HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

18 July 2007

TRACLEER 62.5 mg, film-coated tablet
Box of 56 (CIP: 563 621-1)

TRACLEER 125 mg, film-coated tablet
Box of 56 (CIP: 563 622-8)

Applicant : ACTELION PHARMACEUTICALS FRANCE

Bosentan

List I
Medicinal product restricted to hospital prescription by certain specialists and/or facilities specialising in cardiology, pneumonology, or internal medicine services.
Medicine requiring specific monitoring during treatment.

Date of Marketing Authorisation (centralised procedure): 15 May 2002
Date of revision of Marketing Authorisation (extension of indication): 27 October 2006

Reason for request: inclusion on the list for hospital use in the extension of indication: "treatment of pulmonary arterial hypertension associated with left-right shunt type congenital heart disease with Eisenmenger syndrome".

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Bosentan

1.2. Indications

Treatment of pulmonary arterial hypertension (PAH) with the aim of improving exercise capacity and symptoms in patients with NYHA grade III[1] functional status.
Efficacy has been shown in:

- Primary (idiopathic and familial) pulmonary arterial hypertension
- Pulmonary arterial hypertension secondary to scleroderma without significant interstitial pulmonary disease.

Indications previously assessed by the Committee (see Opinion dated 5 February 2003)

- Pulmonary arterial hypertension associated with left-right shunt type congenital heart disease and Eisenmenger syndrome.

1.3. Dosage

Treatment with TRACLEER should only be initiated and monitored by a physician specialising in the treatment of pulmonary arterial hypertension. This 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.

In the case of clinical deterioration (such as decreased 6-minute walking test distance by at least 10% compared with pre-treatment measurement) despite TRACLEER treatment for at least 8 weeks (target dose administered for at least 4 weeks), an alternative therapy 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. If the decision to withdraw TRACLEER is taken, it should be done gradually while an alternative therapy is introduced.

In the case of late clinical deterioration despite treatment with TRACLEER (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 TRACLEER's liver toxicity is dose dependent.

[1] The NYHA Classification (New York Heart Association Functional Classification) classifies patients according to functional capacity. It classifies patients into 4 classes:

- Class I: No limitation of physical activity. Ordinary activity does not cause dyspnoea or fatigue.
- Class II: Slight limitation of physical activity. Comfortable at rest, but significant physical activity results in discomfort.
- Class III: Marked limitation of physical activity. Comfortable at rest, but even slight ordinary activity results in discomfort.
- Class IV: Unable to carry out any physical activity without significant discomfort. Discomfort at rest.

Discontinuation of treatment
There is limited data on the consequences of abrupt discontinuation of treatment with TRACLEER. No evidence of rebound effect has been observed. However, to avoid the possible occurrence of clinical deterioration due to potential rebound effect, a gradual dose reduction (halving the dose for 3 to 7 days) should be considered and intense monitoring is recommended.

Dosage in hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (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 dosage adjustment is required in patients over the age of 65 years.

Children
The safety and efficacy of TRACLEER in children under the age of 12 years have not been substantially documented.

Table 1: Dosing regimen used in study AC-052-356 (BREATHE-3):

Body Weight (kg)	Initial Dose (4 weeks)	Maintenance Dose
10 ≤ × ≤ 20	31.25 mg once daily	31.25 mg twice daily
20 < × ≤ 40	31.25 mg twice daily	62.5 mg twice daily
> 40 kg	62.5mg twice daily	125 mg twice daily

This study was primarily designed to assess TRACLEER pharmacokinetics in children. The number of children studied in each dose group was insufficient to establish the optimal dosing regimen in patients under the age of 12 years. The pharmacokinetic findings showed that systemic exposure was lower than in adults with pulmonary arterial hypertension. The data for the doses utilised in this study suggest the possibility of a sub-optimal effect on pulmonary vasculature. However, the safety of higher doses has not been established in children.

There are no data available on children under 3 years of age.

Patients with low body weight
There is limited data available on patients with a body weight below 40 kg.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification 2007

C: Cardiovascular system
C02: Antihypertensives
C02K: Other antihypertensives
C02KX: Other antihypertensives
C02KX 01: Bosentan

2.2. Medicines in the same therapeutic category

Comparator medicines

Bosentan (TRACLEER) is the only dual endothelin receptor antagonist indicated in the treatment of PAH associated with left-right shunt type congenital heart disease with Eisenmenger syndrome.

2.3. Medicines with a similar therapeutic aim

Other than bosentan, no other medicine is indicated in the treatment of PAH associated with left-right shunt type congenital heart disease and Eisenmenger syndrome.

3 ANALYSIS OF AVAILABLE DATA

To support its request, the company has submitted the results of one published study[2], Study BREATHE-5, whose objective was to assess the efficacy and safety of TRACLEER compared to placebo over 16 weeks in patients with grade III functional status pulmonary arterial hypertension associated with left-right shunt type congenital heart disease and Eisenmenger syndrome.

This study included an open-label extension of 40 weeks. The results of this extended study are not detailed in the opinion.

Methodology

Comparative, randomised, double-blind study conducted on 54 patients (37 in the TRACLEER group, 17 in the placebo group).

The primary objective of this study was to show that TRACLEER did not worsen hypoxemia. To that end, the protocol included a non-inferiority test for the primary endpoint (change in transcutaneous oxygen saturation at rest) compared to placebo. The clinical rationale for this hypothesis was justified by the fear that a treatment-induced drop in blood pressure would worsen left-right shunt and peripheral arterial desaturation, as has been observed with other vasodilatation treatments.

Inclusion criteria

- Men and women (not pregnant) aged ≥ 12 years and weighing ≥ 40 kg
- PAH associated with Eisenmenger syndrome confirmed through echocardiography (IAC of effective diameter ≥ 2 cm and/or IVC of effective diameter ≥ 1 cm) and confirmed through right heart catheterisation (PAPm > 25 mmHg, PAPO < 15 mmHg and PVR > 3 mmHg/L/min, 240 dyn.s.cm^{-5})[3]
- NYHA functional class III
- 6-minute walking test distance ≥ 150 m and ≤ 450 m
- Oxygen saturation (SpO_2) measured through pulse oximeter, at rest and room temperature > 70% and ≤ 90%
- Stable clinical and therapeutic condition since 3 months.

Patients with complex congenital heart disease and patients with Down syndrome (diseases that are frequently associated with Eisenmenger syndrome) were excluded from this study.

[2] Galie N et al. Bosentan therapy in patients with Eisenmenger syndrome, a multicenter, double blind, randomized, placebo-controlled study. Circulation 2006; 114:48-54

[3] IAC: Interatrial Communication
IVC: Interventricular Communication
PAPm: Mean Pulmonary Artery Pressure
PAOP: Pulmonary Artery Occlusion Pressure
PVR: Pulmonary Vascular Resistance

Primary endpoints

1st endpoint:

Change in transcutaneous oxygen saturation (SpO2) at rest, from baseline to end of treatment (week 16)

Hypothesis of TRACLEER non-inferiority compared to placebo

TRACLEER was to be considered as non-inferior to placebo if the mean change in oxygen saturation from baseline to week 16 of treatment for the 2 groups was below a threshold of 5% in absolute value.

2nd endpoint:

If non-inferiority was shown, the protocol called for an analysis of the secondary endpoint: change in iPVR (Indexed Pulmonary Vascular Resistance) from baseline to end of treatment

Secondary endpoints

- 6-minute walk test distance
- Borg dyspnoea index
- PAH functional class
- Percentage of patients with decreased SpO2 ≥10% from baseline to end of treatment
- Haemodynamic parameters

Dosing regimen / Treatment duration

The TRACLEER dosing regimen was 62.5 mg twice daily for 4 weeks then 125 mg twice daily for 12 weeks.

Treatment duration was 16 weeks.

Results

Table 2: Patient characteristics at baseline

	Placebo (n=17)	TRACLEER (n=37)
Mean age (years)	44.2 ± 8.5	37.2 ± 12.0
Mean time since Eisenmenger syndrome diagnosis (years)	20.5 ± 13.0	23.7 ± 13.6
Type of congenital heart disease n (%)		
- IVC*	12 (71)	24 (65)
- IAC*	5 (29)	8 (22)
- IAC + IVC	-	5 (14)
Previous and current treatments n (%)		
- Antithrombotic agents	11 (65)	25 (68)
- Diuretics	10 (53)	13 (35)
- Calcium antagonists	4 (24)	3 (8)

*IAC: Interatrial Communication

*IVC: Interventricular Communication

3.1. Efficacy

- **On primary endpoints:**

Table 3: Transcutaneous oxygen saturation (protocol analysis):

	placebo N=17	TRACLEER N=35
Initial value (%)	83.6 ± 1.2	82.4 ± 0.9
Value at end of treatment (16 weeks) %	84.0 ± 1.6	83.8 ± 0.9
Change versus placebo (CI 95 %)	+1.0 [-0.7 ; 2.8]	

The protocol analysis concludes the non-inferiority of TRACLEER compared to placebo.

Table 4: Pulmonary vascular resistance:

	placebo N=17	TRACLEER N=36*
Initial value (dyne.sec.cm^{-5})	2,870.0 ± 293.3	3,425.1 ± 235.1
Value at end of treatment (16 weeks) dyne.sec.cm^{-5}	3,025.1 ± 298.3	3,108.2 ± 223.7
Change versus placebo (CI 95 %)	-472.0 ± 221.9 [-917.6 ; -26.5] p=0.0383	

A statistically significant reduction in pulmonary vascular resistance was observed between TRACLEER and placebo, from baseline to end of treatment.

- **On secondary endpoints:**

- 6-minute walking test distance

At baseline, the distance was 366.4 ± 16.4 m for the placebo group and 331.9 ± 13.6 m for the TRACLEER group.
At the end of treatment the walking distance was 356.7 ± 29.3 m for the placebo group and 375.3 ± 15.5 m for the TRACLEER group.
The walking distance assessed through 6-minute walk test was improved by 53.1 ± 19.2 m under TRACLEER compared to placebo (CI 95% [14.5; 91.7], p=0.0079).

- Borg dyspnoea index

No change in efficacy was observed between TRACLEER and placebo.

- PAH functional status

Thirteen of 37 patients of the TRACLEER group (35%), compared to 2 of 16 patients of the placebo group (12.5%), went from functional grade III to grade II.

- Percentage of patients with reduced oxygen saturation ≥10% from baseline to end of treatment

No decrease in oxygen saturation ≥10% was observed.

3.2. Adverse events

3.2.1. adverse reported during the study

The most frequently reported undesirable effects were:

- peripheral oedema: 7 patients in the TRACLEER group compared to 1 patient in the placebo group
- headache: 5 patients in the TRACLEER group compared to 2 patients in the placebo group
- palpitations: 4 patients in the TRACLEER group only
- dizziness: 3 patients in the TRACLEER group compared to 1 patient in the placebo group
- chest pain: 3 patients of the TRACLEER group only
- asthenia: 2 patients of the placebo group only

Two patients from each group discontinued treatment as a result of adverse events.

3.2.2. SPC

Liver toxicity

Four patients in the TRACLEER group and none in the placebo group experienced increased liver transaminases (ALAT/ASAT>3 times the maximum normal limit). Of these four patients, one presented increased enzymes at a rate of 5 times the maximum normal limit and discontinued treatment; one presented a serious adverse event (biliary colic) associated to enzyme increase at more than 8 times the maximum normal limit, which resolved in spite of continued TRACLEER treatment.

Elevations in serum ASAT and/or ALAT levels, observed under TRACLEER, are dose-dependent. These liver enzyme changes generally occur within the first 26 weeks of treatment but may also occur at a later time.

Liver serum aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment. Furthermore, liver aminotransferase levels must be measured 2 weeks following any dosage increase.

Pregnancy

TRACLEER should be considered a teratogen product and should not be used during pregnancy. Pregnancy should not be considered for at least 3 months after stopping treatment with TRACLEER.

3.3. Conclusion

The efficacy and safety of TRACLEER have been assessed in patients with functional grade III pulmonary arterial hypertension associated with left-right shunt type congenital heart disease and Eisenmenger's syndrome in a placebo-controlled, randomised, double-blind study conducted on 54 patients (37 in the TRACLEER group, 17 in the placebo group).

This study analysed 2 endpoints: changes in transcutaneous oxygen saturation from baseline to the end of treatment between TRACLEER and placebo, according to a hypothesis of non-inferiority; change in pulmonary vascular resistances between TRACLEER and placebo from baseline to the end of treatment, according to a hypothesis of superiority.

The non-inferiority of TRACLEER compared to placebo was demonstrated for the criterion "change in transcutaneous oxygen saturation". A statistically significant reduction of pulmonary vascular resistance was observed between TRACLEER and placebo from baseline to end of treatment (decrease of 472.01 dyne..sec.cm^{-5}). However, this decrease is moderate and relates to an interim endpoint.

The selection of a clinical criterion, as primary endpoint, such as 6-minute walking test (the most rigorous criterion) or improvement of NYHA functional status would have been more relevant in terms of assessing the clinical benefit of TRACLEER in the treatment of Eisenmenger's syndrome.

The most frequently observed adverse events of TRACLEER were peripheral oedema, headache, palpitations, dizziness, and chest pain. Liver toxicity was observed and strict monitoring is prescribed for this treatment in the RCP.

Data on the efficacy and safety of TRACLEER beyond 40 weeks in patients with Eisenmenger's syndrome is not available.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Eisenmenger's syndrome is the most advanced form of PAH associated with left-right shunt type congenital heart disease. This is characterised by cyanosis. This is a chronic pathology. Chronic hypoxia induces numerous potentially fatal complications.
These medicinal products are intended as a curative treatment.
The efficacy / undesirable effect ratio is high.
This medicinal product is a first-line treatment.
There are no medicinal treatment alternatives.

Public health benefit:
Pulmonary arterial hypertension associated with congenital heart disease (left-right shunt type) and Eisenmenger's syndrome is a serious clinical condition that is life-threatening. However, the burden on public health caused by this pathology is low, based on the small number of patients involved.
Improvement in managing pulmonary arterial hypertension is a necessity falling within the scope of an identified health priority (Rare disease plan: GTNDO).
Based on the clinical results, and in light of the insufficiency of existing therapies, the expected impact of the medicinal product TRACLEER, in population norms of morbidity and quality of life associated to this pathology, can only be minimal.
It is, however, not possible to affirm that the medicinal product TRACLEER will meet the identified public health need.
Therefore, it is not expected that TRACLEER will benefit public health in this indication.

The actual benefit of TRACLEER is substantial.

4.2. Improvement in actual benefit

TRACLEER provides a moderate improvement in actual benefit (IAB III) in managing pulmonary arterial hypertension associated to left-right shunt type congenital heart disease with Eisenmenger's syndrome.

4.3. Therapeutic use[4]

Management of PAH with Eisenmenger's syndrome

Current treatment is based on prevention of complications, conventional therapies, and heart and lung transplant.

General measures include recommendations against physical activity, exposure to high altitudes (over 1,500 m), infections; pregnancy; appropriate assessments should be undertaken prior to any elective surgery, and psychological assistance should be provided as necessary.

The initial recommendation is to begin with a conventional treatment (level of evidence C) with oral anticoagulants (if not contraindicated), diuretics (in case of sodium and water retention) and oxygen therapy (in case of hypoxia).

Patients should then be referred to a specialist centre for acute vasodilatation testing and specific PAH treatment. Only those patients with confirmed acute vasodilator response (according to strictly defined criteria), are eligible for long-term calcium antagonist treatment.

The selection of a first-line treatment depends on several factors, in particular the method of administration, safety profile, and physician experience. In the absence of comparative studies, international recommendations have not been issued regarding optimal first-line therapy.

The role of calcium antagonists, anticoagulants, and oxygen therapy is controversial or limited in the treatment of Eisenmenger syndrome.

Calcium antagonists are rarely indicated as they risk affecting the shunt.

In certain centres, patients with Eisenmenger syndrome are treated with anticoagulants in the same manner as those patients with idiopathic PAH, unless contraindicated. However, in light of the potentially fatal risk of bleeding, it is recommended that anticoagulants and anti-platelet aggregants be reserved for well-defined indications and strict monitoring be observed.

The indication of oxygen therapy is controversial. This is reserved for cases in which O_2 supplementation results in a substantial O_2 arterial saturation and/or subjective clinical improvement. This does not affect morbidity or survival.

Lung transplant with correction of the congenital heart disease, or, preferably, heart and lung transplant are therapeutic options available only to a select number of patients or those with a poor prognosis and/or where 1-year life expectancy is less than 50%. This option is exceptional in light of its morbidity-mortality, the waiting times for transplant, and the rarity of donors.

Place of TRACLEER therapeutic strategy

TRACLEER represents a new treatment option in the management of PAH associated with Eisenmenger syndrome. It is the only medicinal product with a Marketing Authorisation in this indication.

[4] 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.

4.4. Target population

The target population for TRACLEER comprises patients of NYHA functional class III (final progressive stage of PAH associated with left-right shunt type congenital heart disease with Eisenmenger syndrome).

There is no epidemiological data on the prevalence of Eisenmenger syndrome in France.
Nevertheless, the population may be estimated from the following data:
- In France, there were 796,800 births in 2006 [5]
- Congenital heart diseases are the most common congenital malformations, with an incidence of approximately 8 per 1,000 births[6]; 60% of these abnormalities are characterised by left-right shunt[6], i.e., 3,825 patients affected by congenital heart disease with left-right shunt. Approximately 15% of children die before adulthood (specialist opinion).
- Eisenmenger syndrome represents approximately 20% of these congenital heart diseases.

The target population for TRACLEER is therefore estimated at approximately 650 new cases per year, maximum.

The tendency is that this population will decrease, as early surgery for congenital shunt prevents the onset of Eisenmenger syndrome.

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 this extension of indication.

[5] INSEE – bilan démographique 2006 – naissances et fécondité
[6] M. Beghetti. Hypertension artérielle pulmonaire des cardiopathies congénitales. Rev Mal Resp 2006 ; 23 : 13S49 – 13S59