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

tadalafil 20mg tablets (Adcirca®) SMC No. (710/11)

Eli Lilly and Company Limited

08 June 2012

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

tadalafil (Adcirca®) is accepted for restricted use within NHS Scotland.

Indication under review: treatment of adults with pulmonary arterial hypertension (PAH) classified as World Health Organisation functional class (WHO-FC) II and III, to improve exercise capacity.

SMC restriction: To initiation by specialists working in the Scottish Pulmonary Vascular Unit or similar specialists.

Tadalafil demonstrated statistically significant improvement in 6 minute walking distance (6MWD) compared with placebo in patients with PAH, WHO-FC II or III. Approximately half of the study patients were receiving a concomitant endothelin receptor antagonist.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Tadalafil is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as World Health Organisation (WHO) functional class (FC) II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

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

Dosing Information

The dose is 40mg once daily orally (2 x 20mg tablets) taken with or without food.

Product availability date

January 1st 2011

Summary of evidence on comparative efficacy

Pulmonary arterial hypertension (PAH) is a rare, progressive, and life-threatening disease. It is characterised by an increase in pulmonary arterial pressure and pulmonary vascular resistance leading to right ventricular failure and ultimately death.

Tadalafil is a potent and selective phosphodiesterase type-5 inhibitor that blocks the degradation of cyclic guanosine monophosphate (cGMP) in the pulmonary vasculature in patients with PAH resulting in relaxation of the pulmonary vascular smooth muscle and vasodilatation of the pulmonary vascular bed. Although PAH is an orphan disease, tadalafil does not have orphan drug status in the European Union.

The submission includes one 16 week pivotal phase III parallel, randomised, double-blind, placebo controlled study (PHIRST 1).[1,2] A total of 405 patients were randomised equally to one of five groups to receive once daily oral doses of tadalafil 2.5mg (n=82), 10mg (n=80), 20mg (n=82), 40mg (n=79) or placebo (n=82). Stratification included background bosentan on a yes/no basis at enrolment. [1,2]

Eligible patients were at least 12 years old, with body weight ≥40kg and a diagnosis of PAH that was idiopathic, related to collagen disease, related to anorexigen use, related to human immunodeficiency virus infection, associated with an atrial septal defect, or associated with surgical repair of at least one year in duration of a congenital systemic-to-pulmonary shunts. Eligible patients had a 6 minute walking distance (6MWD) test ≥150 and ≤450 metres at screening and WHO FC I, II, III, or IV status. Permitted concomitant therapy included bosentan (stable maintenance dose up to 125mg twice daily) and chronic anticoagulation, digoxin, diuretics and oxygen. More than half (53%) of study patients were receiving concomitant bosentan therapy. Most patients were in WHO-FC II (32%) or III (65%).

The primary efficacy endpoint was the difference in 6MWD from baseline to week 16 in the ITT study population defined as all randomised patients who received study drug. In patients treated with the licensed dose of tadalafil (40mg once daily) the primary analysis achieved statistical significance at the pre-specified value ($p<0.01$) (permutation test, $p=0.0004$). In the tadalafil 40mg group, the median 6MWD increased from 380 metres at baseline to 402 metres at week 16 (median change 35 metres) compared with an increase from 367metres to 381 metres in the placebo group (median change 12 metres). This corresponded to a significant placebo-adjusted median increase of 26 metres (95%

confidence interval [CI]: 9.5 to 44, p=0.0004), using the pre-specified Hodges-Lehman method. The corresponding mean placebo-adjusted increase in 6MWD was 33 metres (95% CI: 15 to 50, p=0.0003).

There were no statistically significant differences between tadalafil 40mg and placebo in WHO-FC improvement or in the Borg dyspnoea score. The time to clinical worsening was significantly improved by 6 days in the tadalafil 40mg group as compared to placebo. The incidence of clinical worsening was reduced in the tadalafil 40mg group (p=0.038, relative risk reduction 68% versus placebo, [absolute values 5% versus 16%]).[2]

Quality of Life data was analysed using the SF-36 survey. In six of eight domains (Physical-Functioning, Role-Physical, Bodily Pain, General Health, Vitality, and Social Functioning), there were statistically significant improvements for tadalafil 40mg compared with placebo. The tadalafil 40mg treatment group also had statistically significant improvements in the EuroQoL current health-state visual analogue scale and the two index scores (US and UK) compared with placebo.

After the 16 weeks pivotal study, PHIRST 1, eligible patients (n=357) were entered in to a 52-week double-blind extension study, PHIRST 2, primarily to study safety.[3] Patients were assigned to once daily treatment with tadalafil 40mg or 20mg. The tadalafil 40mg group (n=294) consisted of those who were taking placebo, tadalafil 2.5, 10, or 20mg in PHIRST 1 and had discontinued PHIRST 1 due to clinical worsening or who had clinical worsening at the end of PHIRST 1; and those who completed PHIRST 1 without clinical worsening and were taking placebo, tadalafil 2.5, 10, or 40mg. Patients allocated to the tadalafil 20mg group (n=63) were those who were taking tadalafil 20mg in PHIRST 1 and had completed the study without clinical worsening. 82% (n=293) of these patients completed the 52-week extension study, of which 82% (n=241) received tadalafil 40mg and 18% (n=52) received tadalafil 20mg. The final results of the extension study are not yet published; however, examination of the data has demonstrated that 40mg is the optimal dose.

Patients who received unchanged treatment of tadalafil 40mg through both PHIRST 1 and PHIRST 2 had a mean baseline 6MWD measurement at the start of study PHIRST 2 of 403.31 metres (95%CI: 383.08, 423.54; n=69).[3] At endpoint, the mean 6MWD was 400.26 metres (95%CI: 379.93, 420.59; n=67).[3] These results indicate the durability of effect over 52 weeks on the primary efficacy endpoint in study LVGY at the licensed dose.

Summary of evidence on comparative safety

There are no comparative safety data with other drugs for the treatment of PAH. In the pivotal study, treatment-related adverse events were significantly more frequent in patients receiving the licensed dose of tadalafil 40mg daily: 66% (52/79) compared with 34% (28/82) receiving placebo. The incidence of serious adverse events (SAE) and discontinuations was similar across all treatment groups.[1,3]

The most common adverse events reported were headache, nausea, back pain, dizziness, dyspepsia, flushing, myalgia, nasopharingitis and pain in extremity. These were generally mild to moderate with all doses of tadalafil.

A total of 23% (n=83) of patients reported SAE's during the 52-week extension study of which 14 events in ten patients were considered to be treatment-related (one led to a fatality). There were two deaths between the pivotal study and the extension study which were thought to be related to tadalafil.[3]

Summary of clinical effectiveness issues

The licensed dose of tadalafil 40mg daily improved 6MWD test compared with placebo, and this achieved the protocol-defined level of significance, with a placebo-adjusted median increase of 26 metres from a median baseline of 380 metres. The EPAR states that this improvement is below the average of other drugs licensed for this indication.[3] The European Medicines Agency has advised that the suitability of the 6MWD as a stand-alone primary endpoint for PAH has limitations with respect to the lack of clear correlation between improvement in exercise capacity and survival.[3] Not all secondary endoints in the pivotal study were achieved although tadalafil did improve quality of life more than placebo.

It has been shown that there is a pharmacokinetic interaction between bosentan and tadalafil which leads to lower systemic exposure of tadalafil. For this reason, bosentan may have a negative effect on the efficacy of tadalafil. As over 50% of patients in the study were receiving concomitant bosentan, this subgroup was investigated to evaluate the efficacy of tadalafil as an add-on therapy to bosentan. This exploratory analysis was based on a small sample size and had insufficient power to determine statistically significant differences within subgroups. The efficacy of tadalafil in patients who are already treated with bosentan was not conclusively demonstrated.

An adjusted indirect comparison, using Bucher methodology, was used to compare tadalafil 40mg once daily and sildenafil 20mg three times daily using the placebo arms as a common comparator. The company considered that the most clinically similar and therefore appropriate patient populations from each study were those not taking concomitant bosentan. Therefore the bosentan-naïve sub-population was used from the tadalafil study and the intent to treat (ITT) population from the sildenafil study. There were no significant differences between arms for the primary endpoint (6MWD) or for the secondary endpoints of WHO-FC improvement, clinical worsening and cardiac haemodynamics. The indirect comparison has limitations in terms of internal validity, namely lack of similarity between studies (primary endpoint measured at different times [12 and 16 weeks] and differences in baseline WHO-FC, connective tissue disease aetiology and age of patients) and small patient numbers. There were also limitations in terms of external validity, as extrapolation of results to patients in whom tadalafil is used in combination with bosentan is not possible.

Tadalafil offers a once daily dosing option for treatment with a PDE5 inhibitor in PAH.

Summary of comparative health economic evidence

The submitting company presented a simple cost-minimisation analysis over a 1-year time horizon comparing tadalafil 40mg once daily with sildenafil 20mg three times daily for the treatment of PAH in patients with WHO FC II and III. The comparator was justified on the basis that tadalafil will be used at the same point in the treatment pathway as sildenafil and is therefore the treatment most likely to be displaced. The assumption of comparable efficacy of tadalafil and sildenafil was based on an adjusted indirect comparison in patients who were not taking concomitant bosentan. The analysis included the bosentan-naive sub-population from the tadalafil LVGY study and the sildenafil ITT population from the SUPER study. The results of the indirect comparison showed that tadalafil and sildenafil achieved similar outcomes in terms of the primary endpoint of 6MWD.

The analysis included only the drug acquisition costs of tadalafil and sildenafil and it was assumed that patients were fully compliant for a year. No other resource use was included.

The annual cost of tadalafil was estimated to be £6,403 and the cost of sildenafil was estimated to be £4,544 resulting in an increased cost of £1,859 with tadalafil. 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. Under the PAS, a discount is given on the list price of tadalafil.

SMC clinical experts have confirmed that higher off-label doses of sildenafil are used in practice in around 50% of PAH patients so the potential for cost savings associated with tadalafil may be higher.

The following limitation was noted:

- There are weaknesses with the indirect comparison which introduce some uncertainty to the assumption of comparable efficacy of tadalafil and sildenafil which underpins the cost-minimisation analysis. It should be noted that the indirect comparison only assessed the efficacy of tadalafil and sildenafil when used as monotherapy in bosentan-naive patients. The comparative efficacy of tadalafil and sildenafil as combination therapy has not been established. However, on balance it is reasonable to conclude that efficacy is similar.

Despite this limitation, the economic case has been demonstrated.

*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

UK National Pulmonary Hypertension Centres (NPHC) of the UK and Ireland: Consensus Statement on the Management of Pulmonary Hypertension in Clinical Practice (published in 2008) (NPHC, 2008):

- First line: bosentan
- Second line: sildenafil, prostanoids, sitaxentan*

European Society of Cardiology and European Respiratory Society guidelines (ESC & ERS), Diagnosis and Treatment of Pulmonary Hypertension (published in 2009):

- WHO-FC II, initial therapy options: ambrisentan, bosentan, sildenafil, tadalafil
- WHO-FC III, initial therapy options: ambrisentan, bosentan, sitaxentan*, sildenafil, epoprostenol (IV), iloprost inhaled, tadalafil, treprostinil (SC,inhaled), iloprost (IV), treprostinil (IV), beraprost.

*Sitaxentan was withdrawn from the world market 10/12/2010

Additional information: comparators

Sildenafil (Revatio®) is the only other PDE5 inhibitor licensed to treat PAH. Endothelin receptor antagonists (bosentan, ambrisentan) are also used.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Tadalafil	40mg orally once daily	6,386
Sildenafil	20mg orally three times daily	4,532
Bosentan	125mg to 250mg orally twice daily*	19,656 to 39,308
Ambrisentan	5mg – 10mg orally once daily	20,020

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27 March 2012.

*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.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 127 patients in all years with an estimated uptake rate of 25% in year 1 rising to 50% in year 5 and a discontinuation rate of 14.8%.

The company presented two scenarios depending on the dose of displaced sildenafil. The gross medicines budget impact without PAS was estimated to be £174k in year 1 and £347k in year 5. Assuming displacement of sildenafil 20mg three times daily the net medicines budget impact was estimated to be £50k and £101k in years 1 and 5 respectively. If, however, higher off-label doses of sildenafil were displaced, the net medicines budget impact was estimated to be £2k and £5k in years 1 and 5 respectively.

SMC clinical experts have confirmed that off-label doses of sildenafil are currently used in PAH.

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

References

The undernoted references were supplied with the submission.

1. Barst, R., Oudiz, R. J., Beardsworth, A.,et al.. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. *J Heart Lung Transplant, 30*(6), 632-643.

2. Galie, N., Brundage, B. H., Ghofrani, H. A., et al. Tadalafil Therapy for Pulmonary Arterial Hypertension. Circulation. 2009; 119: 2894-2903. Circulation available online at: http://circ.ahajournals.org

3. European Medicines Agency Assessment Report for Adcirca EMEA/H/C/1021/II/0001 www.ema.europa.eu

This assessment is based on data submitted by the applicant company up to and including 11 May 2012.

**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. These have been confirmed from the eVadis drug database. 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.