Opsumit® 10 mg
macitentan

Frequently Asked Questions Brochure for Healthcare Professionals

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Contents

1. What is the purpose of this brochure? 3
2. What is macitentan? 3
3. What is macitentan indicated for? 3
4. What dose of macitentan should be used? 3
5. What are the main risks associated with the use of macitentan? 4
6. How can the risk of anaemia be prevented and managed? 4
7. What should I know about the risk of teratogenicity associated with macitentan and how can it be prevented? 4
8. What is meant by women of childbearing potential? 5
9. What should I consider before prescribing macitentan to a woman of childbearing potential? 5
10. What is considered a reliable method of contraception? 5
11. What should I do in case a patient taking macitentan becomes pregnant? 6
12. What should I know about the risk of hepatotoxicity associated with macitentan? 6
13. What other important safety information should I be aware of in order to minimise the risks associated with macitentan? 7
14. What should I discuss with my patients, and what assessments need to be performed before initiating treatment with macitentan? 7
15. What is the role of the prescribing checklist? 8
16. What is the patient card? 8
17. Where can I obtain further information? 8
18. How can I obtain additional copies of the tools? 8
19. Reporting of adverse drug reactions and pregnancies 9
20. Notes 10

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 macitentan for whom you have determined are capable of complying with the requirements for the safe use of macitentan.

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

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

2. What is macitentan?

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

3. What is macitentan indicated for?

Macitentan, 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 macitentan should be used?

Macitentan 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.

5. What are the main risks associated with the use of macitentan?

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

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

As with other ERAs, treatment with macitentan has been associated with a decrease in haemoglobin concentration (see section 4.8 of the SmPC). 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 macitentan 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 standard Actelion Drug Safety reporting form, or by telephone +44 20 8987 3333 or email medinfo_uk@its.jnj.com. Copies of the forms are provided within your prescriber kit.

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

There are no data on the use of macitentan in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3 of the SmPC). The potential risk for humans is still unknown. Macitentan is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception. Women should not become pregnant for 1 month after discontinuation of macitentan.

8. 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 childbearing 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 childbearing potential.

9. What should I consider before prescribing macitentan to a woman of childbearing potential?

Women of childbearing potential should not start treatment with macitentan 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 macitentan and for one month after treatment discontinuation

10. 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 intrauterine system (IUS)
- Male partner sterilisation (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)
- Abstinence

11. What should I do in case a patient taking macitentan becomes pregnant?

If a pregnancy occurs during macitentan 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. Consideration should be given as to whether it is appropriate to refer the patient to a Consultant specialised in teratology and its diagnosis for further education and advice.

Patients should be told to report immediately any possible pregnancy that occurs during macitentan use.

If a pregnancy occurs during macitentan therapy, please inform Actelion Drug Safety using a pregnancy reporting form available in your prescriber kit, or by telephone +44 20 8987 3333 or email medinfo_uk@its.jnj.com
All cases of pregnancy should be reported to Actelion.

12. What should I know about the risk of hepatotoxicity associated with macitentan?

Elevations of liver aminotransferases (ALT, AST) have been associated with PAH and with endothelin receptor antagonists (ERAs).

Macitentan 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 macitentan.

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), macitentan treatment should be discontinued.

Re-initiation of macitentan 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 standard Actelion Drug Safety reporting form, or by telephone +44 20 8987 3333 or email medinfo_uk@its.jnj.com
Copies of the forms are provided within your prescriber kit.

13. What other important safety information should I be aware of in order to minimise the risks associated with macitentan?

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 macitentan 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 macitentan could occur. The combination of macitentan with strong CYP3A4 inducers (e.g., rifampicin, St. John's wort, carbamazepine, and phenytoin) should be avoided.

Caution should be exercised when macitentan 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 macitentan should be used with caution in this population.

Macitentan tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Macitentan tablets contain lecithin derived from soya. If a patient is hypersensitive to soya, macitentan must not be used.

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

A pregnancy test, liver function tests and measure of haemoglobin concentrations should be performed before initiation of treatment with macitentan. 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 macitentan, teach patients how to recognise relevant symptoms and signs of 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 childbearing potential of the risks to the foetus in case of pregnancy both from PAH and from macitentan, 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 the patient about this important safety information regularly during their treatment with macitentan.

15. 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 macitentan.

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

16. 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 minimise 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 macitentan
- 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 macitentan 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 macitentan.

17. Where can I obtain further information?

For further information, please refer to the SmPC, available on the electronic Medicines Compendium (eMC) at www.medicines.org.uk/emc or the EMA website at www.ema.europe.eu.

Electronic copies of the additional risk minimisation materials for macitentan are available from the HRPA website www.hpra.ie.

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

You can order additional copies directly from your Actelion medical science liasion contact.

19. Reporting of adverse drug reactions and pregnancies

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Health Products Regulatory Authority, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland, D02 XP77.

Tel: +353 (1) 676 4971
Fax: +353 (1) 676 2517
Website: http://www.hpra.ie
Email: medsafety@hpra.ie

Adverse reactions should also be reported to Actelion Pharmaceuticals UK Ltd by email: medinfo_uk@its.jnj.com

For further information, please refer to the SmPC, available on the electronic Medicines Compendium (eMC) at www.medicines.org.uk/emc.

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