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TRANSPARENCY COMMITTEE

OPINION

10 February 2010

TRACLEER 32 mg, dispersible tablets
B/56 (CIP: 399 351-0)

Applicant: ACTELION PHARMACEUTICALS FRANCE

bosentan

List I
Medicine for hospital prescription only.
Prescription restricted to specialists and/or hospital departments specialising in pneumology, cardiology, rheumatology, dermatology, or internal medicine.
Medicine requiring special monitoring during treatment.

Orphan medicinal product (initial date of designation for TRACLEER products: 14 February 2001)

ATC code: C02KX01

Date of Marketing Authorisation (centralised procedure): 1 July 2009

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

Medical, Economic, and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

bosentan

1.2. Indications

"Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III[1].

Efficacy has been shown in:

- primary (idiopathic and familial) PAH;
- PAH secondary to scleroderma without significant interstitial pulmonary disease;
- PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology.

Some improvements have also been shown in patients with PAH WHO functional class II.

TRACLEER is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease."

1.3. Dosage

"TRACLEER tablets are to be taken orally morning and evening, with or without food.

The dispersible tablets should be added to a little water on a spoon, and the liquid stirred to aid dissolution, before swallowing. A little more water should be added to the spoon and swallowed by the patient, to make sure all of the medicine has been administered. If possible, a glass of water should be taken to ensure that all the medicine has been ingested. If necessary the dispersible tablet can be divided into 4 by breaking it along the lines cut into the surface.

The dispersible tablet has been studied only in paediatric patients. Direct bioavailability comparison has not been performed between dispersible tablets and film-coated tablets. Thus its use should be reserved for patients who cannot take the film-coated tablet.

Pulmonary arterial hypertension

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

In adult patients, TRACLEER treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily.

For paediatric patients aged 2 years or older, the optimal maintenance dose has not been defined in well-controlled studies. However, pediatric pharmacokinetic data have shown that bosentan plasma concentrations in children were on average lower than in adult patients and were not increased by increasing the dose of TRACLEER above 2 mg/kg twice daily. Based on these pharmacokinetic results, higher doses are unlikely to be more effective, and greater adverse event rates cannot formally be excluded in young children if the dose is increased.

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[1] Barst RJ et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2004 ;43:S40-S47. The NYHA classification (New York Heart Association Functional Classification) is based on the functional capacity of the patient. It divides patients into 4 classes:

- Class I: no limitation of physical activities. No dyspnoea and no fatigue during everyday activities
- Class II: moderate limitation of physical activities. Discomfort during strenuous physical activities. No discomfort at rest.
- Class III: marked limitation of physical activities. Discomfort during even moderate everyday activities. No discomfort at rest.
- Class IV: unable to undertake most everyday activities without considerable discomfort. Discomfort at rest.

No clinical study has been conducted to compare the efficacy/safety ratio of 2 mg/kg to 4 mg/kg twice daily in children.

There is only limited clinical experience in paediatric patients under 2 years of age.

In the case of clinical deterioration (e.g., decrease in 6-minute walk test distance by at least 10% compared with pre-treatment measurement) despite TRACLEER treatment for at least 8 weeks (target dose for at least 4 weeks), alternative therapies should be considered. However, some patients who show no response after 8 weeks of treatment with TRACLEER may respond favourably after an additional 4 to 8 weeks of treatment.
In the case of late clinical deterioration despite treatment with TRACLEER (i.e., after several months of treatment), the treatment should be re-assessed. Some patients not responding well to 125 mg twice daily of TRACLEER may slightly improve their exercise capacity when the dose is increased to 250 mg twice daily. A careful risk/benefit assessment should be made, taking into consideration that the liver toxicity is dose dependent.

Discontinuation of treatment
There is limited experience with abrupt discontinuation of TRACLEER. No evidence for acute rebound has been observed. However, to avoid the possible occurrence of harmful clinical deterioration due to potential rebound effect, gradual dose reduction (halving the dose for 3 to 7 days) should be considered. Intensified monitoring is recommended during the discontinuation period.
If the decision to withdraw TRACLEER is taken, it should be done gradually while an alternative therapy is introduced.

Systemic sclerosis with ongoing digital ulcer disease
Treatment should only be initiated and monitored by a physician experienced in the treatment of systemic sclerosis.
TRACLEER treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. TRACLEER tablets are to be taken orally morning and evening, with or without food.
Controlled clinical study experience in this indication is limited to 6 months.
The patient's response to treatment and need for continued therapy should be re-evaluated on a regular basis. A careful risk/benefit assessment should be made, taking into consideration the liver toxicity of bosentan.
There are no data on the safety and efficacy in patients under the age of 18 years. Kinetic data are not available for TRACLEER in young children with this disease.

Special populations
Dosage in hepatic impairment
No dose adjustment is needed in patients with mild hepatic impairment (i.e., Child-Pugh class A). TRACLEER is contraindicated in patients with moderate to severe liver dysfunction.
Dosage in renal impairment
No dose adjustment is required in patients with renal impairment. No dose adjustment is required in patients undergoing dialysis.
Dosage in elderly patients
No dose adjustment is required in patients over the age of 65 years."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

C: Cardiovascular system
C02: Antihypertensives
C02K: Other antihypertensives
C02KX: Other antihypertensives
C02KX01: bosentan

2.2. Medicines in the same therapeutic category

The other TRACLEER products containing 62.5 mg and 125 mg bosentan, in film-coated tablet form and having the same indications and the same dosage regimen as the TRACLEER 32 mg product.

2.3. Medicines with a similar therapeutic aim

- Endothelin receptor antagonists

- THELIN 100 mg (sitaxentan), coated tablet, the SPC of which states that: "This medicine is not recommended for use in children below 18 years due to a lack of data on safety and efficacy."
- VOLIBRIS 5 mg (ambrisentan), film-coated tablet, the SPC of which states that: "Volibris is not recommended for use in children below 18 years of age due to a lack of adequate data on safety and efficacy."

- Prostacyclin analogues

- FLOLAN (epoprostenol sodium, administered by continuous i.v. infusion, the SPC of which states that: "in the absence of sufficient data on the treatment of PAH in childhood, the MA for epoprostenol recommends that the doctor weigh the expected benefit to the child against the risk of not giving this therapy. On the basis of the available clinical studies it is not possible to establish whether the efficacy and safety of the recommended adult dosage regimen can be extrapolated to children and to adolescents."

- VENTAVIS (iloprost) 10 µg/ml, nebuliser solution, the SPC of which states that: "There is no experience with iloprost in children or adolescents."

- REMODULIN (treprostinil sodium), administered by the continuous subcutaneous route, the SPC of which states that: "There are few data on patients under 18 years of age. On the basis of the available clinical studies it is not possible to establish whether the efficacy and safety of the recommended adult dosage regimen can be extrapolated to children and to adolescents."

- Phosphodiesterase inhibitor

REVATIO (sildenafil), administered orally, the SPC of which states that: "Safety and efficacy in children and adolescents (< 18 years) have not been investigated in large-scale controlled clinical trials. Use of sildenafil in these patients is therefore not recommended."

3 ANALYSIS OF AVAILABLE DATA

In support of its request, the company has supplied:
- literature data, including 2 cohort studies[2, 3] of children followed up over the long term and treated with bosentan in the form of film-coated tablets (TRACLEER 62.5 mg and 125 mg); these data were not admitted by the Committee because they did not evaluate TRACLEER 32 mg which is the subject of this request,
- pharmacovigilance and postmarketing surveillance study data of the TRACLEER 62.5 mg and 125 mg products, not examined because they are not for the product to be evaluated,
- the results of 2 pharmacokinetic studies, BREATHE-3 and FUTURE-1.

The BREATHE-3 study evaluated the pharmacokinetics of TRACLEER 62.5 mg and 125 mg film-coated tablets in a paediatric population[4]. This study, which did not specifically evaluate TRACLEER 32 mg in dispersible-tablet form, will not be described in this document.

Only the results of the FUTURE-1 study, which specifically evaluated the TRACLEER 32 mg product, will be described.

3.1. Results of the FUTURE-1 study

The main aim of this study was to show that the area under the curve (AUC) after administration of the bosentan 32 mg cross-scored dispersible tablet in children aged 2 to 12 years with idiopathic or familial PAH of WHO functional class II or III was equivalent to that observed in adults after administration of 125 mg.
The secondary aim was to analyse tolerability. The duration of the study was 12 weeks.
Other criteria were evaluated on an exploratory basis. Thus there was an evaluation in the 12th week of treatment of the change, compared to baseline, in WHO functional class, quality of life according to the SF-10 questionnaire and Clinical Global Impression assessed using a scale on which the parents and the doctor separately gave an opinion on the child's general health status (5 possible answers ranging from "significantly better" to "significantly worse").

36 children with a mean age of 6.8 years (2.0 to 11.0) and a mean weight of 22.3 kg (9.5 to 42.0) were included; most of them had idiopathic PAH. The children were given the bosentan in dispersible tablet form at a dosage of 2 mg/kg twice daily for 4 weeks, then at a dosage of 4 mg/kg twice daily.

Results
The AUC were not comparable, and an absorption plateau seems to be reached at lower dosages in children. In children, increasing the dosage to twice-daily 4 mg/kg does not lead to higher exposure than with a dosage of twice-daily 2 mg/kg.

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[2] Rosenzweig EB et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. J Am Coll Cardiol 2005; 46: 697–704.
[3] Maiya S et al. Response to bosentan in children with pulmonary hypertension. Heart 2006 ; 92: 664-670
[4] the dosage section of the SPC for TRACLEER 62.5 mg and 125 mg below mentions the results of the BREATHE-3 study.
"The safety and efficacy of TRACLEER have not been fully investigated in children under 12 years of age.
This trial was designed primarily to determine the pharmacokinetics of TRACLEER in children. The number of children investigated in each dose group was insufficient to be able to establish the optimal dosage in subjects under 12 years of age. The systemic exposure was found to be lower in children than in adults with pulmonary arterial hypertension. These data suggest the possibility of an incomplete effect on the pulmonary vasculature at the doses used in this trial. However, the tolerability of administration of higher dosages in children has not been established.
No data are available in regard to children under 3 years of age."

In view of this absorption plateau of the medicinal product, the recommended dosage of bosentan is 2 mg/kg twice daily.

By the 12th week of treatment, out of the 23 patients in functional class II at the start of the study, 1 had moved to class III, 2 had moved to class I, and 20 had remained unchanged. Of the 12 patients in functional class III at the start of the study, none had got worse and 3 had moved into functional class II[5].

The mean physical score (PHS of SF-10 – Physical summary) of the SF-10 questionnaire improved slightly between the start and the end of the treatment, rising from 26.7 to 28.3. No change in the psychological score (PSS of SF-10 – Psychological summary) was observed.

Out of the 17 patients whose parent-rated Global Clinical Impression had been *neither good nor bad* or *bad* at the start of the study and 11 patients who had been given the same clinical impression rating by the doctor, 9 had an impression rating of *better* or *significantly better* at the end of the study.
Of the 24 patients whose status had been judged by the doctor to be *good* or *very good* at the start of the study, 2 gave a *worse or significantly worse impression* at the end of the study. No change was found for 13 patients, and 9 patients gave a *better* clinical impression.

This study is the subject of a follow-up extension (FUTURE-2 study) until TRACLEER 32 mg becomes available. In March 2008 (most recent available analysis), stabilization or improvement of functional class had been observed in the 33 patients included.
The survival rate was 94% in the 6th month of follow-up and 91% in the 12th, 18th, and 24th month of follow-up.

3.2. Tolerance data

The paediatric formulation of bosentan was well tolerated overall. In the FUTURE-1 study, the commonest adverse events were infections, chiefly of the respiratory tract, which were observed in 15 patients and intestinal disorders (mainly abdominal pain, discomfort), which were seen in 12 patients.
No increase in hepatic transaminases and no anaemia were observed during the study or during the post-treatment follow-up period.

At the request of the EMEA, the epidemiological data of the French registry (ItinérAIR pédiatrie), those of the international TOPP registry and the REVEAL registry for the United States, and also those of a Dutch registry are going to be used to better describe PAH in children and, in particular, its possible impact on growth and puberty.

3.3. Conclusion

Of the studies provided, only the pharmacokinetics study FUTURE-1 specifically evaluated TRACLEER 32 mg in 36 children between 2 and 12 years of age suffering from idiopathic or familial PAH of functional class II or III.
No pharmacokinetic data are available in regard to children under 2 years of age.
No efficacy study carried out specifically in children, including in PAH associated with congenital heart disease – a very common aetiology in children, is available.
As bioequivalence between the dispersible tablets and the film-coated tablets has not been established, it is difficult to extrapolate the data obtained in the clinical studies of the film-coated tablets to this new form.
The safety profile was similar to that observed in the studies carried out in adults with PAH. The main adverse effects were of an infectious and gastrointestinal nature.

[5] One patient was excluded from the analysis as he had not been treated in accordance with the recommendations of the SPC

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

PAH is a potentially fatal lung disease characterised by elevated blood pressure in the pulmonary arterial system. Asthenia, dyspnoea, chest pain, and retardation of height and weight are the most frequent clinical signs in children. Patients' life expectancy without specific treatment for PAH is short, less than a year in children (around 4.8 years in adults).
This product falls under the category of symptomatic treatment.
The efficacy/adverse effects ratio is high.
This medicinal product is a first-line therapy.
Aside from the other available dosages of TRACLEER, there are few alternative drug therapies that can be administered to children. Furthermore, their use has not been validated by the registration authorities.

Public health benefit:
In public-health terms, the burden imposed by functional class II or III pulmonary arterial hypertension (PAH), whether primary or associated with congenital heart disease or connective tissue disease, is small on account of the limited number of patients affected. In view of the estimated prevalence of the disease in children (3.7 cases per million[6]), the burden of the disease in the paediatric population can only be small.
Improving the management of pulmonary arterial hypertension is a public health need that is an established priority (Rare Diseases Plan).
Because it is formulated as a cross-scored dispersible tablet, TRACLEER 32 mg is expected to allow better adjustment of the dose of the treatment in children and also easier administration, including in adults who are unable to swallow the film-coated tablets.
However, in the absence of available clinical data for TRACLEER 32 mg in children on the one hand and of a study of bioequivalence between the dispersible tablets and the film-coated tablets on the other, it is hard to estimate TRACLEER's impact on morbidity/mortality, which might only be small in population terms. Furthermore, no improvement of quality of life has been demonstrated.
The available data thus do not permit the assumption that TRACLEER will make an additional contribution towards meeting the identified public-health need.
Consequently, in the current state of knowledge, TRACLEER 32 mg is not expected to have any public health benefit.

The actual benefit is considered to be substantial, pending re-evaluation of all therapies for PAH by the Transparency Committee.

4.2. Improvement in actual benefit (IAB)

In the absence of clinically relevant data, the Transparency Committee is unable to quantify the contribution of TRACLEER 32 mg dispersible tablets in the management of patients with functional class II or III PAH of a primary nature or associated with scleroderma or congenital heart disease.
It is a useful addition to the range for the management of PAH in children in particular.
TRACLEER 32 mg dispersible tablets do not bring an improvement in actual benefit (IAB V).

4.3. Therapeutic use[7]

There is as yet no treatment recommendation in regard to patients with functional class II PAH.

[6] Fraisse A et al. A French registry of pulmonary arterial hypertension in children: baseline characteristics. European Heart Journal 2007; 28 (Abstract supplement), 631.
[7] ESC guidelines on the diagnosis and treatment of pulmonary arterial hypertension. Eur Heart J 2004; 25:2243-78. Deanfield J et al. Management of grown up congenital heart disease. Task force on the management of grown up congenital heart disease. European Society of Cardiology. Eur Heart J 2003;24:1035-84.

The treatments offered at present remain wholly palliative and symptomatic (improvement of function, prevention of complications, conventional therapy, etc.). Conventional treatment for PAH combines anticoagulants, diuretics, oxygen therapy, and calcium inhibitors.

In patients with class II PAH
- benefit of early management of PAH has not been demonstrated,
- only one other medicine, ambrisentan (VOLIBRIS), is indicated.

TRACLEER's place in the treatment strategy for PAH in patients in functional class II has yet to be defined in view of the available data and in the absence of recommendations, as in the case of VOLIBRIS.

Most of the patients (50 to 75%) are diagnosed at a late stage, in functional class III-IV[8].
In patients with PAH of class III in particular, the following can be used:
- by the oral route: bosentan (TRACLEER), sitaxentan (THELIN), ambrisentan (VOLIBRIS), or sildenafil (REVATIO)
- by the inhalational route: iloprost (VENTAVIS), in cases of a contraindication to, or hepatic intolerance of, bosentan
- by the continuous subcutaneous route: treprostinil (REMODULIN), which can be offered for the same reasons as iloprost (VENTAVIS). The decision to embark on treprostinil therapy must take account of the high probability of its being necessary to continue continuous subcutaneous infusion in the long term.
- by continuous infusion: epoprostenol (FLOLAN).
  A lung or heart-and-lung transplant is the treatment of last resort. It is generally considered in patients who have not improved after 3 months of medical treatment.

PAH treatment in children is identical to that in adults. The medicines used at present are those that have been evaluated in adults (with dose adjustments), including the products TRACLEER 62.5 mg and 125 mg film-coated tablets.

The formulation of TRACLEER 32 mg dispersible tablets allows adjustment of the dosage to the patient's weight and administration appropriate to the child in the treatment of PAH. This product is also appropriate for adult patients who are unable to swallow the film-coated tablets.
The other treatments available in France, aside from the other TRACLEER products containing 62.5 mg and 125 mg, are not recommended for patients under 18 years of age. Only epoprostenol can be used in children – after the doctor has weighed the expected benefit in this population against the risk of not giving treatment.

4.4. Target population

The target population for TRACLEER 32 mg is children between 2 and 12 years of age with functional class II and III, chiefly idiopathic and familial, PAH and PAH associated with congenital heart disease, which in total account for around 90% of paediatric PAH cases.
This population can be estimated from the following data:
The French population of children between 2 and 12 years of age was estimated at around 8.3 million in 2008.
As defined by the observational study of PAH in children (ItinérAIR pédiatrie 2005 to 2006), the minimal prevalence of PAH (all causes together, including PAH associated with congenital heart disease, but not PAH due to other kinds of heart disease) was evaluated at 3.7 cases per million, which corresponds to 31 children.
PAH associated with or due to congenital heart disease accounts for about 50% (each for about half of this) of all PAH cases. Roughly ten patients with PAH due to congenital heart disease thus need to be added to the figure given by the ItinérAIR pédiatrie registry, making a total of about forty, though this is a minimum as not all of the centres that may treat disorders of this kind were included in the registry.

[8] Humbert M et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;73:1023 - 1030

It thus seems reasonable to estimate the number of PAH patients between 2 and 12 years of age as being between 40 and 50.
70% of this population are in functional class II or III and may be treated with TRACLEER 32 mg.
On the basis of the above, the target population for TRACLEER 32 mg would be 30 to 40 patients.
To this population must be added the adult patients who are unable to swallow the film-coated tablets, though the number of such patients is hard to quantify.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications and at the dosage of the marketing authorisation.