European Medicines Agency

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ASSESSMENT REPORT FOR TRACLEER

International non-proprietary name/Common name:
bosentan

Procedure No. EMEA/H/C/000401/X/0039

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

Tracleer contains bosentan, a non-peptide antagonist of human endothelin-1 receptors (ETa and ETb).

Tracleer 62.5 mg and 125 mg film-coated tablets were granted a marketing authorisation in the European Union on 15 May 2002, through a centralised procedure.

The currently approved indication for Tracleer 62.5 mg and 125 mg film coated tablets is:
"Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status. Efficacy has been shown in:

- *primary PAH*
- *PAH secondary to scleroderma without significant interstitial pulmonary disease.*
- *PAH associated with congenital systemic-to-pulmonary shunts and and Eisenmenger's physiology*

Some improvements have also been shown in patients with PAH WHO functional class II (see section 5.1.).
Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease (see section 5.1.)."

This submission seeks for a line extension with a new strength and pharmaceutical form : Tracleer 32 mg dispersible tablets to make bosentan available in a more flexible dosing regimen according to low body weight especially for children suffering from Pulmonary Arterial Hypertension (PAH).

In the treatment of PAH and in the treatment of systemic sclerosis, the current Summary of Product Characteristics (SPC) of Tracleer 62.5 mg film coated tablets and Tracleer 125 mg film coated tablets state that Tracleer 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. The dose can be increased in some patients not responding well to 125 mg twice daily to 250 mg twice daily to attempt to slightly improve their exercise capacity.
No dose adjustment is needed in elderly patients over the age of 65 years, neither in patients with renal impairment nor in patients with hepatic impairment (i.e. Child-Pugh class A), but it is contraindicated in patients with moderate to severe liver dysfunction.

In 2002, when the MA was granted for Tracleer 65 mg and 125 mg film coated tablets, since no data had been initially provided to document neither the pharmacokinetic (PK) nor the clinical use in children and patients with low body weight, the SPC initially stated under the subheading "Special population – Children" in Section 4.2. : *"Safety and efficacy in patients under the age of 12 years have not been established."* Under the subheading "Patients with low body weight", the SPC stated "*There is limited experience in patients with a body weight below 40 kg.".*

In February 2003, the MAH provided the paediatric pharmacokinetic study BREATHE-3 (study AC-052-356) including 18 children less than 12 years and less than 40 kg. This study was performed with film coated tablets administered in a dosing regimen of approximately 2mg/kg b.i.d. (3 dosings : 125 mg b.i.d.; 62.5 mg b.i.d.; 31.25 mg b.i.d.) and showed a lower systemic exposure in young children as compared to the exposure in adults treated with 125 mg b.i.d. Since it was known that Tracleer was already used in children as pulmonary hypertension was an orphan fatal disease, the CHMP concluded that mentioning the kinetic findings and results from the BREATHE-3 paediatric study in section 4.2 was warranted in order to inform on the specificity of the pharmacokinetics in children with special attention to the lack of data to establish the optimal dose in this population. Indeed, the scarcity of the clinical paediatric study (the sole clinical study BREATHE-3) did not allow to establish the optimal dose in children less than 12 years bearing in mind that, in one hand, a lower systemic exposure could lead to a suboptimal treatment in children (as compared to adult) and, on the other hand, that safety concerns could not be excluded when the dose would be increased to reach a higher effect. (EMEA/H/C/401/II/02, Commission Decision on 26 June 2003)

The clinical part of the application submitted in May 2008 to support the present application focuses on the paediatric usage primarily based upon the compilation of paediatric data from the paediatric PK

study AC-052-356 (BREATHE-3), a new paediatric PK study: AC-052-365 (FUTURE-1), currently available results from its open-label extension study AC-052-367 (FUTURE-2, with data cut-off for this submission of 1 March 2008) and a review of post marketing safety data. The publications available on paediatric use of Tracleer from individual series have also been provided as supporting data.

The SPC proposed in May 2008 by the applicant for Tracleer 32 mg dispersible tablets was mainly similar to the one adopted for Tracleer 62.5 mg and 125 mg film-coated tablets with some changes regarding the information in children in sections 4.2, 4.8 and 5.2.

The MAH also sought for the harmonisation of the two film coated tablets (125 mg and 62.5 mg) and the dispersible tablets with respect to the information in children (EMEA/H/C/401/II/0041, CHMP opinion adopted in parallel in April 2009).

2. Quality aspects

Introduction

Tracleer is presented as immediate release film-coated tablets containing 62.5 mg or 125 mg bosentan as the monohydrate.

The new pharmaceutical form and strength, i.e., Tracleer 32 mg dispersible tablets has been developed for children as a more suitable pharmaceutical form for this population. In addition, the new strength also allows a more flexible dosing regime.

The new paediatric formulation is a pale yellow to off-white, clover-shape dispersible tablet, quadrisected on one side and debossed “32” on the other side containing 32 mg of bosentan (in the form of bosentan monohydrate).

Active Substance

The active substance used in the pharmaceutical form is the same as that used in the manufacture of the already approved strengths of Tracleer film coated tablets. There were no changes made to active substance and therefore no additional data was submitted.

Medicinal Product

- Pharmaceutical Development

The aim of the pharmaceutical development was to propose a new dosage form of bosentan containing 32 mg of drug substance, adapted for children. A quadrisected dispersible tablet containing 32 mg of bosentan was developed to be dispersed in a teaspoon with water.

The excipients used in the formulation of the dispersible tablets were calcium hydrogen phosphate anhydrous and microcrystalline cellulose (fillers), silica colloidal anhydrous (flowability), croscarmellose sodium (disintegration), aspartame, acesulfame potassium and tutti frutti flavour (taste masking), tartaric acid (acidifying agent) and magnesium stearate (lubricant).

- Adventitious Agents

Not applicable

- Manufacture of the Product

The finished product is obtained through a standard process for tablets manufacture (dry blending, sieving followed by compression step). Appropriate process flow diagram and description of the manufacture including the operating parameters and the equipment used have been presented.

Adequate in-process controls including mass of the tablets, friability, disintegration times have been selected and monitored during the manufacture.

Dissolution properties of the dispersible tablets were studied on the three validation batches using a dissolution method developed specifically for the dispersible tablets. Profiles are similar, 80 % of bosentan is dissolved in 20 min.

Validation was performed on three production-scale batches and results were found satisfactory.

All excipients are compendial (PhEur), except the tutti frutti flavour. The specifications for tutti frutti flavour are based on the supplier's data. None of the excipients used is of animal or human origin therefore the risk of TSE could be excluded.A certificate of analysis has been provided for each excipient and results were in line with the specifications.

- Product Specification

The finished product specification includes the following parameters: appearance (visual), average mass (weight), identification of bosentan (HPLC), friability (PhEur), uniformity of content (PhEur), bosentan content (HPLC), related substances (HPLC), disintegration time (PhEur), fineness of dispersion (PhEur), microbial contamination (skip testing, PhEur).

Specifications were adequately justified and non-compendial methods were validated in accordance with the ICH requirements.

Results were presented for two validation batches and three pilot-scale batches. All results conform to the proposed specifications.

The dispersible tablets are packaged into Alu/Alu blisters composed of a blister pack bottom foil and a child resistant push through foil. Appropriate information about the material used (bottom foil and child resistant push through foil) has been described.
Each blister will contain 14 dispersible tablets. The secondary packaging will be a carton box containing 56 dispersible tablets.
Appropriate identification and controls of the packaging materials have been carried out.

- Stability of the Product

The stability of bosentan dispersible tablets 32 mg was conducted on three pilot-scale batches kept in the commercial packaging under ICH conditions: accelerated (6 months at 40 °C/75% RH) and long-term conditions (24 months at 25 °C/60% RH).
All the parameters remained within the specifications during long-term and accelerated storage conditions apart from a slight increase of the friability at 40 °C/75% RH.

Based on these results, the proposed shelf life of 3 years is considered justified under the precautions of storage as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The new pharmaceutical form and strength, i.e., Tracleer 32 mg dispersible tablets has been developed for children as a suitable pharmaceutical form for this population. The lower strength quadrisected dispersible tablet allows a more flexible dosing regime for children.

A dissolution method has been specifically developed for the dispersible tablets. This new dissolution method has proven to be discriminatory for the 32 mg dispersible tablets (effect of granulation and hardness on dissolution rate). Although this new method is not fully suitable for other dosage forms, such as film-coated, it can better support the similarity between the 62.5 mg film-coated formulation and the 32 mg dispersible formulation. However, this *in vitro* dissolution method cannot fulfil requirements for a biowaiver for the dispersible tablet.

In conclusion, the results of test carried out indicate satisfactory consistency and uniformity of product quality characteristics, and these in turn lead to the conclusion that the new strength and pharmaceutical form should have a satisfactory and uniform performance in the clinic.

3. Non-clinical aspects

The dossier does not contain any non-clinical parts. No new non clinical data are provided. No trial is provided in juvenile animals. This is acceptable.

4. Clinical aspects

Introduction

The clinical part of the application submitted in May 2008 to support the present application focuses on the paediatric usage primarily based upon the compilation of paediatric data from the paediatric PK study AC-052-356 (BREATHE-3), a new paediatric PK study: AC-052-365 (FUTURE-1), currently available results from its open-label extension study AC-052-367 (FUTURE-2, with data cut-off for this submission of 1 March 2008) and a review of post marketing safety data. The publications available on paediatric use of Tracleer from individual series have also been provided as supporting data.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

- Study AC-052-356 (BREATHE-3)

BREATHE-3 (Study AC-052-356) was previously submitted and assessed (EMEA/H/C/401/II/02, Commission Decision on 26 June 2003).

This was a 12-week multicenter, open-label, non-controlled, parallel-group single- and multiple-dose study, with stratification for weight and epoprostenol use.

The primary objective was to investigate the pharmacokinetics of bosentan given as single and multiple oral doses in pediatric patients with PAH. The secondary objectives were to evaluate the tolerability and safety of single and multiple oral doses of bosentan and to obtain preliminary data on changes in exercise capacity, Borg dyspnea index, hemodynamics, and WHO functional class after 12 weeks of treatment in pediatric patients with PAH.

This study was conducted in 18 children with a body weight less than 40 kg (aged from 3 to 15 years (mean: 9.7 years), with pulmonary hypertension, and treated with a maintenance dose according to their body weight of approximately 2 mg/kg b.i.d. (125 mg b.i.d.; 62.5 mg b.i.d.; 31.25 mg b.i.d.) as dispensed with Tracleer film coated tablets. Following a screening period of 3 to 21 days, eligible patients were assigned to one of three parallel bosentan treatment arms on the basis of body weight as summarised in the Table 1 below.

Table 1 - Dosage for each body weight group

Body weight	Single dose (Day 1 and at the Week-12 visit)	Initial dose (Day 2 through the Week-4 visit)	Target dose (starting Week 5)
> 40 kg	125 mg	62.5 mg b.i.d.	125 mg b.i.d.
20 < x ≤ 40 kg	62.5 mg	31.25 mg b.i.d.	62.5 mg b.i.d.
10 ≤ x ≤ 20 kg	31.25 mg	31.25 mg q.d.	31.25 mg b.i.d.

The Pharmacokinetics parameters of bosentan and its metabolites are presented in the Table 2 below.

Table 2 - Descriptive statistics of the pharmacokinetic parameters of bosentan and its metabolites in pediatric patients with PAH after single- and multiple-dose administration of bosentan 31.25 mg, 62.5 mg, and 125 mg

bosentan					
Treatment	**$AUC_{0-\infty}$ (ng•h/ml)**	**AUC_{τ} (ng•h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}(\beta)$ (h)**
31.25 mg SD	5453 (56)		959 (69)	1.0 (1.0 - 6.0)	4.7 (40)
31.25 mg MD		3496 (49)	685 (77)	2.5 (0.0 - 9.0)	6.0 (61)
62.5 mg SD	6118 (55)		815 (108)	2.5 (1.0 - 4.0)	5.3 (35)
62.5 mg MD		5428 (79)	1136 (85)	1.0 (0.0 - 2.5)	5.6 (25)
125 mg SD	10777 (32)		1709 (39)	4.0 (2.5 - 6.0)	4.2 (44)
125 mg MD		6124 (27)	1200 (50)	1.8 (1.0 - 6.0)	5.3 (38)
Ro 47-8634					
Treatment	**AUC_{0-t} (ng•h/ml)**	**AUC_{τ} (ng•h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	
31.25 mg SD	71.8 (45)		15.4 (45)	3.3 (2.5 - 6.0)	
31.25 mg MD		91.5 (38)	13.8 (34)	2.5 (1.0 - 9.0)	
62.5 mg SD	136 (72)		18.6 (91)	4.0 (2.5 - 12.0)	
62.5 mg MD		176 (81)	31.8 (72)	2.5 (1.0 - 15.0)	
125 mg SD	253 (52)		43.6 (48)	4.0 (2.5 - 6.0)	
125 mg MD		178 (64)	29.8 (71)	2.5 (2.5 - 4.0)	
Ro 48-5033					
Treatment	**AUC_{0-t} (ng•h/ml)**	**AUC_{τ} (ng•h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	
31.25 mg SD	492 (80)		52.9 (73)	6.0 (4.0 - 12.3)	
31.25 mg MD		511 (41)	87.6 (46)	1.7 (0.0 - 9.2)	
62.5 mg SD	465 (86)		46.3 (110)	6.0 (4.0 - 15.0)	
62.5 mg MD		712 (115)	95.0 (103)	0.0 (0.0 - 3.8)	
125 mg SD	946 (60)		106 (89)	6.0 (4.0 - 6.9)	
125 mg MD		713 (53)	114 (86)	5.0 (0.0 - 9.0)	
Ro 64-1056					
Treatment	**AUC_{0-t} (ng•h/ml)**	**AUC_{τ} (ng•h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	
31.25 mg SD	333 (35)		48.5 (34)	4.0 (2.5 - 6.0)	
31.25 mg MD		450 (37)	61.4 (43)	3.9 (0.0 - 9.0)	
62.5 mg SD	349 (105)		40.4 (116)	6.0 (4.0 - 12.0)	
62.5 mg MD		468 (141)	70.9 (111)	2.5 (0.0 - 6.0)	
125 mg SD	807 (52)		104 (58)	4.0 (4.0 - 6.0)	
125 mg MD		601 (70)	85.8 (98)	4.0 (0.0 - 6.0)	

Data are expressed as geometric mean (and coefficient of variation %) or, for t_{max}, as median (and range). The single-dose data from Patient 2026 were excluded from the descriptive statistics.
MD = multiple-dose administration, PAH = pulmonary arterial hypertension, SD = single-dose administration.

In summary, the results showed a lower exposure to bosentan in paediatric patients as compared to adult patients treated with 125 mg b.i.d. (based on a historical control with PK data from study AC-052-357 performed in adults).

- Study AC-052-365 (FUTURE-1)

This study was an open-label, multicenter, uncontrolled, 12-week study to assess the pharmacokinetics (as primary objective) and tolerability and safety (as secondary objective) of bosentan orally administered with 32 mg dispersible tablets in children with idiopathic or familial pulmonary arterial hypertension.

The study consisted of a screening period of a maximum of 4 weeks, a treatment period of 12 weeks, and a post-treatment follow-up period of 28 days. Patients were to receive the bosentan with a 32 mg dispersible tablet formulation orally for 12 weeks, with the dosage adjusted to the patient's body weight at study start. After 4 weeks of treatment, the initial dose of 2 mg/kg b.i.d. was to be up-titrated to the maintenance dose of 4 mg/kg b.i.d. All patients were to start the study drug at the 2 mg/kg b.i.d. dose, whether or not they were previously treated with bosentan. Patients weighing 30 kg or more i.e. to receive a maximum of 120 mg b.i.d. of bosentan, unless down-titration was necessary, in which case they were to receive 64 mg b.i.d.

Patient demographics are summarised in the table below.

Table 3 – Summary of patient demographics

	Bosentan N=36
SEX [n (%)]	
n	36
Males	21 58.3%
Females	15 41.7%
AGE (years)	
n	36
Mean	6.8
Standard deviation	2.7
Median	7.0
Min , Max	2.0 , 11.0
AGE [n (%)]	
n	36
2 - 3 years	4 11.1%
4 - 5 years	9 25.0%
6 - 11 years	23 63.9%
WEIGHT (kg)	
n	36
Mean	22.3
Standard deviation	8.0
Median	20.7
Min , Max	9.5 , 42.0
HEIGHT (cm)	
n	36
Mean	119.5
Standard deviation	18.6
Median	119.0
Min , Max	79.0 , 153.0
RACE [n (%)]	
n	36
Caucasian/white	32 88.9%
Black	1 2.8%
Hispanic	2 5.6%
Other	1 2.8%
DURATION OF PAH (months)	
n	36
Mean	31.6
Standard deviation	31.0
Median	25.8
Min , Max	0.0 , 133.5
ETIOLOGY OF PAH [n (%)]	
n	36
Idiopathic	31 86.1%
Familial	5 13.9%

The primary objective was to demonstrate that exposure to bosentan in paediatric patients with IPAH or familial PAH is similar to that in adults with PAH, using the new dispersible tablet. The primary endpoint was defined as the area under the plasma concentration time curve during a dose interval (AUC_{τ}) of bosentan following treatment with the paediatric formulation.

The PK assessment was to be performed at least 2 weeks after up-titration to the maintenance dose (i.e., between Weeks 6 and 12). For patients remaining on the initial dose (i.e., no up-titration to the maintenance dose at Week 4) or who started with the maintenance dose, the PK assessment was to be performed at any time after Week 4.

Initial evaluation of the PK results from the first 10 patients indicated lower than expected exposure to bosentan, and the protocol was therefore amended to require two PK assessments instead of one (protocol Amendment 2). The new PK assessment (PK1) was performed at least 2 weeks after the initiation of study drug at 2 mg/kg b.i.d. (i.e., between Week 2 and Week 4). The second PK assessment (PK2) continued to be performed at least 2 weeks after up-titration to the maintenance dose of 4 mg/kg b.i.d. (i.e., between Week 6 and Week 12). Blood samples were taken immediately prior to drug administration and then at 0.5h, 1h, 3h, 7.5h, and 12h post-dose

A total of 36 patients were enrolled in the study. Twenty-five patients were enrolled into the study as per the original protocol, while 11 patients were enrolled following implementation of protocol Amendment 2. Four patients were aged 2–3 years, 9 were aged 4–5 years and 23 were aged 6–11 years, and all patients received at least one dose of bosentan. summarized in Table 6. One patient (patient 104–132) was excluded from the Per-protocol PK analysis set because the patient received incorrect study medication: the evening dose was administered about 1 hour prior to the 12-hour blood sample being withdrawn. Pharmacokinetic analysis therefore comprised 35 patients

Table 4 - Descriptive statistics of pharmacokinetic parameters of bosentan and its metabolites (M±SD) following administration of 2 and 4 mg/kg of bosentan in paediatric patients with PAH (n=11) after multiple-dose

bosentan			
Treatment mg/kg	**AUC_τ ng.h/ml**	**Cmax ng/ml**	**Tmax h**
2	4364 ± 2909	733 ± 482	3.1 ± 2.4
4	3869 ± 2236	761 ± 518	3.0 ± 1.8
Ro 48-5033			
Treatment mg/kg	**AUC_τ ng.h/ml**	**Cmax ng/ml**	**Tmax h**
2	593 ± 382	84 ± 45	1.6 ± 2.3
4	557 ± 433	75 ± 59	3.2 ± 3.0
Ro 64-1056			
Treatment mg/kg	**AUC_τ ng.h/ml**	**Cmax ng/ml**	**Tmax h**
2	674 ± 479	99 ± 73	4.0 ± 3.2
4	548 ± 389	69 ± 40	3.5±2.2

In the 11 patients who underwent two PK assessments, the exposure to bosentan following both the initial dose of 2 mg/kg and the maintenance dose of 4 mg/kg was similar, i.e., there was no increase in exposure to bosentan after doubling of the dose.

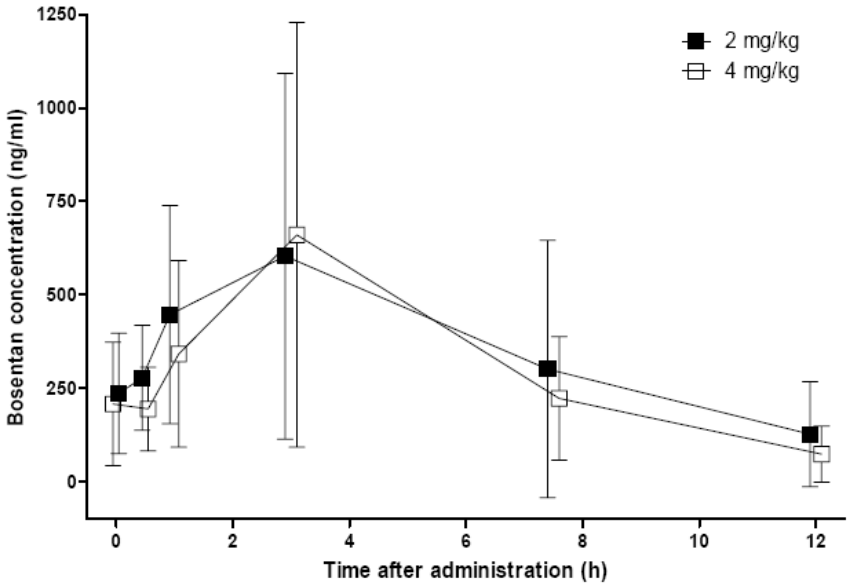

Figure 1 - Plasma concentration (M±SD) versus time profiles following administration of 2 and 4 mg/kg of bosentan in paediatric patients with PAH (n=11) after multiple-dose

Table 5 - Descriptive statistics of pharmacokinetic parameters of bosentan and its metabolites (M±SD) following administration of 4 mg/kg of bosentan in paediatric patients with PAH (n=35) after multiple-dose

	bosentan	
AUC_τ ng.h/ml	**Cmax ng/ml**	**Tmax h**
5716 ± 5467	1193 ± 1166	2.5 ± 1.8
	Ro 48-5033	
AUC_τ ng.h/ml	**Cmax ng/ml**	**Tmax h**
739 ± 681	142 ± 192	2.4 ± 2.9
	Ro 64 1056	
AUC_τ ng.h/ml	**Cmax ng/ml**	**Tmax h**
649 ± 521	92 ± 83	3.2 ± 2.7

The primary objective of the study was not met: the geometric mean of the AUC**τ** following treatment with the pediatric formulation of bosentan (and 95% confidence interval) was 4,383 ng.h/ml (3,461; 5,552). The ratio of the geometric means for AUC**τ** (and 90% confidence interval) was 0.5 (0.4, 0.8), indicating that exposure to bosentan in adults was almost twice the exposure in children. The confidence interval around the ratio of the geometric means of AUC**τ** was not entirely within the predefined equivalence limits of 0.66–1.5.

The exposure to bosentan observed in FUTURE-1 was in the range of exposures found in BREATHE-3.

Analysis of different covariates on the pharmacokinetics of bosentan did not show any trend for an effect of gender, WHO class, concomitant epoprostenol, or previous treatment with bosentan.

- Discussion on pharmacokinetics

The results of BREATHE-3 showed a lower exposure to bosentan in paediatric patients as compared to adult patients treated with 125 mg b.i.d. (based on a historical control with PK data from study AC-052-357 performed in adults).

In the 11 children who underwent PK assessments in Study FUTURE 1 at both doses, the exposure to bosentan following both the initial dose of 2 mg/kg and the maintenance dose of 4 mg/kg was similar, i.e. there was no increase in exposure to bosentan after doubling of the dose, suggesting that in paediatric patients an exposure plateau is reached at lower doses when compared to adults (study AC-052-357).

The exposure to bosentan observed in FUTURE-1 (with the dispersible tablet) was in the range of exposures found in BREATHE-3 (with the currently approved film-coated tablet) and was almost half lower than in adults.

Table 6 - Comparison of AUCτ (ng.h/ml) of bosentan following administration twice daily in PAH pediatric (4 mg/kg new formulation) and adult PAH patients (125 mg)

Adult	**Children**
Study AC-052-357	**Study AC-052-365 (FUTURE-1)**
8912 ± 3899	5716 ± 5467

The “plateau” of systemic concentrations at 2 mg/kg per day was observed in the youngest children of the PK paediatric studies which have included mainly moderate PAH (mainly class II functional status) children suggesting very few right heart failure and hepatic impairment that might interfere with systemic exposure. Also, it should be reminded that bosentan has a well known high variability and a large overlap of kinetics from these studies was observed with findings in adults. The applicant made the assumption that the concentration plateau phenomenon in children could be explained by a

limited absorption occurring at a lower ingested dose in children than in adults (may be related to a lower available surface for absorption in children as compared to adults), rather than by an increased metabolism or bile excretion. While it could be a possible explanation, this remains an assumption not fully documented and subsequently not confirmed. The age (or weight) at which the pharmacokinetic behaviour of bosentan would differ from adults is not clearly defined.

No direct comparison of in vivo bioavailability study has been conducted between the dispersible tablets and the already approved and marketed film coated tablets. The applicant justified the lack of direct bioequivalence demonstration based on extrapolations from kinetic data collected from a study performed in adults with an oral suspension of bosentan (not approved) which was compared to the film-coated tablets in Study AC-052-106, that was assessed during the initial marketing authorisation application and accepted as demonstrating bioequivalence between film coated tablets and the oral suspension.

The approach of bridges between the different formulations of bosentan as claimed by the applicant is not in accordance with the current recommendation. Indeed, firstly, according to the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), biowaiver is applicable to dosage forms such as tablets, capsules and oral suspensions if the active substance shows a high solubility and high permeability that is to say BCS-class I, while bosentan is BCS-class II.

Besides, the qualitative and quantitative compositions of the different bosentan formulations film coated tablets (approved and marketed), oral suspension (not approved) are completely different. It is also noticed that even though similar in-vitro dissolution profiles have been provided for the three bosentan formulations (currently registered film-coated tablet, oral suspension and dispersible tablet), in-vitro dissolution cannot be considered representative of in-vivo behaviour. The in-vitro dissolution methods have been shown discriminatory towards manufacturing parameters only. Furthermore, all the physiologically relevant pH conditions have not been tested. In-vitro dissolution data cannot be used for waiving comparison of in vivo bioavailability studies.

However, in both adults and children bosentan, displays non-linear pharmacokinetics with less than proportional increase in exposure with increased dose. This non-linearity seems to start at lower doses in children and no difference in AUC was observed after administration of doses 2 and 4 mg/kg dispersible tablet. The pharmacokinetics of bosentan are variable both in children and in adults. Pharmacokinetic data show a large overlap in exposure in children in studies FUTURE 1 and BREATHE-3 and in adults in studies EARLY and AC-052-357. The BREATHE-3 data were thoroughly evaluated regarding relationship between demographic factors and pharmacokinetic parameters with no clear trends for an effect of age or body weight on AUC or CL/F. Likewise there is no relationship between age and exposure in FUTURE 1. The variability in exposure is large over the whole age range.

Therefore, the CHMP considered that a comparison of in vivo bioavailability study between dispersible tablet and film-coated tablet should be conducted in adults as a post-approval commitment. Until these data are available the use of the dispersible tablet should be reserved for patients who cannot take the film-coated tablet.

Clinical efficacy

The supportive clinical efficacy data provided in this application is based primarily upon the paediatric use :

- Study AC-052-356 (BREATHE-3), a PK children study with film-coated tablets that has been already submitted and assessed in 2002, (EMEA/H/C/401/II/02, Commission Decision on 26 June 2003).
- Study AC-052-365 (FUTURE-1), a PK children study newly submitted, with dispersible tablets.
- Study AC-052-367 (FUTURE-2), an open-label extension of FUTURE-1 with data cut-off for this submission of 1 March 2008. The study is still on going

- Bibliographic individual studies and experiences from investigators with film-coated tablets.

- Study AC-052-356 (BREATHE-3, film coated tablets)

As discussed above, this was a 12-week multicenter, open-label, non-controlled, parallel-group single- and multiple-dose study, with stratification for weight and epoprostenol use. The secondary objectives were to evaluate the tolerability and safety of single and multiple oral doses of bosentan and to obtain preliminary data on changes in exercise capacity, Borg dyspnea index, hemodynamics, and WHO functional class after 12 weeks of treatment in pediatric patients with PAH.

19 pediatric patients were enrolled:
- 6 patients > 40 kg (3 on epoprostenol, 3 not on epoprostenol)
- 6 patients 20 < x ≤ 40 kg (3 on epoprostenol, 3 not on epoprostenol)
- 7 patients 10 ≤ x ≤ 20 kg (4 on epoprostenol, 3 not on epoprostenol)

Demographics and Baseline Characteristics :
The majority of patients were Caucasian (78.9% overall), and about half were male 9 (47.4%) and 10 were female (52.6%). The mean age was 9.7 years old (Min ; Max : 3.0 ; 15.0 years).
6 patients were < 8 years.
The mean weight was 30.8 kg (Min ; Max : 13.9 kg ; 54.0 kg).

All 19 patients suffered from either primary pulmonary hypertension (PPH) (n = 10) or PAH related to congenital systemic-to-pulmonary communications (n = 9). Congenital heart defects associated with PAH in patients in this study included atrial septal defect (ASD) (n=4), ventricular septal defect (VSD) (n=2), and patent ductus arteriosus (n=2). In addition, one patient was reported to have had ASD, VSD, and anomalous pulmonary venous return.
All patients were in either WHO functional class II (n=10; 78.9%) or class III (n= 4; 21.1%) at baseline.

Efficacy results
Efficacy was assessed only as exploratory analysis.

Haemodynamic parameters
Pulmonary hemodynamics were improved after 12 weeks of bosentan treatment, with a decrease in mean PAP observed in 15 of the 18 patients and an increase in cardiac index observed in 11 of the 17 patients with measurements. Changes in haemodynamic parameters are summarized in the Table X below.

Table 7 – Important changes in haemodynamic parameters for study AC-052-356 (BREATHE-3)

	Mean ± SD		
	Baseline	**Change**	**p value**
mPAP (mmHg)	59.9 ± 18.0	−8.0 ± 8.6	0.0003
Cardiac output (L/min)	4.29 ± 1.83	0.61 ± 1.35	0.049
mSAP (mmHg)	78.7 ± 11.6	−8.6 ± 9.1	0.0003
Stroke index (mL/m^2)	0.042 ± 0.016	0.006 ± 0.012	0.0267
PVR (dyn·sec/cm^5)	1194 ± 755	−389 ± 616	0.0021
PVRI (dyn·sec·m^2/cm^5)	1209 ± 650	−300 ± 537	0.0026

Notes: N = 17 patients for all parameters except mPAP (n = 18); change expressed from baseline to Week 12
FSR = final study report; mPAP = mean pulmonary arterial pressure; mSAP = mean systemic arterial pressure; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; SD = standard deviation;
Source: Appendix 11 of study AC-052-356

Exercise Parameters

For exploratory purposes, exercise parameters (6-minute walk test, Borg dyspnea index, progressive cycle ergometry test) were evaluated in 12 patients who were at least 8 years of age.

Changes in exercise test parameters at weeks 12 from baseline were highly variable and none were significant. Although some patients showed beneficial effects, no firm conclusions could be drawn. The mean and median changes from baseline in peak VO_2 were 53.0 and −3.5 ml/min, respectively (p = 0.4697).

WHO Functional Class

WHO functional class was assessed by the investigator based on knowledge of the patient and parental input. During the 12 weeks of treatment, five patients (26.3%) improved by one functional class: three patients moved from class III to class II, and two improved from class II to class I. One patient deteriorated (class II to III). The other 13 remain in the same WHO functional class (12 remain class II, one remain class III).

Electrocardiography
No clinically relevant change in mean heart rate or PQ, QRS, QT, or QTc interval was observed.

- Study AC-052-365 (FUTURE-1, dispersible tablets)

In addition to PK assessment previously discussed, the following variables were descriptively assessed:

- Change in concomitant medication records.
- Physical examination.
- ECG (12-lead).
- Vital signs and body weight.
- WHO Functional Class.
- Quality of life (SF-10) questionnaire completed by the parents or legal representatives.
- Global Clinical Impression scale assessed by parents and physician.
- Laboratory tests including hematology, chemistry, LFTs, and serum pregnancy test for females of childbearing potential.
- AE and SAE records.
- Return of study medication.

No pulmonary hemodynamics measurements were performed.

One of the study's 36 patients was excluded from the analysis of clinical efficacy because of the development of a confounding condition (i.e. an atrial septostomy performed after reconsideration of the pre-existing severity of the disease [syncope present in the medical history]). Two patients had study treatment discontinued prematurely. One was discontinued because of patient difficulties with the administration of the oral dispersible tablets formulation, the second one died during the study (suspected infection otitis triggering right ventricular failure).

At baseline 23 patients were in WHO class II, and 12 were in WHO class III functional status.
A total of 15 patients had "previous bosentan" intake prior to study treatment start (9 in WHO class II, 5 in WHO class III) and 21 patients were identified as "bosentan naïve" patients (14 in WHO class II, 7 in WHO class III).
The most common treatments reported at baseline by frequency were epoprostenol (9 patients, 25.0%), furosemide (8 patients, 22.2%), and oxygen (7 patients, 19.4%).

Efficacy results
Efficacy was assessed only as exploratory analysis.

The changes from baseline to week 4, 8, and 12 in the *WHO functional class* showed the majority of patients were stable. At Week 12, out of the 23 patients at baseline who were diagnosed class II, one worsened to class III and two improved to class I (the remaining 20 patients were stable at class II), and out of the 12 patients at baseline who were diagnosed class III, none worsened, and three improved to class II. The improvements were mainly observed in bosentan naïve patients while in contrast patients previously treated with bosentan remained largely stable with one patient worsening from class II to class III.

- Study AC-052-367 (FUTURE-2, dispersible tablets)

FUTURE-2 is an on going extension of FUTURE-1. It is multicenter (11), prospective, open-label, non-controlled with the primary objective to collect additional safety data and additional exploratory efficacy and outcome data in paediatric patients with IPAH or familial PAH. It will also allow patients to stay on bosentan until marketing approval of the oral dispersible tablets formulation.

Patients continuing into FUTURE-2 were to continue receiving the 4 mg/kg b.i.d. maintenance dose they were receiving at the end of FUTURE-1 unless this dose was not tolerated. In such cases, patients were down titrated to 2 mg/kg b.i.d. Of the 36 patients enrolled in FUTURE-1, 33 patients continued to FUTURE-2.

In summary, exploratory efficacy analysis was presented by the applicant as the cumulative review for FUTURE-1 an FUTURE-2 at the cut-off date of 1 March 2008 (change from baseline in FUTURE-1 to study end or premature study drug discontinuation in FUTURE-1 or FUTURE-2). According to the applicant, the change from baseline (FUTURE-1) to Months 6 (n = 29), 12 (n = 26), and 18 (n = 17) with respect to WHO functional class in patients still participating in the study and with the assessments available showed that most patients remained stable. At Month 6, 14/20 patients in class II at baseline remained in class II and 6/20 improved to class I. Six of 9 patients in class III at baseline remained in class III and 3/9 improved to either class II or I. At Month 12, 11/17 patients in class II at baseline remained in class II and 6/17 improved to class I. Six of 9 patients in class III at baseline remained in class III and 3/9 improved to either class II or I. At Month 18, 7/11 patients in class II at baseline remained in class II and 4/11 improved to class I. Four of 6 patients in class III at baseline remained in class III and 2/6 improved to either class II or I. The Kaplan-Meier survival estimate (95% CI) at Month 6 was 94.2% (86.4%, 100%), and 91.2% (81.6%, 100%) at Months 12, 18, and 24. There were 3 deaths in the first 9 months of treatment (one in each of the first 3 quarters of treatment), and none thereafter.

Pulmonary hypertension (PH) worsening occurred in 5 (13.9%) patients, followed by right ventricular failure and systemic-pulmonary artery shunt (2 patients each). Three patients died, one in FUTURE-1 (suspected infection otitis triggering right ventricular failure), and 2 in FUTURE-2 (right heart failure after Potts' anastomosis and cardiac failure, respectively).

- Bibliographic data (film-coated tablets)

The applicant also provided a detailed review of the published experience from 9 studies. Clinical experience from the literature refers to non controlled, open label investigator's experience. About 9 articles referred to children (up to 18 years) that were receiving bosentan in pulmonary hypertension. Patients with mild to moderate conditions were in general stabilised. However, they included various aetiologies, various concomitant treatments, and different maintenance dose i.e. 2 mg/kg b.i.d. or also 4 mg/kg that was requested.

- Discussion on clinical efficacy

Only exploratory efficacy analysis is available in children from those two open-label, not controlled clinical studies primarily designed for pharmacokinetics assessment (BREATHE-3, FUTURE-1). Study BREATHE-3 was conducted using the film coated tablets, and FUTURE-1 was conducted using the 32 mg dispersible tablets.

In BREATHE-3, 18 children aged from 3 to 15 years (mean: 9.7 years old with 6 patients under 8 years) were included. Pulmonary hemodynamic improvement as compared to baseline was obtained after 12 weeks of maintenance doses of bosentan treatment, as dispensed with the film coated tablets, at a dosing regimen adjusted according to body weight (approximately 2 mg/kg b.i.d. i.e. 3 dosing regimen groups : 31.5 mg b.i.d.; 62.5 mg b.i.d. ; 125 mg b.i.d.). Statistically significant decreases from baseline in pulmonary vasculature pressures (systolic, diastolic, mean) and pulmonary vasculature resistance (PVR, PVRI) were observed, as were statistically significant increases in cardiac output and Stroke index. Significant decreases in systemic pressures (systolic, diastolic, mean) and systemic vasculature resistance (SVR, SVRI) were also seen. Changes in exercise test parameters from baseline (6-minute walk distance, cycle ergometry test variables), assessed in 12 children at weeks 12 were highly variable and none were significant. Five patients among the 19 included (26.3%) improved by one functional class (WHO). These results are in favour of a stabilisation at short term with 2 mg/kg b.i.d. but the duration of the study was short and half of the patients were concomitantly receiving epoprostenol. No reliable conclusion can be drawn to establish whether the 2 mg/kg b.i.d. of bosentan had indeed provided the optimal effect on efficacy grounds.

The newly submitted pharmacokinetic study FUTURE-1 (Study AC-052-365) was conducted with a maintenance dose of 4 mg/kg b.i.d. (as dispensed with 32 mg dispersible tablets) in 35 children aged from 2 to 11 years (mean age = 6.7 ± 2.7 years; mean weight: 22.4 ± 8.1 kg) Nine patients were receiving concomitant epoprostenol. Exploratory analysis of efficacy was performed on WHO functional status measurement, patients' and physicians' clinical impression rate, and SF10 questionnaire. Neither any exercise capacity tests nor pulmonary hemodynamic measurements were performed. After 12 weeks treatment, most patients remained stable from baseline to Weeks 4, 8, and 12 with respect to WHO functional class. At Week 12, out of the 23 patients at baseline who were diagnosed with class II PAH, only one worsened to class III and two improved to class I. Out of the 12 patients who were diagnosed as class III PAH at baseline, none worsened, and three improved to class II. Out of the 24 patients whose condition the physician rated as 'good' or 'very good' at baseline, two were considered to be doing 'worse' or 'significantly worse', with the majority of responses being 'no change' or 'better', at Week 12. Pulmonary clinical worsening occurred in 2 patients leading to study treatment discontinuation, one of them died.

Study FUTURE-2 is an open label extension study of FUTURE-1 still on going until patients reached 12 years of age or dispersible tablets are marketed. Since the enrolment in study FUTURE-1, pulmonary worsening occurred in 5 patients (with 2 death) leading to discontinuation of the treatment. At the cut-off date of 1er March 2008, 17 patients reached 18 months exposure among the 28 children who are remaining in the study. Based on the interim data with cut-off date of 1st March 2008, the maintenance dose of 4 mg/kg allows most of the patients included to remain stable with respect to WHO functional status and this, with an acceptable tolerance.

No analysis of pulmonary haemodynamics or any exercise tests are planned. Further to the request of the CHMP, the applicant provided an assessment of the evolution on growth profile in the children treated in FUTURE 1-2. Despite difficulties to draw conclusions based on such limited number of patients; it seems that bosentan does not have any effect on height and weight of the treated paediatric patients. The baseline percentile median values for both criteria were low but remained stable through the study.

Additional supportive data based on the review of published experience refer to the currently marketed film coated tablets used in open-label (none used the dispersible tablets). All are referring to not controlled heterogeneous series of patients with various aetiology of pulmonary hypertension and various maintenance doses (2 mg/kg and 4 mg/kg b.i.d.). They do not allow any comparison neither to establish whether bosentan provides the optimal efficacy in children nor to directly compare 2 mg/kg b.i.d. versus 4 mg/kg b.i.d. on safety/efficacy grounds in children.

Clinical safety

In this application, the safety part focused on paediatric data. Safety paediatric data with bosentan are available from study BREATHE-3 (AC-052-356) using the film coated tablets, FUTURE-1 (AC-052-365) using dispersible tablets, and the currently available results from its open label extension FUTURE-2 (with data cut-off for this submission of 1st March 2008) and from the literature and post-marketing experience that all refer to film coated tablets uses. All the studies are open-label and non-comparative.

- Clinical trials experience

The number of paediatric patients included in the BREATHE-3 and FUTURE-1/2 clinical studies is limited (n = 55), all the more if one only considers the study using the new dispersible formulation (n = 36 from FUTURE-1).

In BREATHE-3, 19 patients were exposed to bosentan film coated tablets for a mean and median of 23.9 weeks (0.46 years). The mean extent of exposure to bosentan as dispensed with 32 mg dispersible tablets (over both FUTURE-1 and FUTURE-2 study periods up to the data cut-off of 1 March 2008) is 94.2 weeks.

Most cases of AEs reported in the 3 clinical studies were mild to moderate in intensity. The most frequently reported AEs are not unexpected with bosentan (i.e. flushing, headache, abnormal hepatic function, dizziness, fluid retention, abdominal pain, vomiting, nasopharyngitis or pulmonary hypertension). Similarly, most SAEs are not unexpected and have been usually considered as unrelated to study medication. Nevertheless, one case of autoimmune hepatitis reported positive rechallenge. Although the patient presented complex medical history (including Down's syndrome and prematurity), bosentan may have unmasked an autoimmune process. Only a limited number of laboratory abnormalities have been reported during the 3 clinical studies.

In these studies, the safety profile of bosentan does not seem to be influenced by age, doses or indications. There is a trend for a higher frequency of AEs in paediatric patients exposed to bosentan for more than 12 weeks compared to those exposed less than 12 weeks.
However, taking into account the low number of children included and the limited time for follow-up, no definite conclusions can be drawn from these clinical studies.

- Bibliographic data

A total of 10 bibliographic studies has been presented in this submission: Penny 2003, Ivy 2004, Gilbert 2005, Maiya 2005, Rosenzweig 2005, Simpson 2006, Brun 2007, Fasnacht 2007, Humbert 2007 (this reference describes post-marketing data on the safety profile of bosentan as requested by the CHMP; results were based upon the findings already reported within the Tracleer PMS system), van Loon 2007.

From these articles 367 paediatric patients were involved. LFTs abnormalities are the most frequently reported events in the published articles. However, since most cases are poorly documented, no data on doses, time to onset, patients' conditions or history, conditions of occurrence are available. Therefore, these cases remain unassessable.

- Post marketing experience

The final report for TRAX PMS was assessed in April 2005. It was concluded that there were no events detected through the TRAX PMS system that were determined to be safety signals or warrant specific action beyond the current recommended provisions. The safety profile of Tracleer observed through the TRAX PMS is similar to that previously observed.

The total number of patients enrolled in Tracleer PMS was 4,994, of which 4,623 (used as denominator and for exposure calculations) were bosentan naïve patients. Of those, 169 were paediatric (< 12 years): 23 patients < 2 years and 146 patients ≥ 2 years and < 12 years. The mean duration of exposure was similar in both groups, 36.2 weeks in paediatric and 34.2 weeks in non-paediatric populations. Regarding specifically paediatric population, no particular pattern for the safety profile arose.

The applicant also submitted a cumulative safety review of ADRs and a cumulative review of hepatobiliary events at the request of the CHMP, both reported in paediatric patients. The applicant estimated that more than 2,000 paediatric patients < 18 years have been treated during the post marketing period worldwide. A total of 497 cases (related and unrelated) have been reported for paediatric patients during the post marketing period of Tracleer.

The global safety profiles seem comparable for both populations since the most frequent SOCs involved in ADRs reported are similar for adult and paediatric populations. However, for the related cases, there is a slight trend for a higher reporting rate in paediatrics for cardiac disorders (9.6 % versus 4.9 %; mainly cardiac failure, cyanosis and right ventricular failure) and gastrointestinal disorders (8.3 % versus 6.7 %; mainly nausea, vomiting, abdominal pain and diarrhoea).

Regarding liver safety, the profile is consistent with the known safety profile of bosentan in the adult population. No new concerns have been evidenced from these data. Based on the worldwide exposure data and the number of case reports with at least 1 hepatobiliary event, it is estimated that the global overall reporting rate for hepatobiliary events (reported as primary or secondary event) in paediatric patients was 4.2 % (83/2 000) for the review period. This estimated reporting rate in the paediatric population is slightly lower compared to the global reporting rate of 5.7 % (3 509/62 000) (up to May 2008) for patients of all ages treated with Tracleer.

However, the applicant did not provide a specific analysis of the post marketing safety profile according to the dose administered (especially 2 mg/kg as compared to 4 mg/kg). This information is lacking for about 30 % of cases (142/466). For the remaining 60 % of patients: most adolescents received maximum daily dose > 62.5 and ≤ 250 mg; most children daily received maximum daily dose > 31.5 and ≤ 125 mg and infants received maximum daily dose ≤ 31.25 mg.

- Discussion on clinical safety

Data provided in this submission are in majority from the film coated tablets (only 35 children with 32 mg dispersible tablets in short term) and do not raise any new safety concerns regarding paediatric use of bosentan. However, data in young children are limited and the studies do not allow comparing the 2 mg/kg and 4 mg/kg on safety grounds. Based on these data, firm conclusions cannot be drawn.

The safety profile of bosentan in the paediatric population needs to be specifically monitored and adequately addressed in future PSURs in addition to what is planned in the RMP. The PSUR and Liver Safety Update Report (LSUR) submission cycle should continue to be submitted every 6 months, until otherwise specified by the CHMP.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system (DDPS)

The CHMP considered that the Pharmacovigilance system as described in the version 4 of the DDPS provided by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAH has submitted an updated risk management. Despite the fact that no efficacy/safety controlled studies were performed in children and that the safety information on paediatric population was limited, no additional pharmacovigilance activities were proposed by the applicant in the initial

version submitted in May 2008 to follow the use and the safety of in paediatric patients while the new developed dispersible tablet was presented as the more flexible dosing form that will subsequently promote the usage in children. In this way, no evaluation of the need for risk minimisation was discussed by the applicant.

The CHMP requested that the applicant plan to set-up a post-marketing study, in addition to the controlled distribution system, to follow all paediatric patients who will be treated with Tracleer in the EU aiming at collecting further long term safety and clinical data with at least the following criteria:

- effect on bosentan on general development of paediatric patients including weight, height, sexual maturation, puberty);
- Clinical worsening, hospitalisation and death due to PAH;
- Demographic criteria ;
- Indication, dose treatment, duration ;
- Serious adverse events and all AEs of special interest (hepatic disorders and related events, anaemia and related events, worsening PAH).

As an alternative to address the CHMP's concerns on long term safety and clinical data in paediatric bosentan-treated patients, the applicant proposed to use data collected through four ongoing registries on paediatric PAH disease (in the USA, EU, France and Netherlands) supported by the applicant. The MAH agreed to provide the protocols of these registries to the CHMP for review. This proposal was acceptable to the CHMP.

Table 8 – Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Teratogenicity	Routine Pharmacovigilance	• Contraindication in section 4.3. of the SPC: "Pregnancy, Woman of child bearing potential who are not using reliable methods of contraception" (see sections 4.4, 4.5, and 4.6). • Warning in sections 4.4 that: "Tracleer must not be initiated in women of childbearing potential unless they practise reliable contraception (see section 4.5 Interaction with other medicinal products and other forms of interaction) and the result of the pre-treatment pregnancy test is negative. (See section 4.6 Pregnancy and lactation, Use in women of child-bearing potential)." • Sections 4.4 and 4.6: "Before the initiation of Tracleer treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods of contraception provided, and reliable contraception initiated." • Sections 4.4 and 4.6: Patients and prescribers must be aware that, due to potential pharmacokinetic interactions, Tracleer may render hormonal contraceptives ineffective (see section 4.5). Therefore, women of child-bearing potential must not use hormonal contraceptives (including oral, injectable, transdermal, and

		implantable forms) as the sole method of contraception but should use an additional or an alternative reliable method of contraception. If there is any doubt on what contraceptive advice should be given to the individual patient, consultation with a gynaecologist is recommended. • Section 4.5 (interaction with other medicinal products and other forms of interaction): "…hormone-based contraceptives alone, regardless of the route of administration (i.e. oral, injectable, transdermal, and implantable forms), are not considered as reliable methods of contraception." • Educational material as Prescriber Kit for prescribers. • Patient Reminder Card specifically aimed at informing patients of the need to avoid pregnancy and to ensure effective contraceptive measures are used. • Sending a 'Reminder Letter' to all Tracleer prescribers identified via the controlled distribution system to reinforce these messages.
Hepatotoxicity	Routine Pharmacovigilance	• Information in sections 4.4 (Special warnings and precautions for use) on Liver function: Elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases (AST and/or ALT), associated with bosentan are dose-dependent. Liver enzyme changes typically occur within the first 26 weeks of treatment, but may also occur late in treatment (see section 4.8). • Information on possible mechanisms for liver aminotransferases provided and warning that the risk may be increased if inhibitors of bile export pumps are co-administered (see sections 4.3 and 4.5). • Warning that: Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Tracleer (see further recommendations for dose adjustments in case of ALT/AST elevations and treatment re-introduction under section 4.4 of SPC). • Labelled in section 4.8 • Educational material as Prescriber Kit for prescribers. • Patient Reminder Card specifically aimed at facilitating patient's awareness of the need for regular blood tests for liver function.
Decrease in	Routine	Warning in section 4.4 that treatment with bosentan

haemoglobin concentration, thrombocytopenia	Pharmacovigilance	associated with a dose-related decrease in haemoglobin concentration and proposals for monitoring. Labelled in section 4.8
Fluid retention	Routine Pharmacovigilance	Warning in section 4.4 of the SPC that, in patients with severe chronic heart failure, treatment with bosentan resulted in an increased incidence of hospitalisation during the first 4-8 weeks which could have been due to fluid retention. Recommendation that patients should be monitored for signs of fluid retention and appropriate treatment given. Peripheral oedema and oedema labelled in section 4.8
Pulmonary oedema associated with veno-occlusive disease	Routine Pharmacovigilance	Warning in section 4.4 that pulmonary oedema has been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive (PVOD) disease and to consider PVOD if pulmonary oedema occurs
Interaction with substrates, inducers or inhibitors of cytochrome (CYP) P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives)	Routine Pharmacovigilance	Warnings in section 4.4 regarding concomitant use with glibenclamide, fluconazole and rifampicin and warning against concomitant administration of both a CYP3A4 inhibitor and a CYP2C9 inhibitor. Information about specific interactions (including hormonal contraceptives) in section 4.5 of the SPC.
Interaction with sildenafil	Routine Pharmacovigilance COMPASS studies (associated use of bosentan and sildenafil)	Information in section 4.5 of the SPC
Long term safety and efficacy in digital ulcer population	Routine Pharmacovigilance Digital ulcer registry	
Long term safety and outcomes in the paediatric population	Routine Pharmacovigilance Consolidated reporting from ongoing paediatric registries	
Possible interaction with anti-retroviral compounds	Routine Pharmacovigilance	Warning in section 4.4 of the SPC that because bosentan is a CYP450 inducer, there is a potential for interaction and decreased efficacy of antiretroviral therapy and that the risk of hepatic toxicity and haematological adverse events may be increased.

Interaction with lopinavir+ritonavir or other ritonavir boosted protease inhibitors	Interaction study of bosentan and Kaletra in healthy volunteers.	Warning in section 4.4 that when treatment with Tracleer is initiated in patients on ritonavir-boosted protease inhibitors, the patient's tolerability of Tracleer should be monitored. Information in section 5.1 Warnings in section 4.4 regarding concomitant use with lopinar/ritonavir and other ritonavir-boosted protease inhibitors in PAH associated with HIV infection. Information about specific interactions in section 4.5 of the SmPC
Possible seminiferous tubule atrophy	Routine Pharmacovigilance Results of the AC-052-402 Study (Testicular study)	
Possible Vasculitis	Routine Pharmacovigilance	

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those already agreed for the currently approved strengths.

6. Overall conclusions, risk/benefit assessment and recommendation

The 32 mg dispersible tablet allows a more flexible dosing regimen according to low body weight. As dispersible pharmaceutical form in water, it may also be a convenient pharmaceutical form in patients who may have difficulties in swallowing hard tablets (including adults, adolescent and children).

No direct comparison of in vivo bioavailability study has been conducted between the dispersible tablets and the already approved and marketed film coated tablets. In accordance with the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), biowaiver is applicable to dosage forms such as tablets, capsules and oral suspensions if the active substance shows a high solubility and high permeability that is to say BCS-class I, while bosentan is BCS-class II.

However, in both adults and children bosentan, displays non-linear pharmacokinetics with less than proportional increase in exposure with increased dose. This non-linearity seems to start at lower doses in children and no difference in AUC was observed after administration of doses 2 and 4 mg/kg dispersible tablet. The pharmacokinetics of bosentan are variable both in children and in adults. Pharmacokinetic data show a large overlap in exposure in children in studies FUTURE 1 and BREATHE-3 and in adults in studies EARLY and AC-052-357. The BREATHE-3 data were thoroughly evaluated regarding relationship between demographic factors and pharmacokinetic parameters with no clear trends for an effect of age or body weight on AUC or CL/F. Likewise there is no relationship between age and exposure in FUTURE 1. The variability in exposure is large over the whole age range.

Therefore, the CHMP considered that a comparison of in vivo bioavailability study between dispersible tablet and film-coated tablet should be conducted in adults as a post-approval commitment.

Until these data are available the use of the dispersible tablet should be reserved for patients who cannot take the film-coated tablet.

From an efficacy point of view, the observed plateau in systemic concentration would suggest that increasing the dose of bosentan beyond 2 mg/kg in paediatric patients in a b.i.d. regimen will unlikely result in any increased exposure to bosentan and subsequent increased effect on pulmonary vasculature. The available short term PK studies suggests that children were stabilised (based only surrogate not very sensitive markers WHO functional status and hemodynamics) with 2 mg/kg for short term periods (12 weeks maximum in BREATHE-3 including 18 patients) and maintenance dose of 4 mg/kg in the available longer term data (FUTURE-1-2). But, these studies were short terms, uncontrolled, conducted in a limited number of patients, whom a significant part of them were receiving concomitant eposprostenol.

No clinical study primarily designed for efficacy/safety assessment has been performed in children and especially comparing the two maintenance regimen 2 mg/kg b.i.d. versus 4 mg/kg b.i.d. on safety/efficacy grounds. Based on the PK observation, it would appear "logical" that no benefit would be obtained with higher than 2 mg/kg b.i.d. in children. Nevertheless, the age limit (or weight) for such a reasoning remains unclear and whether the optimal clinical efficacy/safety ratio will actually be gained with 2 mg/kg remains unexplored.

Data provided in this submission are in majority from the film coated tablets (only 35 children with 32 mg dispersible tablets in short term) and do not raise any new safety concerns regarding paediatric use of bosentan. However, data in young children are limited and the studies do not allow comparing the 2 mg/kg and 4 mg/kg on safety grounds. Based on these data firm conclusions cannot be drawn.

Therefore, the CHMP considered that further long term safety and clinical data should be collected in paediatric patients. The CHMP agreed for these data to be collected through four ongoing paediatric PAH disease (in the USA, EU, France and Netherlands) supported by the applicant.

The safety profile of bosentan in the paediatric population needs to be specifically monitored and adequately addressed in future PSURs in addition to what is planned in the RMP. The PSUR/LSUR submission cycle should continue to be submitted every 6 months, until otherwise specified by the CHMP.

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Tracleer 32 mg dispersible tablet was favourable and therefore recommended the granting of the marketing authorisation of this new strength and pharmaceutical form.