Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

macitentan, 10mg film-coated tablets (Opsumit®) SMC No. (952/14)

Actelion Pharmaceuticals Limited

07 March 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission:

macitentan (Opsumit®) is accepted for restricted use within NHS Scotland.

Indication under review: as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension in adult patients of World Health Organisation Functional Class II to III.

SMC restriction: to initiation and prescribing by specialists in the Scottish Pulmonary Vascular Unit or similar specialists.

In a pivotal phase lll study in patients with pulmonary arterial hypertension, macitentan significantly increased the time to a first event related to morbidity or mortality from any cause compared with placebo. The effect was maintained for up to two years.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of macitentan. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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

Dosing Information

10mg once daily, with or without food. The film-coated tablets are not breakable and are to be swallowed whole with water. Macitentan should be taken every day at about the same time.

Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

Product availability date

13 January 2014. Macitentan was designated as a orphan medicinal product in September 2011[1]

Summary of evidence on comparative efficacy

Pulmonary arterial hypertension (PAH) is characterised by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death. It may be idiopathic (primary) or secondary to other conditions. Endothelin-1 is a key mediator in the pathogenesis and progression of PAH with two receptors in smooth muscle endothelin-A and B. Macitentan is a dual endothelin A/B receptor anatagonist, chemically related to bosentan[2] and is the third endothelin receptor antagonist to be marketed in the UK. The Scottish Medicines Consortium (SMC) has previously accepted bosentan and ambrisentan for use restricted to initiation and prescription by specialists working in the Scottish Pulmonary Vascular Unit or similar specialists.

The evidence is based on one pivotal phase lll, placebo-controlled, double-blind study in 742 adult PAH patients with World Health Organisation (WHO) functional capacity ll to lV.[2] Included patients could be treatment naïve or receiving other PAH therapies. Following an initial screening period, eligible patients were randomised (stratified by centre) to macitentan 3mg daily (n=250), 10mg daily (n=242) or placebo (n=250). Permitted concomitant medicines included oral or inhaled prostaglandins (but not intravenous or subcutaneous), oral phosphodiesterase-5 inhibitors, calcium channel blockers, L-arginine and stable dose of oral diuretics.

The study was event driven with statistical analysis estimating 285 events would be required to detect a hazard ratio (HR) for the primary outcome. Events were confirmed by a Clinical Event Committee. Patients could discontinue study treatment at any time with an end-of-treatment (EOT) value, the date of discontinuation. Reaching 285 events was the study endpoint, end-of-study (EOS), the date of study discontinuation. For patients who were still on study treatment at the EOS, their EOT time-point coincided with EOS.

The composite primary outcome was the reduction in the risk of a morbidity or mortality event assessed as the time from start of treatment to the first morbidity or mortality event (defined as worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, or atrial septostomy or death from any cause), up to EOT measured in the

intention to treat population which included all randomised patients. Worsening of PAH required the presence of decreased 6 minute walking distance, worsening of symptoms and need for additional treatment.

Mean duration of treatment was 104 weeks in the macitentan group and 85 weeks in the placebo group. A total of 287 patients had a primary event over a median treatment period of 115 weeks; reported in 46% (116/250) of placebo patients, 38% (95/250) of macitentan 3mg patients and 31% (76/242) of macitentan 10mg patients. The primary outcome in patients receiving the 3mg daily dose did not reach statistical significance and therefore this dose is not licensed and will not be discussed further. The HR for the primary outcome for macitentan 10mg versus placebo was 0.55 (97.5% confidence interval [CI]: 0.39 to 0.76; p<0.001 by the log-rank test). Worsening of PAH was the most frequent primary event, reported in 24% (59/242) of macitentan patients and 37% (93/250) of placebo patients. There was no difference in death from any cause between groups, 6.6% versus 6.8%, respectively. Sub-analysis of the primary outcome in 64% of patients receiving background PAH therapy found an HR of 0.62 (95% CI: 0.43 to 0.89) compared with an HR of 0.45 (95% CI: 0.28 to 0.72) in patients naïve to treatment. The most commonly reported background PAH therapy was sildenafil.

There were a number of pre-specified secondary outcomes. Change from baseline to month 6 in the 6-minute walk distance increased by a mean of 12.5m in the macitentan group and decreased by a mean of 9.4m in the placebo group giving a treatment effect of 22m (97.5% CI: 3.2 to 40.8). The proportion of patients with an improvement in WHO functional class at month six, was reported in 22% of macitentan and 13% of placebo patients. Death due to PAH or hospitalisation for PAH up to the EOT was reported in 21% (50/242) of macitentan patients compared with 34% (84/250) of placebo patients; HR 0.50 (97.5% CI: 0.34 to 0.75) with hospitalisation accounting for most events.

Premature discontinuation of macitentan was reported in 13% (94/242) of patients who discontinued without a primary outcome event. These patients' data were censored at their EOT in the primary outcome analysis. Sensitivity analyses to account for this premature discontinuation were consistent with the primary analysis.

Patients who discontinued prematurely from double-blind treatment could enrol in an open label ongoing extension study (SERAPHIN OL) for treatment with macitentan 10mg daily, or alternatively receive other appropriate treatment between their EOT and EOS.

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the Summary of Product Characteristics (SPC) for full details of adverse effects.[3]

The number of patients discontinuing from the pivotal study due to adverse events was similar in both groups, 12% (31/250) in the placebo group compared with 11% (26/242) in the macitentan group.

The most commonly reported adverse events in the macitentan group were upper respiratory tract infection, nasopharyngitis, headache, bronchitis and anaemia. There was a greater reported use of antibiotics in the macitentan group which may suggest an increased risk of infection.[4]

Similar to other endothelin receptor antagonists, macitentan has an effect on both haemoglobin concentration and liver function test (LFT) abnormalities which is dose dependent. Anaemia was the main adverse event of concern reported in the pivotal study. Severe anaemia was reported more frequently in the macitentan group, 2.5% (n=16), compared with 0.4% (n=5) in the placebo group. There was also a slightly higher incidence of laboratory abnormalities for serum creatinine in the macitentan group, (1.3% versus 0.4%).[4] Elevations in liver enzymes were noted in only small numbers of macitentan patients but this should still be regarded with caution. The SPC recommends liver enzyme testing prior to initiation with subsequent monthly monitoring.[3]

Summary of clinical effectiveness issues

PAH in Scotland is managed through a central unit, the Scottish Pulmonary Vascular Unit. SMC has previously accepted the two other marketed endothelin receptor antagonists (bosentan and ambrisentan), the two phosphodiesterase-5 inhibitors (sildenafil and tadalafil) and nebulised iloprost for use restricted to initiation by specialists in this unit or similar specialists. The introduction of IV epoprostenol for PAH pre-dates SMC. Similar to other medicines for PAH, macitentan has an orphan designation for this indication. Clinical study data for the other available treatments are based on short-term clinical studies measuring surrogate outcomes. Macitentan is the first treatment for PAH which has reported clinical study data for a clinically relevant, event driven composite primary outcome over two years. It should be noted that the marketing authorisations for bosentan, ambrisentan and macitentan are all slightly different.

In the pivotal phase lll study macitentan was shown to significantly increase the time to an event related to morbidity or mortality from any cause compared with placebo. The composite endpoint was mainly driven by a reduction in morbidity as most first events were hospitalisations due to PAH. Patients included in the study were either receiving background treatment or were treatment naïve. Macitentan was effective in both patient groups but had a greater response in treatment naïve patients.

The pivotal study was well conducted. The main limitation was the lack of an active comparator. Another more minor limitation was that patients who discontinued prematurely prior to a primary event were not followed to the end of the study. However, sensitivity analyses suggest that this did not impact on the primary analysis. Whilst only a small number of patients reported elevation of liver enzymes in the pivotal study, this should still be treated with caution. Liver function monitoring is recommended during treatment.

No direct comparative efficacy or safety data are available so the company presented a Bayesian mixed treatment comparison versus bosentan and ambrisentan. The comparison was limited to short-term efficacy endpoints, the results should be considered with caution and cannot be extrapolated to long-term outcomes.

Clinical experts consulted by SMC consider that macitentan is a therapeutic advancement due to availability of long-term clinical data to support its use. They consider place in therapy as an alternative to existing endothelin receptor antagonists for new patients and for those in whom bosentan or ambrisentan is insufficient.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The submission included a cost-minimisation analysis comparing macitentan to bosentan and to ambrisentan. A semi-Markov state transition model was used, with a time horizon of 2-3 years. In terms of efficacy the results of the indirect treatment comparison were used as the basis of the analysis. It was stated that adverse event rates could not be derived from the indirect comparison so instead they were taken from the main clinical study in the case of macitentan and from U.S. prescribing information in the case of comparators; the only adverse events considered were oedema and liver toxicity.

Costs included were medicines (including costs of administration and of monitoring), treating adverse events, costs of switching when treatment was discontinued, and costs of on-going care (which varied by functional class [FC] stage). Resource use for the medicines came from the regimes used in clinical trials. On-going care costs included drug treatment for symptoms, consultations with health care staff, and hospital admissions. The rates at which resources were used were based on the main clinical study, a Delphi Panel with specialist nurses in England, and consultation with a Scottish based clinical expert.

In the base case analysis, macitentan was the most expensive of the three options, with a total NHS cost of £61,008. Bosentan had the lowest total cost (£48,679) followed by ambrisentan (£49,115). One-way and scenario analyses were presented. None of the scenario analyses changed the rank order of the three treatment options in terms of NHS costs. The smallest cost difference between macitentan and the other medicines was when the time horizon was reduced to one year. Most scenario analyses considered made almost no difference to the results.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS was a simple discount which lowered the list price of macitentan. When the PAS was taken into account, macitentan became a cost-effective treatment option.

The economic evaluation followed the logic of the company's position that macitentan has similar efficacy because a cost-minimisation analysis was selected. However, the company's disease-progression model did not fit well with the cost-minimisation approach. Following discussions at committee, it was agreed that the SMC's decision should be based on the cost-minimisation aspect of the model only. It was noted that there were a number of issues with the disease progression model but these were not relevant to the decision problem. It was also noted that the inclusion of the extended model had considerably reduced the transparency of the submission.

Two possible issues were identified that called the cost-minimisation approach into question:

- There were some weaknesses associated with the indirect comparison which could call into question the assumption of comparable efficacy needed to support a cost-minimisation analysis. However, the committee acknowledged this was inevitable to some extent and the small sample in each clinical study reflected the orphan status of this disease and led the committee to conclude the assumption of broad equivalence should be accepted.

- In the company's submission they had included costs of adverse events but only for oedema and liver toxicity and based on rates from a crude indirect comparison using American data. In response to a question the company confirmed they had no evidence the comparative rates were statistically significant, and therefore SMC's usual practice is to exclude them from the costs.

Having been reassured on these points, the committee felt there was sufficient evidence to conclude that macitentan is likely to be a cost-effective alternative to bosentan and ambrisentan.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The consensus statement on the management of pulmonary hypertension in clinical practice in the UK (2008)[5] provides an algorithm for treatment of idiopathic PAH (IPAH), familial PAH or anorexogen-associated PAH. Treatment options included either sildenafil or sitaxentan* for the management of FC II PAH, and bosentan as first-line choice for patients with FC III PAH (and sildenafil as a second-line option). A separate algorithm is given for PAH associated with connective tissue disease in which bosentan is the first line choice in patients with scleroderma (and sildenafil is listed as one of three alternative second-line options).

The European Society of Cardiology and the European Respiratory Society published guidelines for the diagnosis and treatment of pulmonary hypertension in 2009.[6] These guidelines recommend ambrisentan, bosentan, sildenafil (evidence level 1-A) or tadalafil (evidence level 1-B) for initial treatment of PAH of FC II or III, with epoprostenol, iloprost (evidence level 1-A) and treprostinil** (intravenous or inhaled) (evidence level 1-B) also recommended as treatment options in PAH of FC III only. Other treatment options with a lower level of evidence for PAH of FC III include intravenous iloprost or treprostinil.** Combination therapy of established PAH drugs is recommended for patients not responding adequately to monotherapy and this should only be initiated in specialist treatment centres. No specific recommendations are made on the choice of combination agents, when to switch treatment or combine treatments, or whether combination treatment should be used in treatment-naïve patients. When combination therapy is considered, patients should be treated within clinical trials or registries wherever possible.

The American College of Cardiology and American Heart Association published an expert consensus document on pulmonary hypertension in 2009.[7] For patients who are considered lower risk based on clinical assessment, oral therapy with an endothelin receptor antagonist or a phosphodiesterase-5 inhibitor would be the first line of therapy recommended. If oral treatment is not appropriate, inhaled iloprost or subcutaneous treprostinil** are recommended. For patients considered high risk based on clinical assessment, intravenous prostacyclin (epoprostenol or treprostinil**) is recommended as first line therapy. Combination therapy should be considered in patients who do not respond adequately to initial monotherapy.

* Sitaxentan was withdrawn from the world market in December 2010; ** Treprostinil is not licensed in the UK (EU application withdrawn by company in 2010).

The guidelines predate the availability of macitenan for the treatment of PAH.

Additional information: comparators

Two other endothelin receptor antagonists are licensed for the treatment of PAH: bosentan (WHO FC III PAH only) and ambrisentan (WHO FC II to III).

Other treatments licensed for PAH include sildenafil (WHO FC II to III), tadalafil (WHO FC II to III), nebulised iloprost (NYHA FC III) and IV epoprostenol (WHO FC III to IV).

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
macitentan	**10mg orally daily**	**27,979**
ambrisentan	5 to10mg orally daily	19,633
bosentan	125 orally twice daily	19,633
tadalafil	40mg orally daily	6,386
sildenafil	20mg orally three times daily	4,532

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMs on 7 January 2014.
*Initial bosentan dose is 62.5mg twice daily for four weeks increasing to 125mg twice daily; maximum dose of 250mg twice daily. 62.5mg and 125mg tablets are costed equally. Costs do not take into consideration any Patient Access Schemes.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 103 with an estimated uptake rate of 3% in year 1 and 72% in year 5.

Without PAS
The gross impact on the medicines budget was estimated to be £2k in year 1 and £1.2m in year 5. As other drugs were assumed to be displaced the net medicines budget impact is expected to be £1 in year 1 and £352k in year 5.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. European Medicines Agency. Rare disease designations EU/3/11/909 Macitentan, published 17/10/11. European Medicines Agency - Human medicines - EU/3/11/909
2. Pulido T, Adzerikho I, Channick RN et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. NEnglJMed 2013;369:809-18 including supplementary index
3. Macitentan Opsumit® 10mg film-coated tablets, Summary of Product Characteristics, last updated October 2013
4. Macitentan. Centre for Drug Evaluation and Research. Medical Review. Application number: 204410Orig1s000. www.accessdata.fda.gov website accessed 16/12/13.
5. National Pulmonary Hypertension Centres of the UK and Ireland. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. Thorax 2008; 63 (Suppl II): ii1 to ii41.
6. The task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). European Heart Journal 2009; 30: 2493 to 2537.
7. ACCF/AHA 2009 Expert consensus document on pulmonary hypertension: A report of the American College of Cardiology foundation task force on expert consensus documents and the American Heart Association: Developed in collaboration with the American College of Chest Physicians, American Thoracic Society Inc., and the Pulmonary Hypertension Association. Circulation 2009; 119: 2250 to 2294.

This assessment is based on data submitted by the applicant company up to and including 14 February 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of

guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.