HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

20 June 2007

THELIN 100 mg, coated tablets
B/28 (CIP: 379 171-7)

Applicant : ENCYSIVE FRANCE

sitaxentan

List I
Medicinal product for hospital prescription only. Prescription restricted to specialists and/or departments in cardiology, pneumology or internal medicine.
Medicinal product requiring specific monitoring during treatment.

Date of Marketing Authorisation (MA) (centralised procedure): 10 August 2006

Reason for request: Inclusion on the list of medicinal products for hospital use.

Health Technology Assessment Division

1 PROPERTIES OF THE MEDICINAL PRODUCT

1.1. Active substance
sitaxentan

1.2. Indications
Treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III[1], to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.

1.3. Dosage
The treatment must only be initiated and monitored by a doctor experienced in the management of pulmonary arterial hypertension.

THELIN should be administered orally at the dose of 100 mg once a day. It can be taken with or without food, at any time of day.

In the event of a clinical deterioration despite treatment with THELIN for at least 12 weeks, other treatments should be considered. Nevertheless, some patients who presented no response after 12 weeks' treatment reacted favourably by the 24th week; consequently, 12 weeks' additional treatment could be considered in some cases.

An increase in dose does not provide any benefit taking into account the likely adverse effects, especially in terms of liver toxicity.

Discontinuation of treatment
Abrupt discontinuation of sitaxentan treatment is not well documented. No events suggesting a rebound effect have been observed.

Liver impairment
The drug has not been studied in patients with liver impairment. THELIN is contraindicated in patients with elevated liver transaminases before the start of treatment [> 3 times the upper limit of the normal range (ULN)].

Kidney impairment:
No dose adjustment is necessary in patients with kidney impairment.

Children and adolescents (< 18 years).
In view of the absence of efficacy and safety data, this drug is not recommended for use in children aged under 18 years.

[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.

Elderly patients:
No dose adjustment is necessary in patients aged over 65 years.

Patients taking other medicinal products:
The efficacy and safety of THELIN during concomitant administration with other drugs used for the treatment of pulmonary arterial hypertension (e.g. epoprostenol, sildenafil and iloprost) have not been studied in controlled clinical studies. Consequently, prudence is recommended in the event of concomitant administration.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2007 classification

C: Cardiovascular system
C02: Anti-hypertensives
C02K: Other anti-hypertensives
C02KX: Other anti-hypertensives
C02KX02: sitaxentan

2.2. Medicines in the same therapeutic category

Comparator drugs
TRACLEER (bosentan) film-coated tablets, indicated in the treatment of pulmonary arterial hypertension (PAH) with the aim of improving exercise tolerance and symptoms in patients in functional class NYHA III.
The efficacy of the drug has been demonstrated in:
- primary (idiopathic and familial) PAH
- PAH associated with scleroderma without significant associated interstitial disorder.
- PAH associated with congenital left-right shunt heart disease with Eisenmenger's syndrome.

2.3. Medicines with a similar therapeutic aim

- REVATIO (sildenafil), an oral phosphodiesterase inhibitor indicated for the treatment of PAH in patients in functional class III according to the WHO classification, to improve their exercise capacity. The efficacy of the drug has been demonstrated in idiopathic PAH and PAH associated with connective tissue disease.
- FLOLAN (epoprostenol sodium), a prostacyclin administered by continuous I.V. infusion, indicated in the long-term treatment by continuous infusion of pulmonary arterial hypertension (PAH): idiopathic / familial or sporadic pulmonary arterial hypertension, pulmonary arterial hypertension associated with systemic collagenosis, in patients at functional clinical stage III or IV (on the New York Heart Association severity scale).
- VENTAVIS (iloprost) 10 µg/ml, solution for inhalation by nebuliser, a prostacyclin analogue indicated in the treatment of primary PAH with the aim of improving the exercise tolerance and symptoms of patients in functional class III.
- REMODULIN (treprostinil sodium), a prostacyclin analogue for continuous subcutaneous administration, indicated in the treatment of primary pulmonary arterial hypertension with the aim of improving the exercise tolerance and symptoms of patients in NYHA (New York Heart Association) functional class III.

3 ANALYSIS OF AVAILABLE DATA

The manufacturer has filed the results of 5 studies in support of its application:

- Study **FPH01**: phase IIb/III comparative, randomised, double-blind study, whose objective was to evaluate the efficacy and safety of THELIN compared with a placebo in 178 patients suffering from PAH.
- Study **FPH02**: phase III comparative, randomised, double-blind study, whose objective was to evaluate the efficacy and safety of THELIN compared with a placebo in 247 patients suffering from PAH. This study also included an open-label TRACLEER arm.
- Study **FPH03**, an open-label study to evaluate the long-term efficacy and safety of THELIN, for which only intermediate results are available.
- Study **FPH04**: phase III comparative, randomised, double-blind study, whose objective was to evaluate the efficacy and safety of THELIN associated with conventional PAH treatment compared with a placebo in 98 patients suffering from PAH.
- Study **FPH06**: comparative, randomised, double-blind study to evaluate two doses of THELIN after therapeutic failure of treatment with TRACLEER.

This opinion only relates to the comparative, randomised, double-blind studies (i.e. studies FPH01, FPH02, FPH04 and FPH06).

3.1. EFFICACY RESULTS

3.1.1. STUDY FPH01[2]

Design

Phase IIb/III comparative, randomised, double-blind study, whose objective was to evaluate the efficacy and safety of THELIN compared with a placebo in 178 patients suffering from PAH.
The treatment duration was 12 weeks.

Inclusion criteria

Males and females aged 16 to 75 years, suffering from idiopathic or secondary PAH (connective tissue disease or left-right shunt), in functional class II, III or IV.

Dosing regimen / duration of treatment

The patients were randomised to receive for 12 weeks either:

- THELIN 100 mg at the dose of one tablet a day (n=55)
- THELIN 300 mg at the dose of one tablet a day (n=63) or
- placebo (n=60).

The results of the THELIN 300 mg group are not presented, as there is no MA for that dose.

[2] Barst RJ et al. Sitaxentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 2004; 169 : 441-7

Primary endpoint:
Variation, between inclusion and the end of the treatment, in the theoretical maximal oxygen uptake (VO2) measured during the exercise test. A method of controlling alpha-risk inflation due to multiple comparisons has been implemented.

Secondary endpoints:
- 6-minute walk test distance after 12 weeks of treatment
- Stage of NYHA functional class after 12 weeks of treatment

Results

Table 1: Baseline patient characteristics

	Placebo (n=60)	THELIN 100 mg (n=55)
Mean age (years)	48 ± 14	45 ± 14
Type of PAH		
- Idiopathic % (n)	62% (37)	42% (23)
- Secondary % (n)	38% (23)	58% (32)
Functional class II (NYHA) % (n)	37% (22)	29% (16)
Functional class III (NYHA) % (n)	60% (36)	71% (39)
VO2 (%)	47.7 ± 13.65	44.7 ± 14.10
6-minute walking test distance (m)	412.9 ± 105.2	394.2 ± 114.2

- Primary endpoint:

No difference was observed between THELIN 100 mg and the placebo on the primary endpoint.

- Secondary endpoints:

The improvement in the walking distance of patients in the THELIN group compared with the placebo group was 35.0 metres (95% CI [8.5; 58.6], p = 0.006) after 12 weeks of treatment.

An improvement in the NYHA functional class after 12 weeks of treatment was observed in 29% of patients in the THELIN group (16/55) and 15% of patients in the placebo group (9/60), p= 0.04.

This study was extended (follow-up of 42 to 72 weeks). The results of this extension phase do not allow for a formal conclusion to be reached regarding the long-term efficacy or safety of THELIN.

In conclusion, this study and its extension do not provide any clinical or methodological data which would allow the efficacy of THELIN to be quantified.

3.1.2. STUDY FPH02

Design

Phase III comparative, randomised, double-blind study, whose objective was to evaluate the efficacy and safety of THELIN compared with a placebo in 247 patients suffering from PAH. This study also included an open-label TRACLEER arm (whose the descriptive results will not be presented).

The treatment duration was 18 weeks.

Inclusion criteria

Males and females aged 12 to 75 years, suffering from idiopathic or secondary PAH (connective tissue disease or congenital cardiac malformation), in functional class II, III or IV.

Dosing regimen / duration of treatment

The patients were randomised to receive for 18 weeks either:

- THELIN 50 mg at the dose of one tablet a day (n=61)
- THELIN 100 mg at the dose of one tablet a day (n=62)
- placebo (n=62)
- TRACLEER at the dose of 62.5 mg twice a day for 4 weeks, then 125 mg twice a day for 14 weeks, according to the SPC (n=62)

The results of the THELIN 50 mg group are not presented, as there is no MA for that dose.

Primary endpoint:

Result (distance) of 6-minute walking test after 18 weeks of treatment. A method of limiting alpha-risk inflation due to multiple comparisons was implemented.

Secondary endpoints:

Stage of NYHA functional class after 18 weeks of treatment

Results

Table 2: Patient characteristics (ITT population)

	Placebo (n=61)	THELIN 100 mg (n=60)
Mean age (years)	53.0 ± 15.2	54.7 ± 13.8
Type of PAH		
- Idiopathic	61%	63%
- Secondary to connective tissue disease	26%	30%
Functional class II (NYHA) % (n)	38% (23)	43% (26)
Functional class III (NYHA) % (n)	56% (34)	55% (33)
6-minute walking test distance (m)	322.0 ± 85.6	361.7 ± 72.0

The percentage of patients in functional class III included in this study was only 50% (class included in MA).

Efficacy results

Table 3: Efficacy results for the primary endpoint:

	Placebo (n=61)	THELIN 100 mg (n=60)
Mean improvement in walking distance ± standard deviation (m)	-6.5 ± 84.4	24.9 ± 57.5
Mean improvement compared with placebo (m) 95% CI		31.4 [5.4 ; 57.4]
P versus placebo		0.03

A 31.4 metre increase in walking distance was observed (95% CI [5.4; 57.4], p = 0.03) in the patients treated with THELIN compared with those in the placebo group.

For the secondary endpoint:
After 18 weeks of treatment, an improvement in the NYHA functional class was observed in a small proportion of patients: 13% of the patients in the THELIN group (8/60) and 10% of the patients in the placebo group (6/61).

A deterioration in the NYHA functional class was observed in one patient in the THELIN group and eight patients in the placebo group.

This study was followed by an open-label extension, whose the primary objective was to evaluate the safety of THELIN 100 mg compared with that of TRACLEER for an initially scheduled duration of 2.5 years.

The results of this extension phase do not allow for a formal conclusion to be reached regarding the long-term efficacy or safety of THELIN.

3.1.3. STUDY FPH04

Design
Phase III comparative, randomised, double-blind study, whose objective was to compare the efficacy and safety of THELIN, combined with conventional PAH treatment, with those of a placebo in 98 patients suffering from PAH.

The conventional PAH treatments included vasodilators, calcium inhibitors, digitalis glycosides, diuretics, anticoagulants and oxygen therapy.

Inclusion criteria
Males and females aged 12 to 75 years, suffering from idiopathic or secondary PAH (connective tissue disease or congenital cardiac malformation), in functional class II, III or IV.

Dosing regimen / duration of treatment
The patients were randomised to receive for 18 weeks either:
- THELIN 50 mg at the dose of one tablet a day + conventional treatment (n=32)
- THELIN 100 mg at the dose of one tablet a day + conventional treatment (n=32) or
- placebo + conventional treatment (n=34).

The results of the THELIN 50 mg group are not presented, as there is no MA for that dose.

Primary endpoint:
Results (distance) of 6-minute walking test after 18 weeks of treatment

Secondary endpoints:
Stage of NYHA functional class after 18 weeks of treatment

Results

Table 4: Patient characteristics (ITT population)

	Placebo (n=34)	THELIN 100 mg (n=32)
Mean age (years)	39.6 ± 14.0	39.9 ± 13.8
Type of PAH		
- Idiopathic	65%	69%
- Secondary to connective tissue disease	9%	16%
Functional class II (NYHA)	56%	56%
Functional class III (NYHA)	41%	44%
6-minute walking test distance (m)	342.4 ± 82.1	343.9 ± 83.4

The percentage of patients in functional class III included in this study was only approx. 40% (class included in MA).

Efficacy results

Table 5: Efficacy results for the primary endpoint:

	Placebo (n=34)	THELIN 100 mg (n=32)
Mean improvement ± standard deviation (m)	33.8 ± 88.5	58.0 ± 63.6
Mean improvement compared with placebo (m) 95% CI		24.3 [-13.8 ; 62.4]
P versus placebo		0.20

The improvement in walking distance between THELIN and the placebo was 24.3 m. This difference is not statistically significant.

For the secondary endpoint:
At the end of the treatment, an improvement in the NYHA functional class was observed in 47% of patients in the THELIN group (15/32) and 26.5% of patients in the placebo group (9/34), p= 0.04.

At baseline, the majority of patients were in NYHA functional class II (moderate limitation of physical activity).

3.1.4 STUDY FPH06

Design

Phase III comparative, randomised, double-blind study, whose objective was to evaluate the efficacy and safety of 2 doses of THELIN in 48 patients suffering from PAH after the failure of treatment with TRACLEER.

Inclusion criteria

Patients suffering from idiopathic or secondary PAH (connective tissue disease or congenital heart malformation) in any functional class, after failure of treatment with TRACLEER for inefficacy (73% of patients) or intolerance.

Dosing regimen / duration of treatment

The patients were randomised to receive for 12 weeks either:

- THELIN 50 mg at the dose of one tablet a day (n=24) or
- THELIN 100 mg at the dose of one tablet a day (n=24).

Primary endpoint:

6-minute walking test distance after 12 weeks' treatment.

There was no control group for this study. Moreover, no statistical tests were conducted. The number of enrolled patients was low.

Due to these methodological limitations, as specified by EPAR, the benefits of treatment with THELIN after failure of treatment with TRACLEER cannot be determined.

3.2. Adverse events

The only available data are combined data for studies FPH01, FPH02 and FPH04.

The adverse events most frequently observed in the THELIN 100 mg groups (n=149) compared with placebo (n=155) were headache (15% vs. 14%), peripheral oedema (9% vs. 3%), nausea (7% vs. 4%), nasal congestion (9% vs. 5%), increase in INR (6% vs. 3%), and epistaxis (3% vs. 0%).

A reduction in haemoglobin (> 15% below the baseline value and a concentration below the lower limit of the normal range) was observed in 7% of the patients treated with THELIN and 3% of the patients treated with placebo.

A reduction in haemoglobin ≥ 1 g/dL was observed in 60% of patients who received THELIN 100 mg and 32% of the patients in the placebo groups.

An increase in transaminases > 3 times the upper limit of the normal range was observed in 2% of the patients who received THELIN 100 mg and 5% of the patients in the placebo groups.

3.3. GENERAL CONCLUSION

Of the 5 studies submitted by the manufacturer, the only ones considered in this opinion are the comparative, randomised, double-blind studies (namely studies FPH01, FPH02, FPH04 and FPH06).

In study FPH01, no difference was observed between the THELIN group and the placebo group as regards with the primary endpoint, i.e. variation in VO2 uptake during the exercise test. It would have been desirable to evaluate a more significant haemodynamic criterion such as pulmonary vascular resistance to support the clinical data.

In study FPH02, a comparative, randomised, double-blind study including 247 patients suffering from PAH, a statistically significant improvement of 31.4 metres was observed in the 6-minute walking test (primary endpoint of study, 95% CI [5.4 ; 57.4], p = 0.03), but this improvement is modest.

This study also included an open-label TRACLEER arm. It is regrettable that the methodology of the study was not designed to compare TRACLEER with THELIN according to an hypothesis of inferiority or superiority.

In study FPH04, a comparative, randomised, double-blind study to evaluate the efficacy and safety of THELIN combined with conventional PAH treatment by comparison with a placebo in 98 patients suffering from PAH, no difference in the primary endpoint was observed (6-minute walking test distance).

Study FPH06 does not enable the benefits of THELIN treatment after failure of treatment with TRACLEER to be determined.

All things considered, the evidence level of these studies is too low to assess the clinical benefit for patients. There are no long-term comparative data with the placebo, and no study comparing THELIN with an active treatment such as TRACLEER or REVATIO as regards with a relevant clinical endpoint such as 6-minute walk test distance.

The safety data for THELIN are limited (due to the short duration of the studies submitted). It should be emphasised that THELIN:

- is hepatotoxic (liver function tests required before and during treatment, treatment contraindicated in patients suffering from liver disease)
- often causes a reduction in the haemoglobin level and the number of red blood cells.
- involves an increased risk of haemorrhage.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual Benefit

PAH is a potentially fatal pulmonary disease characterised by increased blood pressure in the pulmonary arterial system. Asthenia, dyspnoea, chest pain and fainting are the most frequent clinical signs.
This proprietary pharmaceutical product forms part of a symptomatic treatment.
The efficacy/adverse effects ratio is high.
This proprietary drug is intended for first-line therapy.
There are alternative drug therapies.

Public health benefit:
Pulmonary arterial hypertension, idiopathic or associated with connective tissue disease, in functional class III, constitutes a low public health burden due to the small number of patients concerned.
Improved management of pulmonary arterial hypertension, idiopathic or associated with connective tissue disease, constitutes a public health need which falls within the scope of an identified priority (Rare Disease Plan: GTNDO).
According to the results of the studies and in view of the existing treatments, no impact is expected for the proprietary product THELIN in population terms on the morbidity and quality of life associated with this disorder.
There are no factors to suggest that THELIN will provide an additional response to the need identified.
Consequently, given the current data, no public health benefit is expected for the proprietary product THELIN in this indication.

The actual clinical benefit of THELIN is substantial.

4.2. Improvement in actual benefit

The Transparency Committee was unable to quantify the contribution of THELIN compared with existing treatments due to the absence of comparative studies of good methodological quality. The Transparency Committee therefore considers that THELIN does not provide any improvement in actual benefit (IAB V) compared with the available medicinal products indicated for the treatment of primary pulmonary arterial hypertension and arterial hypertension associated with connective tissue disease.

4.3. Therapeutic use[3]

The conventional treatment of PAH combines restrictions on physical activity with a treatment with anticoagulants, diuretics, oxygen therapy and calcium inhibitors.

The development of new oral pulmonary vasodilators has modified the therapeutic approach, especially for patients in NYHA Class III. In these patients, it now seems reasonable to begin with an effective, simple, well-tolerated treatment: bosentan (TRACLEER) or sildenafil (REVATIO), both administered orally.

Despite its constraints in terms of administration, iloprost (VENTAVIS), a prostacyclin administered by inhalation, could be considered as an alternative to bosentan. In particular it could be used in the event of contraindications or hepatic intolerance of bosentan.

According to the 2004 guidelines of the European Cardiology Society, treprostinil (REMODULIN), designed for continuous subcutaneous administration, could be offered to patients suffering from Class III PAH in the same way as iloprost (VENTAVIS). The decision to initiate treatment with treprostinil (REMODULIN) must take account of the high probability of having to maintain continuous subcutaneous infusion in the long term. If a changeover to intravenous treatment with epoprostenol (FLOLAN) is necessary, the transitional stage must be conducted under close medical supervision.

In most patients in NYHA functional class IV, the prognosis has been considerably improved by the availability of the continuous intravenous prostacyclin epoprostenol (FLOLAN). However, this treatment is restrictive, and can involve infection risks associated with the administration method (indwelling central catheter).

Lung or heart-lung transplants are the last-line treatment. In general, they are recommended for patients undergoing medical treatment who have not improved after 3 months.

Sitaxentan (THELIN) provides an additional therapeutic means in the treatment of primary PAH and PAH associated with connective tissue disease.

[3] 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 of THELIN corresponds to adult patients:
- suffering from primary PAH
- suffering from PAH associated with connective tissue disease
- in functional class III (NYHA classification).

The target population can be estimated on the basis of the following data:
- idiopathic PAH is a rare disease that affects between 600 and 700 people in France.
- Approximately 60% of them will be in NYHA Class III.
- PAH associated with connective tissue disease mainly relates to systemic scleroderma, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease and in some cases, rheumatoid arthritis.
- The available data do not enable the target population to be estimated, except with a major degree of uncertainty.
- Of the 9,500 patients in France suffering from systemic scleroderma (expert's opinion), around 12% will have PAH, i.e. approximately 1,150 patients.
- Of the 50,000 patients suffering from systemic lupus erythematosus (expert's opinion), around 2.8% will have PAH, i.e. 1,400 patients.
- Of the 2,000 patients suffering from mixed connective tissue disease (expert's opinion), around 15% will have PAH, i.e. 300 patients.
- Of these patients, around 60% will be in functional class III.

On this basis, the target population of THELIN is approximately 2,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use for the new indication and dosage of the Marketing Authorisation.