HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 February 2006

Revatio 20 mg, film-coated tablet
B/90

Applicant: Pfizer

sildenafil

List I
Medicinal product restricted to hospital prescription by specialists and/or departments specialising in chest medicine, cardiology or internal medicine.

Date of Marketing Authorisation: 28 October 2005 (centralised procedure)

Reason for application: Inclusion on the list of medicinal products approved for use by hospitals.

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

sildenafil

1.2. Background

Phosphodiesterase type 5 inhibitor indicated in pulmonary arterial hypertension (PAH).
Orphan drug.

1.3. Indication

Treatment of pulmonary arterial hypertension (PAH) in patients classified as WHO functional class III, to improve exercise capacity. Efficacy has been proven in idiopathic pulmonary arterial hypertension and in pulmonary arterial hypertension associated with connective tissue disease.

1.4. Dosage

Revatio is intended for oral use.
Treatment must be initiated and monitored only by a doctor experienced in the treatment of pulmonary arterial hypertension. If clinical deterioration occurs in spite of Revatio treatment, alternative therapies should be considered.

Use in adults (≥ 18):
The recommended dose is 20 mg three times daily. Tablets should be taken approximately 6–8 hours apart with or without food.

Use in elderly patients (≥ 65):
Dosage adjustments are not required in elderly patients. The clinical efficacy in terms of distance walked in 6 minutes may be less in elderly patients.
Use in children and adolescents (< 18):
Safety and efficacy in children and adolescents have not been studied in large-scale controlled clinical trials. The use of sildenafil in these patients is therefore not recommended.

Discontinuation of treatment
Limited data suggest that abrupt discontinuation of Revatio is not associated with rebound worsening of pulmonary arterial hypertension. However, to avoid the risk of abrupt clinical deterioration at the time of withdrawal, the dosage should be reduced gradually. Closer monitoring is recommended during the withdrawal period.

Use in patients taking other medicinal products:
The safety and efficacy of sildenafil when coadministered with other pulmonary arterial hypertension therapies (for instance bosentan, epoprostenol or iloprost) have not been studied in controlled clinical trials. The coadministration of sildenafil with these drugs is therefore not recommended. The safety and efficacy of Revatio when coadministered with other PDE5 inhibitors have not been studied in patients with pulmonary arterial hypertension (see SPC).

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

G : Genito-urinary system and sex hormones
04 : Urologicals
B : Other urological preparations, including antispasmodics
E : Erectile dysfunction products
03 : Sildenafil

2.2. Medicines in the same therapeutic category

This is the only phosphodiesterase type 5 inhibitor with this indication.

2.3. Medicines with a similar therapeutic aim

Bosentan: Tracleer, administered orally
Epoprostenol: Flolan, administered by continuous IV infusion
Iloprost: Ventavis, administered by inhalation (idiopathic PAH)
Treprostinil: Remodulin, administered by continuous subcutaneous infusion (idiopathic PAH)

Usual care in pulmonary arterial hypertension (PAH) involves calcium channel blockers, anticoagulants (VKAs), diuretics, oxygen therapy, and sometimes digitalis.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The main evidence for the effectiveness of sildenafil in managing PAH was a placebo-controlled phase III trial (N Engl J Med 2005;353:2148-2157).
At the end of this 12-week trial, most patients were enrolled in an open-label follow-up study with the objective of confirming that the therapy was well tolerated.

Objective: Assessing the safety and efficacy of sildenafil compared with placebo at 12 weeks in patients with PAH.

Methodology:
- randomised, double-blind, placebo-controlled trial
- 277 patients with PAH (63% idiopathic, 30% associated with connective tissue disease and 7% following surgery to repair a congenital cardiac lesion) were randomised into four treatment groups: placebo, sildenafil 20 mg (n=67), 40 mg (n=64) or 80 mg (n=69), three times daily. The trial population was 25% male and 75% female; mean age 49 years (18–81); baseline walking distance 100–450 metres in 6 minutes (mean: 344 metres).
- Most patients were in functional class II (39%) or III (58%), with a mean walking distance in 6 minutes of 378 metres and 326 metres respectively. Three percent (3%) were in functional class IV. Patients with left ventricular ejection fraction < 45% or left ventricular fractional shortening < 0.2 were excluded.

- Sildenafil (or placebo) was added to patients' basic treatment consisting of a combination of anticoagulants, digoxin, calcium channel blockers, diuretics and oxygen. The use of prostacyclin, prostacyclin analogues, endothelin receptor antagonists or arginine supplements was not permitted. Patients who had previously not responded to bosentan therapy were excluded from the trial.
- The primary endpoint for efficacy was change in distance walked in 6 minutes at 12 weeks compared to baseline.
- Analysis was on an intention-to-treat basis.

Result:
- A statistically significant increase in the distance covered in 6 minutes was observed in the 3 sildenafil groups compared with the placebo groups. The placebo-corrected increase was 45 metres ($p < 0.0001$) for the sildenafil 20 mg group, 46 metres ($p < 0.0001$) for the 40 mg group and 50 metres ($p < 0.0001$) for the 80 mg group. No significant difference was observed between sildenafil doses.
- The improvement in walking distance was apparent after 4 weeks of treatment, and this effect was still present at weeks 8 and 12.
- The results were consistent between the various subgroups categorised by walking distance, aetiology (idiopathic PAH and PAH associated with connective tissue disease), functional class, sex, race, location, mean pulmonary arterial pressure (MPAP) and pulmonary vascular resistance index.
- If all dosages are taken together, patients taking sildenafil showed a statistically significant decrease in pulmonary arterial pressure (MPAP) compared to patients taking placebo. Placebo-corrected effects of therapy were –2.7 mmHg ($p=0.04$) for 20 mg of sildenafil three times daily. No difference in efficacy was shown between sildenafil 20 mg and the higher doses studied.
- Mean change in pulmonary vascular resistance (PVR) compared with baseline was 122 dyne.sec/cm^2 for sildenafil at a dose of 20 mg three times daily. Percentage decrease in PVR at week 12 for 20 mg of sildenafil (11.2%) was proportionately greater than percentage decrease in systemic vascular resistance (SVR) (7.2%).
- The effect of sildenafil on mortality is unknown.

3.2. Undesirable effects

During both the pivotal placebo-controlled trial and the subsequent long-term follow-up study (149 patients treated for at least 1 year, 101 of whom took sildenafil 80 mg three times daily), undesirable effects were mild to moderate. The commonest undesirable effects reported (10% or more) were headache, facial flushing, dyspepsia, back pain, diarrhoea and limb pain.

In post-marketing experience with sildenafil for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported in temporal association with the use of sildenafil. Most of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur after the use of sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

3.3. Conclusions

A randomised, double-blind placebo-controlled phase III clinical trial of Revatio was carried out in patients with PAH. After 12 weeks of treatment, the mean placebo-corrected increase in distance walked in 6 minutes compared to baseline was 45 metres ($p < 0.0001$) for the sildenafil 20 mg group.
The effect of sildenafil on mortality is unknown.
The benefit of treatment with Revatio has not been established for patients in the more severe stages of pulmonary arterial hypertension (WHO class IV).
During clinical trials, the most common undesirable effects attributable to Revatio were headache, facial flushing, dyspepsia, back pain, diarrhoea and limb pain.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

PAH is a serious, fast-progressing and life-threatening condition.
Revatio can be used as first-line therapy.
There are few alternative therapies for this condition.
Revatio is a symptomatic therapy.
Public health benefit:

Idiopathic pulmonary arterial hypertension and PAH associated with connective tissue disease, in functional class III, are a low public health burden because of the small number of patients concerned.
The therapeutic need is only very partially covered by existing therapies. There is no evidence to suggest that Revatio will meet this need.
It is not possible to quantify the expected impact of Revatio on morbidity and mortality or quality of life at population level on the basis of the clinical data available.
It is not therefore expected that Revatio will benefit public health.

The efficacy/safety ratio for Revatio is high.
The actual clinical benefit of Revatio in this indication is substantial.

4.2. Improvement in actual benefit:

In view of the recommendations of the European Society of Cardiology and expert opinion, it now seems possible to initiate management of idiopathic PAH or PAH associated with connective tissue disease in functional class III with one of the two oral therapies, bosentan or sildenafil, but no trials have directly compared the two treatments. Taking into account the uncertainty inherent in indirect comparisons, the Transparency Committee notes that the benefit achieved in the sildenafil trials seems to be similar to that achieved in the bosentan trials. The Committee therefore considers that Revatio shares in the improvement in actual benefit afforded by Tracleer.

4.3. Therapeutic use

Usual care for PAH combines restricting physical activity, and medication with anticoagulants, diuretics, oxygen therapy and calcium channel blockers.
The development of new oral treatments has changed the treatment strategy, especially for patients NYHA class III. In these patients, it now seems sensible to begin management with a simple, well-tolerated treatment. According to the recommendations of the European Society of Cardiology (ESC, 2004) updated in 2005 by the WHO, the two oral drugs that may be given to patients with idiopathic PAH or PAH associated with connective tissue disease are bosentan (Tracleer) and sildenafil (Revatio).
The efficacy and safety of sildenafil when coadministered with other PAH therapies (for instance bosentan, epoprostenol or iloprost) have not been assessed in controlled clinical trials. Concomitant administration of sildenafil with these drugs is therefore not recommended.

4.4. Target population

Idiopathic PAH:
- idiopathic PAH is a rare disease affecting 600–700 people in France.
- Of these, around 60% are thought to be NYHA class III.

PAH associated with connective tissue disease:
The group of connective tissue diseases mainly consists of systemic scleroderma, disseminated lupus erythematosus, dermatomyositis, mixed connective tissue disease and sometimes, rheumatoid arthritis.
The target population can only be estimated from the data available with a high degree of uncertainty.
- Scleroderma: of the 9500 patients in France (expert opinion), around 12% (ESC, 2004) are thought to have PAH, i.e. around 1150 patients.
- Lupus: of about 50 000 patients affected (expert opinion), around 2.8% (Pan TL. Lupus 2000) are thought to have PAH, i.e. 1200 patients.
- Mixed connective tissue disease: of about 2000 patients affected (Haas, 1992, Henegar, 2004), 15% (expert opinion) are thought to have PAH, i.e. 300 patients.

Of these patients, around 60% are thought to be in functional class III (Sanchez, 2003).

On this basis, the total target population for Revatio would be around 2000 patients.

4.5. Transparency Committee recommendations

The Committee recommends inclusion on the list of medicinal products approved for use by hospitals and various public services.