HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

16 November 2011

REVATIO 0.8 mg/ml, solution for injection
1 vial of 20 ml (CIP code: 576 957-3)
Each 20 ml vial contains 10 mg of sildenafil

Applicant: PFIZER

sildenafil
ATC code: G04BE03

List I
Medicinal product reserved for hospital use

Date of Marketing Authorisation (centralised procedure): 10 December 2009

Orphan drug status (date of designation: 12 December 2003 for sildenafil in the treatment of pulmonary arterial hypertension (PAH))

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

sildenafil

1.2. Indications

"REVATIO solution for injection is indicated for the treatment of adult patients with pulmonary arterial hypertension who are currently prescribed oral REVATIO and who are temporarily unable to take oral therapy, but are otherwise clinically and haemodynamically stable.

REVATIO (oral) is indicated for treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III,[1] to improve exercise capacity. Efficacy has been shown in idiopathic pulmonary hypertension and pulmonary hypertension associated with connective tissue disease."

1.3. Dosage

"Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension. In case of clinical deterioration in spite of REVATIO treatment, alternative therapies should be considered.

REVATIO solution for injection should be administered to patients already prescribed oral REVATIO as a replacement for oral administration under conditions where they are temporarily unable to take oral REVATIO therapy.

REVATIO solution for injection is administered as an intravenous bolus injection.

Use in adults:
The recommended dose is 10 mg (corresponding to 12.5 ml) three times a day, administered as an intravenous bolus injection.
A 10 mg dose of REVATIO solution for injection is predicted to provide exposure of sildenafil and its N-desmethyl metabolite and pharmacological effects comparable to those of a 20 mg oral dose.

Use in the elderly:
Dose adjustments are not required in elderly patients. Clinical efficacy as measured by 6-minute walk distance could be less in elderly patients.

Use in patients with renal impairment:
Initial dose adjustments are not required in patients with renal impairment, including severe renal impairment (creatinine clearance < 30 ml/min). A downward dose adjustment to 10 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.

[1]The NYHA classification (New York Heart Association Functional Classification) is based on the functional capabilities of the patient. It groups patients into four classes:
- Class I: no limitation to physical activities. No dyspnoea, or fatigue during every day activities
- Class II: moderate limitation to physical activities. Impact on strenuous physical activities. No discomfort when at rest.
- Class III: marked limitation to physical activities. Impact on even moderate everyday activities. No discomfort when at rest.
- Class IV: inability to perform the majority of every day activities without significant discomfort. Discomfort at rest.

Use in patients with hepatic impairment:
Initial dose adjustments are not required in patients with hepatic impairment (Child-Pugh class A and B). A downward dose adjustment to 10 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.
REVATIO is contraindicated in patients with severe hepatic impairment (Child-Pugh class C).

Use in paediatric population and adolescents:
REVATIO is not recommended for use in children below 18 years due to insufficient safety and efficacy data.

Discontinuation of treatment:
Limited data suggest that the abrupt discontinuation of oral REVATIO is not associated with rebound worsening of pulmonary arterial hypertension. However, to avoid the possible occurrence of sudden clinical deterioration during withdrawal, a gradual dose reduction should be considered. Intensified monitoring is recommended during the discontinuation period.

Patients using other medicinal products:
In general, any dose adjustment should be administered only after a careful benefit-risk assessment.
A downward dose adjustment to 10 mg twice daily should be considered when sildenafil is co-administered to patients already receiving CYP3A4 inhibitors like erythromycin or saquinavir. A downward dose adjustment to 10 mg once daily is recommended in case of co-administration with more potent CYP3A4 inhibitors like clarithromycin, telithromycin and nefazodone. Dose adjustments of sildenafil may be required when co-administered with CYP3A4 inducers."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification(2011)

G: Genitourinary system and sex hormones
G04: Urologicals
G04B: Other urologicals, including antispasmodics
G04BE: Drugs used in erectile dysfunction
G04BE03: Sildenafil

2.2. Medicines in the same therapeutic category

Not strictly comparator medicines: oral phosphodiesterase inhibitors

- REVATIO 20 mg (sildenafil), film-coated tablets, indicated "for treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic pulmonary hypertension and pulmonary hypertension associated with connective tissue disease".

- ADCIRCA 20 mg (tadalafil), film-coated tablet indicated "for treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic pulmonary hypertension and pulmonary hypertension associated with connective tissue disease".

2.3. Medicines with a similar therapeutic aim

- oral administration
    - o TRACLEER (bosentan), endothelin antagonist
    - o VOLIBRIS (ambrisentan), endothelin antagonist

- continuous IV administration
    - o FLOLAN (epoprostenol sodium), prostacyclin

- continuous sub-cutaneous administration
    - o REMODULIN (treprostinil sodium), prostacyclin analogue

- by inhalation
    - o VENTAVIS (iloprost) 10 µg/ml, prostacyclin analogue

The actual benefit of pulmonary arterial hypertension treatments in the indications of their marketing authorisations has been described as moderate, with the exception of FLOLAN which has been described as having a substantial actual benefit (see re-assessment Opinion of 5 January 2011).

3 ANALYSIS OF AVAILABLE DATA

The REVATIO 0.8 mg/ml solution for injection development programme is based on:

- three pharmacokinetic studies carried out on healthy volunteers (studies A148-203, A148-208 and A148-215[2]),
- trials on paediatric patients (it should be noted that REVATIO 0.8 mg/ml is not recommended for children),
- two trials that evaluated the pharmacodynamic properties and tolerance in a small number of adult patients with PAH:
  - study A148-1024, with the aim of evaluating the tolerance and effects of IV sildenafil versus placebo, administered in combination with inhaled nitric oxide, on the pulmonary vascular resistance in fifteen patients with PAH. The administration of sildenafil was carried out via a series of injections at different doses[3] not complying with the dosage regimen found in the marketing authorisation.
  - The open-label study A148-1262, which evaluated the tolerance and pharmacokinetics of a single 10 mg dose of sildenafil administered via IV bolus infusion to ten patients with PAH in a stable condition and who were previously treated for at least one month with oral REVATIO 20 mg twice daily (the recommended dose is 20 mg three times daily). Among the ten patients included, eight received bosentan treatment at the same time and one had treprostinil in addition to bosentan and sildenafil. The aetiology and functional class of PAH of the patients was unknown. The majority of patients received another oral PAH treatment. This study did not investigate the use of IV sildenafil, recommended in the Marketing Authorisation, which favours this type of treatment for patients, who, temporarily, are not able to take their medication orally.

In these two trials, the adverse events reported were generally comparable to those observed in the pivotal trials carried out with REVATIO 20 mg tablets. No symptoms of hypotension were associated with changes in diastolic and systolic arterial pressure. In trial A148-1262, flushing, flatulence and pyrexia were observed in two patients.

The company also provided results from the previously evaluated study on REVATIO 20 mg tablets, which had already been examined by the Committee (see Opinion of 15 February 2006) and the results from a study on oral sildenafil administered in combination with epoprostenol (PACES 1 study).

[2]The doses evaluated in the studies were 20 mg via IV (one 20 ml vial at a dose of 1 mg/ml) in study A148-203, 50 mg via IV (one 50 ml vial at a dose of 1 mg/ml) in study A148-208, and 25 mg via IV in trial A148-215.
[3]An initial dose of 5.25 mg over 5 minutes was given followed by a maintenance dose of 0.5 mg over 15 minutes, then a dose of 11 mg over 5 minutes, followed by 2.25 mg over 15 minutes. A final injection of 11 mg over 5 minutes was administered, followed by 4 mg over 15 minutes.

Remarks

There is no data available with a satisfactory level of evidence for REVATIO 0.8 mg/ml in the indication of its Marketing Authorisation. The trials provided did not document the clinical benefit of this medicinal product to patients. The presumed efficacy of IV administered sildenafil only comes from an extrapolation of data from oral sildenafil. With regard to oral sildenafil (REVATIO 20 mg film-coated tablets), there is no long-term data at the recommended dose (20 mg, 3 times per day), or any demonstrated effect in preventing clinical deterioration[4] or on survival rates. Medical professionals believe that this dose may be too low for some patients.

The SPC states that a 10 mg dose of REVATIO solution for injection is predicted to provide exposure of sildenafil and its N-desmethyl metabolite and pharmacological effects comparable to those of a 20 mg oral dose. This statement is based exclusively on pharmacokinetic data. No clinical trial has been performed to demonstrate that the oral and injectable forms have comparable efficacy.

Furthermore, there is also no data supporting a potential deterioration in the health of patients if they temporarily stop treatment.

The adverse effects associated with IV administered REVATIO are similar to those associated with using oral REVATIO. As data on the use of IV REVATIO are limited and pharmacokinetic models predict that 20 mg oral forms and 10 mg IV forms result in a similar plasma exposure, safety information on IV administered REVATIO has been extrapolated from information from the oral form of REVATIO. During the two controlled trials versus placebo for oral REVATIO, the most commonly reported adverse effects (frequency greater than or equal to 10%) were headaches, redness of the face, dyspepsia, diarrhoea and limb pain, which was generally mild to moderate in intensity. According to the SPC, visual impairment and one case of non-arteritic anterior ischaemic optic neuropathy have been reported following the taking of sildenafil.

[4]In trials that enabled REVATIO 20 mg film-coated tablets (SUPER 1 and SUPER 2) to be granted marketing authorisation, previously evaluated by the Committee, there were no differences observed between the sildenafil and placebo groups for the endpoint "delay in deterioration in health", a secondary endpoint defined as the delay, following randomisation, in the occurrence of the following events: death, lung transplant, admission to hospital due to worsening of PAH, atrial septostomy, introduction of a different PAH treatment or worsening in WHO functional class.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Pulmonary Arterial Hypertension (PAH) is a rare, life-threatening disease affecting the lungs, characterised by a progressive obstruction of the small pulmonary arteries resulting in a gradual increase in pulmonary arterial pressure and right-sided heart failure. PAH is defined as an elevation in mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mmHg at rest, without elevation in pulmonary capillary pressure evaluated through right cardiac catheterisation. The most common clinical signs include asthenia, dyspnoea, chest pains and losses in consciousness. The median survival rate under symptomatic treatment is in the order of 2.5 years for patients with functional class III PAH and 4.8 years for those who have functional class II.[5]
REVATIO 0.8 mg/ml, solution for injection, is a symptomatic and temporary treatment for PAH.

Efficacy/adverse effects ratio:
In the absence of relevant clinical data, the efficacy of REVATIO 0.8 mg/ml, solution for injection, cannot be determined. Extrapolation of available data for REVATIO 20 mg film-coated tablets does not allow the clinical benefit of REVATIO 0.8 mg/ml, solution for injection to be documented with a sufficient level of evidence.
Proof that there is clinical benefit can therefore not be established. Furthermore, the potential risks incurred by clinically and haemodynamically stable patients[6] who temporarily stopped treatment was not documented.
As a result, the efficacy/adverse effects ratio for REVATIO 0.8 mg/ml solution for injection cannot be described clinically.

Therapeutic use:[7]
Primarily, the aim of treatment is to improve the survival and quality of life of patients.
PAH is a short-term progressive disease, with regular monitoring necessary in order to detect any deterioration in health early so that treatment can be increased as soon as possible. The prognosis plays an important role in the choice of initial treatment and how the response to treatment is evaluated.[8]

The therapeutic use recommended by the Transparency Committee in its Opinions and found in the literature[9,10, 11] is as follows:

[5] Montani D et al. Actualités thérapeutiques dans l'hypertension artérielle pulmonaire. [Therapeutic advances in pulmonary arterial hypertension] AMC pratique. N°179 . June 2009.
[6] Patients following the marketing authorisation indication.
[7] ESC guidelines on the diagnosis and treatment of pulmonary arterial hypertension. Eur Heart J 2004; 25: 2243-78.
[8] Sanchez O et coll. Diagnostic et prise en charge de l'hypertension pulmonaire en 2009. [Diagnosis and management of pulmonary arterial hypertension in 2009]. Comments on the new European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines 2010; 27: 141-150.
[9] Mc Laughlin et al. ACCCF/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. J Am Coll Cardiol. 2009; 53: 1573-1619.
[10] Goldberg A. Pulmonary Arterial Hypertension in Connective Tissues Diseases. Cardiology in Review. 2010; 18: 85-88.
[11] Anderson JR et al. Pharmacotherapeutic Management of Pulmonary Arterial Hypertension. Cardiology in Review. 2010; 18 –: 148-162.

Standard treatment for PAH combining anticoagulants, diuretics, oxygen therapy and calcium inhibitors.
For patients specifically with class III PAH, the following can be used:
- oral endothelin antagonists (bosentan or ambrisentan) and phosphodiesterase inhibitors (sildenafil or tadalafil)
- via inhalation with iloprost (VENTAVIS), in cases of contraindication or intolerance to bosentan
- via continuous sub-cutaneous administration with treprostinil (REMODULIN), which can be proposed in the same way as iloprost (VENTAVIS). The decision to undergo treatment with treprostinil must take into consideration the increased likelihood of having to have a continuous sub-cutaneous infusion for long durations.
- continuous infusion with epoprostenol (FLOLAN).
A lung or heart and lung transplant are seen as last resort treatment options. Generally, a transplant is proposed for patients who have not seen any improvement after three months of medical treatment.
TRACLEER, VOLIBRIS, ADCIRCA and REVATIO are indicated in the treatment of PAH for patients with functional class II of the disease.

Treatment is evaluated three to four months after starting. If the patient achieves the aims set for their treatment, then it is continued, with regular monitoring at a specialised unit.
It is imperative to stress the importance of regular follow-ups to patients, in order to monitor the efficacy of treatments, or detect any deterioration in health as the result of the medication.

There is no data influencing the choice of one first-line treatment over another based on the class of the disease. Nevertheless, for patients with functional class III, prostacyclins are not used as first-line treatments, even though they have marketing authorisation for this type of patient, but are administered following failure of oral treatments.

For patients who are temporarily unable to take oral medication (mainly due to surgical procedures), European Guidelines[12] recommend switching to IV or nebulised treatments. These treatments, which are currently available as prostacyclins and have a proven efficacy, may be recommended.

In practice, patients taking oral sildenafil medication are not the most severely affected by the disease. They can, in general, miss several days of treatment with sildenafil; more so if they have an operation, as long as they are haemodynamically stable. Moreover, before scheduled surgery, the haemodynamic position of the patient is generally evaluated via right cardiac catheterisation and disease-modifying treatment changed as appropriate; whilst re-assessing the risks and benefits of the procedure.
In exceptional circumstances, such as major emergency surgery with post-op complications, which may lead to prolonged discontinuation of oral treatment, it is likely that a deterioration in haemodynamic stability may occur, resulting in further complications for the patient. In these situations, the use of sildenafil is not recommended[13] and in practice injectable treatments for serious, acute PAH, i.e. dobutamine and nitric oxide, if needed,[14] are given. IV administered

[12] Galie N. et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. 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: 2493-2537.
[13]The SPC states that there is no clinical data available for IV administration of sildenafil to patients who are clinically and haemodynamically unstable. Consequently, its use is not recommended for these patients (see section 4.4).
[14]In this situation, medicinal products with no marketing authorisation indication based on dobutamine and NOXAP and KINOX (both based on nitric oxide) are used. However, INOMAX is indicated in the "treatment of increase in peri- and post-operative pulmonary arterial hypertension within the context of cardiac surgery in adults, newborns, infants, children and adolescents aged from 0 to 17 years, with the

Prostacyclin (epoprostenol) is not normally used in these acute, unstable scenarios, but rather later on (e.g. after several days), sometimes as a combination if PAH is the main cause of deterioration rather than post-op sepsis for example.

The therapeutic use of REVATIO 0.8 mg/ml, solution for injection
REVATIO 0.8 mg/ml, solution for injection, is intended for patients receiving oral REVATIO 20 mg and who are temporarily unable to take this treatment in oral form. This population is difficult to quantify in the absence of detailed epidemiological data. In addition, there is no data supporting a potential deterioration in health of patients when they temporarily discontinue the oral treatment. Furthermore, in situations where some patients are not able to have oral treatment, there are alternatives available with proven efficacy.
Thus, the therapeutic use of REVATIO 0.8 mg/ml solution for injection is difficult to define given the information available.

Public health benefit:
Idiopathic Pulmonary Arterial Hypertension (PAH) and pulmonary hypertension associated with connective tissue disease are rare, but serious conditions. The burden on public health is low, due to the small number of patients concerned, especially for the injectable form of REVATIO.
There is no identified public health need. The therapeutic need linked to the ability to have an injectable treatment available for patients previously treated with oral REVATIO and who are clinically and haemodynamically stable is not clearly proven.
Available data (pharmacokinetic, pharmacodynamic and safety studies) do not allow the expected impact for injectable REVATIO on morbidity and mortality, quality of life and the healthcare system to be quantified and do not ensure the transferability of results to current practice.
Consequently, REVATIO is not expected to be of benefit to public health.

Conclusion:
Taking all the arguments into consideration, the Committee considers that the actual benefit of REVATIO 0.8 mg/ml, solution for injection, is insufficient compared with other therapies available for it to be paid for through public funds.

4.2. Improvement in actual benefit (IAB)

Not applicable

4.3. Therapeutic use

Not applicable (see section 4.1.).

4.4. Target population

Not applicable

4.5. Transparency Committee recommendations

The transparency Committee does not recommend inclusion on the list of medicines approved for hospital use and various public services.

aim of selectively decreasing pulmonary arterial pressure to improve right ventricular function and tissue oxygenation."