



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 January 2009

Reassessment of the following medicines:

TRACLEER 62.5 mg film-coated tablets

Pack of 56 (CIP: 563 621-1)

TRACLEER 125 mg film-coated tablets

Pack of 56 (CIP: 563 622-8)

Applicant: ACTELION PHARMACEUTICALS FRANCE

bosentan

ATC Code: C02KX01

List I

Medicinal product reserved for hospital prescription by specialists and/or units specialised in cardiology, respiratory medicine, rheumatology, dermatology or internal medicine.

Medicinal product requiring special surveillance during treatment.

Orphan medicinal product

Date of initial MA (centralised procedure): May 15, 2002

Date of indication extension (centralised procedure): July 29, 2008

Reason for request: Inclusion on the list of medicines approved for use by hospitals in the indication extension: "certain improvements have also been demonstrated in patients suffering from pulmonary arterial hypertension (PAH) under WHO functional class II".

Medical, Economic and Public Health Assessment Division

1.1. Active ingredient

bosentan

1.2. Indications

“Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients under WHO functional class III¹.

Efficacy has been shown in:

- primary pulmonary hypertension (idiopathic and familial)
- PAH associated with scleroderma without any significant associated interstitial condition.

Indications already evaluated by the Committee (see opinion of February 5, 2003: high actual clinical benefit / IACB I)

- PAH associated with congenital left-to-right shunts and Eisenmenger’s syndrome.

Indication already evaluated by the Committee (see opinion of July 18, 2007: high actual clinical benefit / IACB III)

Certain improvements have also been demonstrated in patients suffering from pulmonary arterial hypertension (PAH) under WHO functional class II.

TRACLEER is also indicated to reduce the number of new digital ulcers in patients with systemic scleroderma and evolutive digital ulcer disease.”

Indication already evaluated by the Committee (see opinion of July 18, 2007: high actual clinical benefit / IACB IV).

1.3. Dosage in the new indication

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

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, at or between mealtimes.

In the event of clinical deterioration (such as a decrease in the 6 minute walk test of at least 10% compared to pre-treatment results) despite treatment with TRACLEER for at least 8 weeks (maintenance dose administered for at least 4 weeks), another treatment should be considered. However, certain patients who show no response after 8 weeks of treatment with TRACLEER can respond favourably after 4 to 8 additional weeks of treatment. When deciding to end TRACLEER treatment, the patient should be weaned off gradually, while introducing the new treatment.

In the event of late clinical deterioration despite taking TRACLEER (for several months), treatment should be reevaluated. The exercise capacity of certain patients not responding sufficiently to the twice daily dose of 125 mg TRACLEER can be improved slightly if the dose is increased to 250 mg twice daily. The benefit/risk ratio of the treatment considered should in this case be evaluated carefully, keeping in mind that the hepatic toxicity of bosentan is dose-dependent.

¹ The NYHA (New York Heart Association) Functional Classification is based on the patient’s functional capacity. Patients are grouped under 4 categories:

- Class I: patients with no limitation of activities; they do not suffer from dyspnoea or fatigue from ordinary activities.

- Class II: patients with moderate limitation of activity; discomfort with strong exertion; comfortable with rest.

- Class III: patients with marked limitation of activity; discomfort with even moderate ordinary activity; they are comfortable only at rest.

- Class IV: unable to carry out most ordinary activities without major discomfort; symptoms occur at rest.

Cessation of treatment

There is little data on the consequences of ceasing TRACLEER treatment suddenly. There is no report to suggest any rebound effects. However, in order to avoid clinical deterioration stemming from a potential rebound effect, a gradual decrease in dosage (halving the dose for 3 to 7 days) is recommended before stopping treatment. The patient should be monitored closely during this period.

Special populations:

Dosage in hepatic impairment

No dose adjustment is required for 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 for patients with renal impairment. No dose adjustment is required for patients undergoing dialysis.

Dosage in elderly patients

No dose adjustment is required for patients over the age of 65.

Children

The safety and efficacy of bosentan have not been studied fully in children under the age of 12.

The following doses were used in study AC-052-356 (BREATHE-3):

Body weight (kg)	Initial dose (4 weeks)	Maintenance dose
10 ≤ x ≤ 20	31.25 mg once daily	31.25 mg twice daily
20 < x ≤ 40	31.25 mg twice daily	62.5 mg twice daily
> 40	62.5 mg twice daily	125 mg twice daily

This study was primarily designed to determine the pharmacokinetics of bosentan in children. The number of children studied in each dosage group was not great enough to establish the best dosage for patients under the age of 12. The systemic exposure observed was lesser in children than in adults suffering from pulmonary arterial hypertension. This data suggests a possible incomplete effect on pulmonary vascularisation for the doses used in this trial. However, the safety of administering greater doses to children has not been determined. There is no data for children under the age of 3.

Patients with a low body weight

There is little data concerning patients weighing less than 40 kg.”

2.1. ATC classification (2008)

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

2.2. Medicines in the same therapeutic categoryComparator medicines:

VOLIBRIS (ambrisentan), film-coated tablets, indicated in the treatment of pulmonary arterial hypertension (PAH) in patients under functional class II and III (WHO classification), to improve exercise capacity. VOLIBRIS has proved effective in idiopathic PAH and PAH associated with a systemic collagen disease.

2.3. Medicines with a similar therapeutic aim

None²

Clinical development of bosentan (TRACLEER) in patients with moderately symptomatic PAH (functional class II) is based on the phase III randomised, double-blind, placebo-controlled EARLY study³ (AC-052-364), lasting 6 months, the aim of which was to determine if initiating bosentan treatment at an early stage of the disease was likely to improve haemodynamics, symptoms and progression. This study involved a one-year open-label follow-up (not included in opinion).

3.1. Efficacy results

Objective: to evaluate the safety of bosentan and its efficacy in improving heart haemodynamics and exercise capacity in patients with functional class II PAH compared to placebo in a total of 185 patients with PAH (93 in the bosentan group, 92 in the placebo group).

Method: randomised, double-blind, placebo-controlled phase III study.
The protocol included stratified randomisation of concomitant sildenafil administration.

² The treatments currently proposed are entirely palliative and symptomatic. Of all the treatments currently available for management of PAH, only VOLIBRIS and TRACLEER are indicated for functional class II patients.

³ Galie N. et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet 2008; 371: 2093-100.

Inclusion criteria:

- aged ≥ 12
- PAH group I: idiopathic or familial PAH, PAH associated with connective tissue disease or autoimmune disease, an interatrial communication diameter of < 2 cm or interventricular communication diameter of < 1 cm or a ductus arteriosus, administration of anorexigenic agents or HIV.
- WHO functional class II PAH
- documented PAH with a mean PAP (pulmonary artery pressure) of ≥ 25 mmHg, PVR (pulmonary vascular resistance) of > 320 dyn.sec.cm⁻⁵, PAOP (pulmonary artery occlusion pressure) of < 15 mmHg
- Distance covered during the walk test $< 80\%$ of the theoretical value or < 500 m with a Borg dyspnoea index of ≥ 2

Exclusion criteria:

- PAH caused by another factor
- severe obstructive pulmonary disease
- significant vasoreactivity during right heart catheterisation, i.e. a decrease in PAPm of ≥ 10 mmHg to a PAPm value of < 40 mmHg with a normal cardiac index (≥ 2.5 L/min/m²). Indeed, such patients, even if rare ($< 10\%$) are likely to benefit from calcium channel blockers
- moderate to severe hepatic impairment (Child-Pugh B or C)
- ALT and/or AST > 3 times the upper limit of normal
- prior treatment with another endothelin receptor antagonist or prostanoids during the 3 months preceding randomisation
- treatment for the PAH over the month preceding randomisation, excluding calcium channel blockers (if prescribed for at least 1 month before randomisation), sildenafil (if prescribed for at least 2 months before randomisation at a steady dose of ≥ 20 mg x 3/day) and anticoagulants.

Dosing regimen:

Patients were randomised to receive:

- either the placebo
- or bosentan at a dose of 62.5 mg twice daily for 1 month, then 125 mg twice daily.

Primary endpoints:

- pulmonary vascular resistance (PVR) at rest after 6 months' treatment, expressed as a percentage of the initial value
- walking capacity on 6 minute walk test after 6 months' treatment

The analysis of these endpoints was ordered as follows: if a statistically significant difference was observed in favour of bosentan compared to the placebo for the "pulmonary vascular resistance" endpoint, the walking capacity in the 6 minute test was analysed.

The protocol involved the inclusion of 85 patients per treatment group to highlight a difference between the bosentan treatment group and the placebo group:

- of 150 dyn.sec. cm⁻⁵ (decrease in PVR of $\geq 20\%$, difference deemed clinically relevant) with $> 99\%$ power and 5% risk of type I error.
- of 35 m in walking capacity with 91% power and a 5% risk of type I error.

NB: the "pulmonary vascular resistance" endpoint is an intermediary endpoint relating to the actual activity of bosentan. Bosentan is a mixed endothelin receptor antagonist. It reduces pulmonary vascular and systemic resistance thus increasing cardiac output without accelerating the heart rate. Currently there are no recommendations concerning the evaluation of the response to treatment in PAH. However, the latter is based on an evaluation of the improvement in the NYHA functional class, the walking distance, the ultrasound measurements of the right ventricular function and/or haemodynamic measurements through right heart catheterisation for prognostic purposes⁴.

⁴ Mc Laughlin VV et al. Pulmonary arterial hypertension. Circulation 2006; 114:1417-31

The walking capacity on the 6 minute walk test remains the reference functional efficacy criterion. However, the sensitivity of this criterion to the effect of treatment on moderately symptomatic patients (functional class II for which the walking capacity improvement margin is limited) has not been established.

Results concerning these endpoints in patient subgroups (according to gender, age, cause of PAH, initial 6 minute test walking distance value and PVR) were submitted. No adjustment method was applied due to multiple comparisons; an overestimated effect is therefore possible. It is impossible to draw any formal conclusion from these results, which are presented for information purposes.

Secondary endpoints:

- Clinical deterioration time⁵
- Change in WHO functional class
- Borg dyspnoea index⁶
- Quality of life⁷
- Haemodynamic criteria, which are not described in this document as they do not demonstrate the clinical benefit to patients:
 - Total pulmonary resistance (TPR)
 - Mean right atrial pressure (mRAP)
 - Mean pulmonary artery pressure (mPAP)
 - Cardiac index (CI), defined as the cardiac output (L/min) divided by the body surface area (m²). The cardiac output reflects the functional consequences of PAH.
 - Mixed venous oxygen saturation (SvO₂) at rest
 - Heart rate (on ECG) and systemic arterial pressure

⁵ Composite endpoint defined by timeline, then randomisation, of the onset of any of the following: death, hospitalisation due to PAH complication, progression of PAH symptoms.

The progression of PAH symptoms is defined as: the occurrence or worsening of right heart failure, a decrease in the walking distance compared to baseline value $\geq 10\%$ (for 2 6 minute walk tests taken at least 2 weeks apart), decrease in the walking distance compared to baseline value $\geq 5\%$ (for 2 6 minute walk tests taken at least 2 weeks apart) associated with an increase in the Borg dyspnoea index of ≥ 2 .

⁶ Evaluation of dyspnoea according to a scale from 0 (no dyspnoea) to 10 (maximum dyspnoea)

⁷ Evaluation according to SF-36 questionnaire: functional physical self-assessment scale including several items enabling the assessment of 8 parameters indicative of physical and mental health

Results: (ITT population)

The treatment duration was 6 months.

Baseline patient characteristics:

Table 1:

Characteristics	Placebo group (n=92)	Bosentan group (n=93)
Gender (% women)	63	76
Mean age (SD)	44.2±16.5	45.2±17.9
Cause of PAH, n (%)		
Idiopathic or familial PAH	58 (63)	54 (58)
PAH-congenital heart disease	16 (17)	16 (17)
PAH-connective tissue disease	16 (17)	18 (19)
PAH-HIV	2 (2)	5 (5)
Time since diagnosis		
Number of years, mean (SD)	3.7 (6.5)	2.9 (5.5)
WHO functional class, n(%)		
II (%)	92 (100)	93 (100)
Mean walking capacity on 6 min test, m, (SD)	431 (91)	438 (86)
PVR dyn.sec. cm⁻⁵ (SD)	805 (369)	839 (531)
Mean Borg dyspnoea index (SD)	3.5 (2.2)	3.3 (1.8)

All patients' characteristics were similar.

The PAH was primarily idiopathic or familial. All patients included came under functional class II. The mean walking capacity was 431 m in the placebo group and 438 m in the bosentan group.

15.7% of the patients included were on sildenafil (15 in the placebo group and 14 in the bosentan group).

The patients included were representative of patients monitored in practice, particularly in terms of walking capacity (according to the French registry of PAH patients⁸, the walking capacity of functional class II patients is 415 ± 86 m).

However, it should be stressed that the baseline PVR values were very high (over 5 times the normal values).

Concomitant treatments administered (conventional PAH treatments: anticoagulants, diuretics, calcium channel blockers) were identical in all the treatment groups. However, a high percentage of patients were pre-treated with digoxin (7.5% of patients in the bosentan group, 17.4% in the placebo group) or calcium channel blockers (30% of patients in the bosentan group, 40% in the placebo group). Normally, about 20% of patients are treated with calcium channel blockers (after response to acute vasoreactivity test).

Primary endpoint results:

⁸ Humbert et al. Am J Respir Crit Care Med 2006 ; 173 : 1023 - 1030

Table 2:

	Placebo group n=92	Bosentan group n=93
1st endpoint		
mean change in PVR ± standard deviation (dyn.sec. cm ⁻⁵)	+128 (50)	-69 (53)
mean change in PVR, % of initial value	107.5	83.2
mean change in PVR compared to placebo (%)		-22.6
95% CI		[-33.5; -10.0]
p versus placebo		<0.0001
2nd endpoint		
mean change in walking capacity in m (6 min walk test)	-7.9	+11.2
mean change in walking capacity compared to placebo (m)		+19.1
95% CI		[-3.6; 41.8]
p versus placebo		NS

After 6 months' treatment, as a statistically significant difference was observed in favour of the bosentan group compared to the placebo group as far as the "pulmonary vascular resistance" endpoint was concerned, the improvement in the 6 minute test walking capacity was analysed. The difference observed, 19.1 m compared to placebo, is not statistically significant. Furthermore, this difference is under the 35 m threshold considered to be clinically relevant.

A statistically significant improvement in PVR was observed compared to placebo:

- in patients given sildenafil or otherwise (-20.4% 95% CI [43.9; 13.0], p=0.0478 with sildenafil and -23.1% 95% CI [-35.1; -8.9], p<0.0001 without sildenafil)
- in each of the subgroups identified in the protocol.

Secondary endpoint results:

Table 3:

Group	Clinical deterioration time HR, p value	Secondary endpoints					
		WHO functional class		Borg dyspnoea index		Quality of life	
		% improvement	% deterioration	Δ compared to baseline (SD)	Δ adjusted to placebo p	% improvement n (%)	% deterioration n (%)
placebo	NA	5.5%	13.2%	0.2 (2,1)	NA	31/81 (38.3)	15/81 (18.5)
bosentan	HR = 0.227 p = 0.0114	6.9%	3.4%	-0.2 (1.7)	-0.4 p: NS	43/75 (57.3) p = 0.02	14/75 (18.7) P: NS

No statistically significant difference was observed between the bosentan and placebo groups for the following endpoints:

- improvement in WHO functional class
- Borg dyspnoea index
- quality of life (deterioration in quality of life).

A statistically significant difference was observed in favour of the bosentan group over the placebo group in:

- the clinical deterioration time (primarily due to the progression in PAH symptoms). A clinical deterioration was noted in 13/92 patients in the placebo group (PAH-related symptoms progressed in 9 patients, 3 were hospitalised for PAH complications, 1 patient died) and 3/93

patients in the bosentan group (PAH-related symptoms progressed for 1 patient, 1 was hospitalised for PAH complications, 1 patient died)

- the deterioration in functional class: 3 patients on bosentan deteriorated to functional class III or IV versus 12 in the placebo group
- the percentage of patients whose quality of life improved.

3.2. Adverse events

Adverse effects occurred in 69.9% of patients on bosentan and 65.2% of patients on placebo. The most common adverse effects in the bosentan group compared to placebo were nasopharyngitis (7.5 versus 8.7%) and abnormal hepatic function (7.5 versus 3.3%).

Headaches were more common with the placebo (9.8% versus 4.3% with bosentan).

Elevated transaminases > 3 times the upper limit of normal (ULN) were observed in 12 patients on bosentan and 2 patients on placebo.

Among those patients given bosentan, the increase in ALT and/or AST was > 8 times the ULN in 5 patients and was asymptomatic in all cases.

A decrease in haemoglobin (defined as < 75% of the lower limit of normal, i.e. < 9.75 g/dl) was observed in 5 patients on bosentan and no patients on the placebo.

Nine patients in each of the treatment groups stopped treatment due to adverse effects: 6 patients in the bosentan group due to an increase in transaminases and 5 patients in the placebo group, due to a worsening in pulmonary hypertension.

3.3. Conclusion

The efficacy and tolerance of bosentan in patients suffering from functional class II PAH were evaluated in the phase III placebo-controlled, randomised, double-blind EARLY study, which involved 185 patients with PAH. The study, which lasted 6 months⁹, did not evaluate long-term efficacy or improvement in terms of survival.

The characteristics of all the patients were similar.

The PAH was primarily idiopathic or familial. All patients included were of functional class II. The mean walking capacity was 431 m in the placebo group and 438 m in the bosentan group, which complies with values seen in practice.

Two primary endpoints were analysed: pulmonary vascular resistance (PVR) at rest and walking capacity on the 6 minute walk test after 6 months' treatment.

The analysis of these endpoints was ordered as follows: if a statistically significant difference was observed in favour of bosentan compared to the placebo for the "pulmonary vascular resistance" endpoint, the walking capacity in the 6 minute test was analysed.

After 6 months' treatment, the difference observed, 19.1 m, compared to placebo, as far as the "6 minute test walking capacity" endpoint is concerned, was not statistically significant. Furthermore, this difference is under the 35 m threshold considered as clinically relevant.

One of the objectives for PAH treatment is the prevention of clinical deterioration. A statistically significant difference was observed in favour of the bosentan group compared to the placebo group in terms of clinical deterioration time (one of the study's secondary endpoints), mainly due to the progression in PAH symptoms (PAH-related symptoms progressed in 9 patients in the placebo group and 1 patient in the bosentan group).

The main adverse effects observed with bosentan compared to placebo were nasopharyngitis and abnormal hepatic function.

⁹ Pivotal trials on bosentan in patients under functional class III – IV demonstrated that a benefit in terms of haemodynamics and exercise capacity could be achieved after 3 to 4 months' treatment with bosentan. As functional class II patients are at an earlier stage of the disease, progression is slower. A treatment duration of 6 months was therefore chosen for the study to increase the possibility of observing an effect from treatment.

The safety profile is similar to that observed in patients at a more advanced stage, in functional class III.

4

TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

PAH is a potentially fatal pulmonary disease characterised by an increase in blood pressure in the pulmonary arterial system. Asthenia, dyspnoea, chest pains and loss of consciousness are the most common clinical signs. The life expectancy of patients on symptomatic treatment is short – about 4.8 years for functional class II patients.

These products are intended for symptomatic treatment.

The efficacy/adverse effects ratio is high.

These products are for first-line treatment.

There are alternative medicinal treatments.

Public health benefit:

Functional class II idiopathic pulmonary arterial hypertension or PAH associated with a connective tissue disease or congenital heart disease is a minor public health burden, due to the limited number of patients concerned.

The improved management of idiopathic pulmonary arterial hypertension or PAH associated with a connective tissue disease is a public health need falling within the scope of identified priorities (national rare diseases plan).

According to the results of the trial and taking into account existing treatments, TRACLEER is not expected to have any impact in population terms on morbidity and mortality or PAH-related quality of life in class II patients.

The available evidence does not suggest that TRACLEER, when used by class II PAH patients, will provide an additional solution to the identified need.

Consequently, given the current knowledge of the subject, TRACLEER is not expected to provide a public health benefit in this indication extension.

The actual benefit is considered as substantial pending the Transparency Committee's reevaluation of all PAH treatments.

4.2. Improvement in actual benefit

Given the clinical data available, the committee has not been able to quantify the benefit provided by TRACLEER in the management of patients with functional class II pulmonary arterial hypertension. The Transparency Committee therefore feels that TRACLEER does not improve actual benefit (IAB V) in the management of idiopathic pulmonary arterial hypertension or PAH associated with a connective tissue disease or congenital heart disease, in functional class II patients.

4.3. Therapeutic use¹⁰

There are currently no treatment recommendations for functional class II PAH patients. The treatments currently proposed are entirely palliative and symptomatic (functional improvement, prevention of complications, conventional treatment, etc.). Conventional PAH treatment combines anticoagulants, diuretics, oxygen therapy and calcium channel blockers.

In patients with class II PAH

- the advantages of early management of PAH has not been demonstrated,
- only one other product, VOLIBRIS, is indicated.

The therapeutic use of TRACLEER in functional class II PAH patients remains to be seen, given the data available and in the absence of recommendations, as for VOLIBRIS.

The majority of patients (50 to 75%) are diagnosed at a late stage, in functional class III-IV¹¹.

In patients suffering from PAH, particularly in class III, it is possible to use:

- bosentan (TRACLEER), sildenafil (REVATIO) or sitaxentan (THELIN) orally
- iloprost (VENTAVIS) inhalant, when the patient shows hepatic intolerance or contraindication to bosentan
- treprostinil (REMODULIN) in a continuous subcutaneous infusion, proposed for the same reasons as iloprost (VENTAVIS). The decision to initiate treatment with treprostinil must factor in the high probability of having to maintain a long-term continuous subcutaneous infusion.
- continuous infusion of epoprostenol (FLOLAN).

A pulmonary or heart-lung transplant is a therapeutic last resort. This is generally envisaged for patients seeing no improvement after 3 month's medical treatment.

4.4. Target population

The target population of TRACLEER in the indication extension concerned by this request corresponds to patients with NYHA functional class II idiopathic PAH and when associated with a connective tissue disease (the most common causes)¹⁰.

The target population may be estimated from the following data:

- Idiopathic PAH is a rare disease affecting 600 to 700 people in France. About 20% of these people are thought to be NYHA class II.¹²

- connective tissue disease-associated PAH concerns mainly systemic sclerosis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease and possibly rheumatoid arthritis.

Based on the data available, the target population can only be estimated with a considerable degree of uncertainty.

¹⁰ 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.

¹¹ Humbert et al. Am J Respir Crit Care Med 2006; 173: 1023 - 1030

¹² Humbert M et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006; 173 (9): 1023-1030

Of the 9,500 patients in France with systemic scleroderma (expert opinion), about 12% are thought to have PAH, i.e. 1,150 patients.

- Of the 50,000 patients suffering from systemic lupus erythematosus (expert opinion), about 2.8% are thought to have PAH, i.e. 1,400 patients.

- Of the 2,000 patients suffering from mixed connective tissue disease, 15% (expert opinion) are thought to have PAH, i.e. 300 patients.

About 25% of these patients are thought to be in class II¹².

Based on these figures, the target population of TRACLEER's new indication is estimated as about 900 patients.

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 indication extension and at the dosage stated in the MA.