within your prescriber kit.

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What other important safety information should I be aware of in order to minimize the risks associated with Opsumit?

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.

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 Opsumit is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered.

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

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

There is limited clinical experience in patients over the age of 75 years, and therefore Opsumit should be used with caution in this population.

Opsumit contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Opsumit contains lecithin derived from soya. If a patient is hypersensitive to soya, Opsumit must not be used

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What should I discuss with my patients, and what assessments need to be performed before initiating treatment with Opsumit?

A pregnancy test, liver function tests and measure of haemoglobin concentrations should be performed before initiation of treatment with Opsumit. Your role in educating patients about their new therapy and its possible effects and side effects is very important. You will need to inform patients about the important side effects associated with Opsumit, teach patients how to recognise relevant symptoms and signs of the side effects, and inform patients of the need to report any side effect that may occur to the prescribing physician immediately.

You also need to inform female patients of child-bearing potential of the risks to the foetus in case of pregnancy both from PAH and from Opsumit, and of the need to:

- **use a reliable method of contraception,**
- **have monthly pregnancy tests**
- **report pregnancy immediately if it occurs**

It is very important that you remind patient about these important safety information regularly during their treatment with Opsumit.

17. How is Opsumit supplied?

Opsumit is available in the form of white, biconvex, round film-coated tablets with "10" on both sides. Opsumit is supplied in blister packs of 15 or 30 film-coated tablets, or in bottles of 30 tablets.

18. How should Opsumit be stored?

Opsumit must be stored at a temperature not exceeding 30°C. Unexposed tablets have a shelf life of 5 years.

19. What is the role of the prescribing checklist?

The prescribing checklist is a tool designed to help you identify key risk information that should be evaluated and discussed with the patient before prescribing Opsumit.

The completed checklist can be stored with the patient chart as helpful evidence that the patient has been informed of the risks associated to treatment with Opsumit.

20. What is the patient card?

The patient card is a small, folding, credit-card sized card, which should be carried by the patients at all times and will contain key information about their treatment:

- **A reminder of the need to report immediately any pregnancy or side effect that may occur during treatment.**
- **Information regarding precautions to be taken to minimize the risk of teratogenicity, i.e. the need to:**
  - **use a reliable method of contraception**
  - **have monthly pregnancy tests**
  - **report pregnancy immediately if it occurs**
- **Information regarding the risks of anaemia and hepatotoxicity, and in particular the importance to contact the prescribing physician in case the patient experiences symptoms of liver injury.**
- **Key information about how to take Opsumit**
- **Name and contact details of the prescribing physician**

Paper copies of the patient card are provided within your prescriber kit. You are encouraged to fill in your contact details on a patient card, give it to each patient receiving Opsumit treatment for the first time or to patients who ask for a copy, and encourage them to carry it with them at all times.

A copy of the patient card is also provided within each box of Opsumit.

21. Where can I obtain further information?

For further information, please refer to the SmPC, which is included in the Prescriber Kit or contact the representatives of the local Distributor (Mangion Ltd).

22. How can I obtain additional copies of the tools?

Additional copies of the tools can be ordered directly from the representatives of the local Distributor (Mangion Ltd).

22. Reporting of Adverse Drug Reactions and Pregnancies

It is believed that the risks associated with Opsumit have been identified by the clinical development programme. However, as with any new medicine, the safety profile of Opsumit in clinical practice might not be completely established.

It is therefore important that you promptly report to Actelion any suspected adverse reactions to Opsumit, to assist in fully characterising the product's safety profile.

In addition, **all cases of pregnancy** should be reported to Actelion.

Reporting can be done via the Actelion standard Adverse Drug Reaction, or by telephone (phone number: +356 23976333) or email (email address: pv@ammangion.com).
Copies of the forms are provided within your prescriber kit.

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For further information, please refer to the SmPC, available within the Prescriber kit.

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Notes

Opsumit® 10 mg
macitentan

CP-100258

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