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ASSESSMENT REPORT FOR REVATIO

International non-proprietary name/Common name: sildenafil

Procedure No. EMEA/H/C/638/II/0021

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

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1. SCIENTIFIC DISCUSSION

1.1. Introduction

Revatio (sildenafil) 20 mg is indicated for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.

Sildenafil is an orally-active, potent and selective inhibitor of the enzyme phosphodiesterase 5 (PDE5), that causes the breakdown of cyclic guanosine monophosphate (cGMP). Given the high levels of PDE5 in the pulmonary endothelium, and the role of the nitric oxide (NO)/cGMP system in modulating pulmonary vascular tone, sildenafil has been studied in PAH. In patients with PAH, inhibition of PDE5 could lead to selective (NO/cGMP-dependent) vasodilatation of the pulmonary vascular bed (with a lesser degree of vasodilatation in the systemic circulation), resulting in reduced pulmonary arterial pressure and symptomatic improvement.

This Type II variation has been submitted by the Marketing Authorisation Holder (MAH) to broaden the existing therapeutic indication to include treatment of patients with pulmonary arterial hypertension classified as WHO functional class II.

The proposed indication is as follows: "Treatment of patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease."
Additional data is also proposed in section 5.1

1.2 Clinical aspects

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries that is characterized by vascular proliferation and remodelling. It results in a progressive increase in pulmonary arterial resistance and, ultimately, right ventricular failure and death. The functional classification (FC) of PAH, modified from the New York Heart Association (NYHA) classification of patients with cardiac disease, is as follows:

- Class I: PAH without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near-syncope.
- Class II: PAH resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
- Class III: PAH resulting a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
- Class IV: PAH resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnoea, fatigue, or both may be present even at rest, and discomfort is increased by any physical activity.

In many patients the course of PAH is one of steady deterioration and reduced life expectancy, with lung or heart and lung transplant being the only curative treatment available (De Backer *et al,* 2002). D'Alonzo *et al* (1991) reported the median survival time for untreated functional class I and class II patients with idiopathic pulmonary hypertension as 58.6 months, while untreated functional class III and class IV patients had median survival times of 31.5 months and 6 months, respectively.

It has been shown that patients who improve from functional class III or class IV to functional class II after treatment have significantly improved survival. Therefore, it might be reasonable to expect that early treatment of WHO functional class II patients might provide an improvement in survival as progression to functional class III might be delayed. Furthermore, early treatment of functional class II patients is supported by the finding that not all patients respond to treatment and if treatment initiation

is delayed until the patient progresses to functional class III or IV, a significant proportion will remain in functional class III or class IV.

In 2005, Revatio was evaluated and approved for the indication of PAH in WHO FC III patients only. At that time the 6 minute walk distance (6MWT) for functional class II patients was considered to be approximately 450 metres based on results of a study conducted by Miyamoto *et al* (2000).
Humbert *et al.* published results from the French National PAH Registry in 2006. The Registry included a substantial number of PAH patients (n=674) from 17 French University hospitals and included all consecutive adult (≥18 years) patients with PAH seen between October 2002 and October 2003. The results from the French National PAH Registry indicated that the 6 minute walk test results correlated with functional class in all forms of PAH and haemodynamic improvement correlated with functional class and 6MWT in all subgroups of patients.

Based on this article, the MAH would like to show that the original studies of Revatio provide evidence that this medication can be used in WHO FC II as well.

Until recently, no therapeutic options were available in Europe for WHO/NYHA functional class II patients. In 2008, ambrisentan (Volibris) was approved as an NCE for both functional class II and III patients, and bosentan (Tracleer) had its functional class III label extended to include benefit in functional class II patients. The basis to include WHO functional class II patients were on two grounds:

1. The functional class II subjects recruited into the trials were a demonstrably different population from the functional class III subjects;
2. Efficacy was demonstrated for both functional class II and class III subjects.

1.2.1 Clinical efficacy

No new clinical research studies were included to support this Type II variation. The MAH re-evaluated data from two previously submitted studies: A1481140 and A1481142. The MAH believes that WHO FC II patients have been adequately studied in these studies.

The MAH refers to ambrisentan (Volibris), a selective endothelin receptor antagonist, which recently was approved for the indication of WHO FC II patients. The MAH is convinced that the considerations of ambrisentan can now be similarly applied to the sildenafil data.

1.2.1.1 Main studies

This Type II variation is based on two studies involving sildenafil (Revatio): A1481140 and A1481142. Data of these studies are re-evaluated.

- **<u>Methods and baseline</u>**

Study A1481140 was a 12-week multinational, multi-center, randomised, double-blind, double-dummy, placebo-controlled clinical trial designed to assess the efficacy and safety of 3 doses of oral sildenafil (20, 40, and 80 mg TID) for the treatment of PAH. The primary objective of the study was to assess the effect of sildenafil therapy on exercise capacity, as measured by the 6-Minute Walk test (6-MWT), after 12 weeks of treatment in subjects with PAH.

Study A1481142 was a multi-center, long-term extension study to assess the safety and toleration of subject optimised treatment regimens of oral sildenafil for PAH in subjects who have completed Study A1481140. The duration of Study A1481142 was until the last enrolled subject in Study A1481142 had completed 3 years of treatment in Study A1481142. All subjects completing Study A1481140 were eligible to receive active therapy in Study A1481142. Subjects were blinded to their Study A1481142 regimens until the last subject entering the study had completed 12 weeks of treatment. This allowed collection of blinded toleration data as subjects optimised their dose (based on tolerability) in the first 12 weeks of Study A1481142. Subjects were followed up in the clinic on a 6-weekly basis for the first 12 weeks and 3-monthly thereafter. Primary Endpoints were 6-MWT, BORG

dyspnoea score, pulmonary hypertension criteria for functional capacity and therapeutic class, QoL and assessment of yearly survival status using the PPH prognostic index.

Representativeness of WHO FC II

– *Baseline 6-MWT and Functional Class*

Baseline 6-MWT for baseline functional class II and baseline functional class III subjects in Study A1481140 are summarised in Table 1.

Table 1 - Baseline 6-MWT by Functional Class for Sildenafil, Ambrisentan and French Registry

	WHO FC	**N**	**Baseline 6-MWT Mean ± SD**	**Median baseline 6-MWT**	**minimum**	**maximum**
sildenafil						
A1481140	II	103	379 ± 60 m	397 m	180 m	450 m
	III	158	325 ± 81 m	334 m	118 m	505 m
ambrisentan						
AMB-320	II	65		380 m	160 m	449 m
	III	117		354 m	192 m	442 m
AMB-321	II	86		398 m	190 m	449 m
	III	99		350 m	150 m	445 m
			Baseline 6-MWT Mean ± SD			
French Registry	I-II	134	415 ± 86 m	N/A	N/A	N/A
	III	359	319 ± 92 m	N/A	N/A	N/A

The difference between the functional class II and functional class III baseline mean 6MWDs was 54 m and the difference between the medians was 63 m. The difference between the functional class II and function class III baseline mean 6MWDs was statistically significant ($p<0.001$).

– *Baseline 6-MWT by Cut-off Point*

Table 2 shows the 6-MWT baseline in functional class II and functional class III subjects characterised by using the cut-off point of 400 metres. In Study A1481140, 48% of functional class II and 20% of functional class III subjects had a baseline 6-MWT of >400 metres.
The functional class II and functional class III subjects were clearly differentiated in Study A1481140 and comparable with the functional class II and functional class III subjects reported in the Volibris EPAR.

Table 2 - Baseline 6-MWT using 400m cut-off point in A1481140 Study and Studies performed by ambrisentan in different WHO functional classes (II/III)

Baseline 6-MWT	Study	WHO FC II	WHO FC III
≤ 400 m	A1481140	52%	80%
> 400m	A1481140	48%	20%
≤ 400 m	ambrisentan	53%	73.1%
> 400m	ambrisentan	47 %	26.9%

Haemodynamics

Statistically significant differences in baseline haemodynamic parameters were observed between the two functional classes in Study A1481140. These are summarised in Table 3.

Table 3 - Summary of Statistically Significant Differences in Baseline Haemodynamic Parameters between Baseline Functional Class II and Baseline Functional Class III Subjects - Study A1481140

Parameter	Baseline Functional Class Mean		Mean Difference (95% CI)	p-value
	II	III		
Cardiac index (litres/min/m^2)	2.57	2.25	0.32 (0.13 to 0.51)	0.001
Cardiac output (litres/min)	4.52	4.04	0.48 (0.12 to 0.85)	0.010
Mixed venous oxygen saturation (%)	64.10	60.86	3.24 (0.79 to 5.69)	0.010
Systolic pulmonary arterial pressure (mmHg)	77.1	84.8	-7.7 (-13.1 to -2.3)	0.005
Pulmonary vascular resistance (dyne.sec/cm^5)	861.64	1011.37	-149.73 (-290.03 to -9.44)	0.037
Pulmonary vascular resistance index (dyne.sec/cm^5/m^2)	1493	1771	-278 (-510 to -46)	0.019
Right atrial pressure (mmHg)	7.27	9.31	-2.04 (-3.33 to -0.75)	0.001
Systemic vascular resistance (dyne.sec/cm^5)	1634.21	1860.95	-226.74 (-389.22 to -64.26)	0.004
Systemic vascular resistance index (dyne.sec/cm^5/m^2)	2858	3285	-427 (-692 to -163)	0.002

In addition, haemodynamic data (Table 4) for baseline functional class II and functional class III subjects in Study A1481140 were compared with the results from the French National Registry (Humbert *et al*, 2006).

Table 4 - Haemodynamic Data in Functional Class II and Functional Class III Subjects: Study A1481140 versus French National Registry

Haemodynamic parameter	Study A1481140 Mean (SD)		French National Registry Mean (SD)	
	WHO functional class II	WHO functional class III	WHO functional class I/II	WHO functional class III
Mean Pulmonary arterial pressure (mmHg)	50.3 (15.6)	53.7 (14.2)	50 (17)	56 (15)
Cardiac index (litres/min/m^2)	2.57 (0.76)	2.25 (0.68)	2.9 (0.9)	2.4 (0.7)
Pulmonary vascular resistance index (dyne.sec/cm^5/m^2)	1493 (813)	1771 (866)	1264 (776)	1720 (784)

Source: Table 9.7.402C and Humbert *et al* (2006)

The baseline 6MWT and haemodynamic parameters observed for baseline functional class II and functional class III subjects in Study A1481140 were comparable to the results in the French National Registry.

Concomitant medication:

Analysis of patients in study A1481140 based on their background medications also showed a differentiation between patients classified as functional class II and III e.g. the use of diuretics, digoxin and oxygen were reported more frequently in patients classified as FC III than II as follows: 71.3% vs. 52.3% and 23.1%% vs. 19.6% and 38.8% vs. 19.6% respectively.

In conclusion, comparison of baseline characteristics demonstrate that functional class II subjects recruited into Study A1481140 were clinically distinguishable from functional class III subjects recruited into Study A1481140, and had less severe PAH. The functional class II and functional class III subjects in Study A1481140 are also comparable to subjects in the French National Registry and the ambrisentan Studies with respect to baseline 6-MWT and haemodynamic parameters.

- **Efficacy in WHO Functional class II**

Study A1481140

– *6-MWT and functional class*

All the efficacy data from Study A1481140 to support this submission relates to change in 6-MWT. Treatment comparisons of change from baseline in 6-MWT at Week 12 (last observation carried forward [LOCF]) for baseline functional class II and functional class III subjects are provided in Table 5.

Table 5 - Treatment Comparisons of Change from Baseline in 6 Minute Walk Distance at Week 12 (LOCF) by Baseline Functional Class (II/III) - Study A1481140

Functional Class	Contrast	Mean Difference (metres)	95% Confidence Interval		p-value
			Lower limit	Upper limit	
II	Sildenafil 20 mg vs. Placebo	49.2	21.5	76.97	<0.001
	Sildenafil 40 mg vs. Placebo	8.8	-19.4	36.90	0.537
	Sildenafil 80 mg vs. Placebo	50.0	23.81	76.16	<0.001
	Sildenafil vs. Placebo	37.5	15.06	59.95	0.001
III	Sildenafil 20 mg vs. Placebo	45.4	15.56	75.26	0.003
	Sildenafil 40 mg vs. Placebo	70.0	40.64	99.44	<0.001
	Sildenafil 80 mg vs. Placebo	51.1	21.42	80.87	<0.001
	Sildenafil vs. Placebo	55.8	30.81	80.83	<0.001

Source: Table 9.7.404C

Comparison of the sildenafil 20 mg treatment group versus placebo demonstrated a statistically significant increase in 6-MWT for baseline functional class II and class III subjects at Week 12. The overall treatment comparison of all sildenafil treatment groups versus placebo demonstrated a statistically significant increase in 6-MWT for baseline functional class II and functional class III subjects at Week 12.

The change from baseline in 6-MWT for baseline functional class II and functional class III subjects treated with sildenafil are comparable with the results reported for ambrisentan subjects.

– *6-MWT By cut off point*

The MAH also performed analyses of change from baseline in 6-MWT by Baseline 6-MWT with cut off 400m and 415m, respectively as stated in the ambrisentan EPAR. The results are provided in the tables below.

Table 6 - Treatment Comparisons of Change from Baseline 6 Minute Walk Distance at Week 12 (LOCF) by Baseline 6 Minute Walk Distance

Baseline 6 Minute Walk Distance	Contrast	Mean Difference (metres)	95% Confidence Interval		p-value
			Lower limit	Upper limit	
≤400 metres	Sildenafil vs. Placebo	51.3	29.32	73.27	<0.001
>400 metres	Sildenafil vs. Placebo	41.0	17.86	64.23	<0.001
≤415 metres	Sildenafil vs. Placebo	49.0	28.34	69.58	<0.001

Baseline 6 Minute Walk Distance	Contrast	Mean Difference (metres)	95% Confidence Interval		p-value
			Lower limit	Upper limit	
>415 metres	Sildenafil vs. Placebo	40.2	16.07	64.42	0.002

Source: Tables 9.7.405C and 9.7.406C

In addition to the original parametric analysis, the MAH provided, at the request of the CHMP, the changes for the different cut-off points used (≤400 m,>400 m and ≤415 m, >415 m) according to a non parametric approach (Hodges-Lehman, 95% CI for the median estimates by treatment group and the median difference and 95% CI in the continuous efficacy variables).

Table 7 - Treatment comparisons of change from baseline 6 minute walk distance at week 12 by baseline 6 minute walk distance (≤400 m / >400 m).

Original Parametric Analysis

Baseline 6MWD	Contrast	Mean Difference (m)	95% CI	P-Value
≤ 400m	Sildenafil 20mg (n=42) vs Placebo	55.5	27.9 , 83.1	<0.001
	Sildenafil 40mg (n=47) vs Placebo	49.0	22.1 , 75.9	<0.001
	Sildenafil 80mg (n=52) vs Placebo	50.0	23.8 , 76.1	<0.001
	Sildenafil (n=141) vs Placebo (n=45)	51.3	29.3 , 73.3	<0.001
> 400m	Sildenafil 20mg (n=25) vs Placebo	24.1	-2.3 , 50.4	0.073
	Sildenafil 40mg (n=17) vs Placebo	50.9	21.7 , 80.1	<0.001
	Sildenafil 80mg (n=17) vs Placebo	55.8	26.8 , 84.8	<0.001
	Sildenafil (n=59) vs Placebo (n=21)	41.0	17.9 , 64.2	<0.001

Non-Parametric Analysis

Baseline 6MWD	Contrast	Median Difference (m)	95% CI	P-Value
≤ 400m	Sildenafil 20mg (n=42) vs Placebo	54	32 , 74	<0.001
	Sildenafil 40mg (n=47) vs Placebo	42	21 , 65	<0.001
	Sildenafil 80mg (n=52) vs Placebo	43	23 , 64	<0.001
	Sildenafil (n=141) vs Placebo (n=45)	46	27 , 62	<0.001
> 400m	Sildenafil 20mg (n=25) vs Placebo	23	-10 , 46	0.164
	Sildenafil 40mg (n=17) vs Placebo	54	30 , 73	<0.001
	Sildenafil 80mg (n=17) vs Placebo	54	23 , 81	<0.001
	Sildenafil (n=59) vs Placebo (n=21)	38	18 , 59	<0.001

Source: Table 9.7.405C and Table 9.7.432C

Table 8 - Treatment comparisons of change from baseline 6 minute walk distance at week 12 by baseline 6 minute walk distance (≤415 m / >415 m).

Original Parametric Analysis

Baseline 6MWD	Contrast	Mean Difference (m)	95% CI	P-Value
≤ 415m	Sildenafil 20mg (n=48) vs Placebo	49.0	23.2 , 74.8	<0.001
	Sildenafil 40mg (n=56) vs Placebo	47.9	23.1 , 72.7	<0.001
	Sildenafil 80mg (n=57) vs Placebo	49.9	25.3 , 74.6	<0.001
	Sildenafil (n=161) vs Placebo (n=49)	49.0	28.3 , 69.6	<0.001
> 415m	Sildenafil 20mg (n=19) vs Placebo	28.6	0.8 , 56.5	0.044
	Sildenafil 40mg (n=8) vs Placebo	48.8	13.4 , 84.3	0.008
	Sildenafil 80mg (n=12) vs Placebo	52.0	20.9 , 83.2	0.002
	Sildenafil (n=39) vs Placebo (n=17)	40.2	16.1 , 64.4	0.002

Non-Parametric Analysis

Baseline 6MWD	Contrast	Median Difference (m)	95% CI	P-Value
≤ 415m	Sildenafil 20mg (n=48) vs Placebo	48	26 , 66	<0.001
	Sildenafil 40mg (n=56) vs Placebo	41	21 , 61	<0.001
	Sildenafil 80mg (n=57) vs Placebo	42	23 , 63	<0.001
	Sildenafil (n=161) vs Placebo (n=49)	42	26 , 58	<0.001
> 415m	Sildenafil 20mg (n=19) vs Placebo	32	-6 , 56	0.078
	Sildenafil 40mg (n=8) vs Placebo	51	14 , 72	0.006
	Sildenafil 80mg (n=12) vs Placebo	57	23 , 84	<0.001
	Sildenafil (n=39) vs Placebo (n=17)	41	14 , 62	<0.001

Source: Table 9.7.406C and Table 9.7.433C

The MAH further characterised the efficacy data for baseline functional class II and functional class III subjects by defining a responder as either:

- A subject whose 6MWD improves by 30 m at Week 12.
- A subject whose 6-MWT improves by 30 m and by 10% over the baseline distance at Week 12.

If the first definition of responder is used, 60% of functional class II subjects and 56% of functional class III subjects were responders. If the second definition of responder is used, 54% of functional class II subjects and 55% of functional class III subjects were responders.

The re-analysed 6-MWT data from Study A1481140 shows the efficacy profile for sildenafil is comparable for baseline functional class II and functional III subjects in Study A1481140, with statistically significant improvements in 6-MWT observed in both groups of subjects. Furthermore, comparable improvements in 6-MWT were observed when baseline 6-MWT rather than baseline functional class was used to define disease severity at baseline in Study A1481140.

– *Secondary endpoints*

Further to the request from the CHMP, the MAH provided results of the investigated secondary endpoints in study A1481140 (changes in mean PAP, time to clinical worsening and change from baseline in BORG Dyspnoea score) for FCII.

Treatment comparisons of change from baseline in mean *PAP* at week 12 (LOCF) by baseline functional class are given below.

Baseline Functional Class	Contrast	Mean Difference (mmHg)	SE	95% CI	P-Value
II	Sildenafil 20mg (n=22) vs Placebo	-3.2	2.05	-7.3 , 0.8	0.118
	Sildenafil 40mg (n=18) vs Placebo	-2.7	2.17	-7.0 , 1 .6	0.218
	Sildenafil 80mg (n=24) vs Placebo	-5.4	1.99	-9.3 , -1.4	0.009
	Sildenafil (n=64) vs Placebo (n=29)	-3.9	1.61	-7.1 , -0.7	0.018
III	Sildenafil 20mg (n=37) vs Placebo	-2.1	1.93	-5.9 , 1.8	0.289
	Sildenafil 40mg (n=43) vs Placebo	-2.9	1.87	-6.6 , 0.8	0.121
	Sildenafil 80mg (n=40) vs Placebo	-5.1	1.91	-8.9 , -1.3	0.008
	Sildenafil (n=120) vs Placebo (n=30)	-3.4	1.62	-6.6 , -0.2	0.039

The numbers (%) of patients with *clinical worsening events*, especially from functional class II, were too small for meaningful evaluation:

Baseline Functional Class		Placebo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
II	Number (%) Worsening	1/32 (3.1)	0/24	1/23 (4.3)	1/28 (3.6)
III	Number (%) Worsening	5/34 (14.7)	2/40 (5.0)	1/44 (2.3)	4/42 (9.5)

The median baseline *BORG Dyspnoea* scores in the WHO FC II population were 2, 3, 3, 2 for placebo, sildenafil 20mg, sildenafil 40mg and sildenafil 80mg respectively, compared to 4, 4, 3 and 4 respectively in the WHO FC III population. Given that there was little scope for improvement with the WHO FC II population (a score of 2 corresponds to 'slight breathlessness') it isn't unexpected that the sildenafil groups show no improvement over placebo below.

Baseline Functional Class	Contrast	Median Difference	95% CI	P-Value
II	Sildenafil 20mg (n=22) vs Placebo	0.0	-1.0 , 1.0	0.640
	Sildenafil 40mg (n=21) vs Placebo	0.0	-1.0 , 0.5	0.683
	Sildenafil 80mg (n=27) vs Placebo	0.0	-0.5 , 1.0	0.974
	Sildenafil (n=70) vs Placebo (n=30)	0.0	-0.5 , 0.5	0.791
III	Sildenafil 20mg (n=40) vs Placebo	-1.0	-2.0 , 0.0	0.020
	Sildenafil 40mg (n=43) vs Placebo	-1.0	-1.5 , 0.0	0.074
	Sildenafil 80mg (n=41) vs Placebo	-1.5	-2.5 , -0.5	0.003
	Sildenafil (n=124) vs Placebo (n=33)	-1.0	-2.0 , 0.0	0.005

Study A1481142

The primary objective of extension Study A1481142 was to assess safety. However, it did provide supportive efficacy data. Change in 6-MWT, survival data, and long term functional class data from Study A1481142 are discussed in this section. It should be noted that care needs to be taken when interpreting data from Study A1481142 because of potential bias from the lack of a control group and open label study design.

Overall, the change in 6-MWT, survival data, and functional class data from extension study A1481142 support the long-term efficacy of sildenafil in functional class II subjects.

– *6-Minute Walk Distance*

At Week 12 in Study A1481142 the mean change from Study A1481140 baseline in 6-MWT was 39 m and 34 m for baseline (Study A1481140) functional class II and functional class III subjects, respectively, where baseline is defined as the pre-randomisation value in Study A1481140. The mean changes in 6-MWT were 50 m and 45 m at 36 months for baseline functional class II and functional class III subjects, respectively. At 36 months 71 of the 96 baseline (Study A1481140) functional class II subjects entered into Study A1481142 remained in study. As already discussed, caution is needed in interpreting the data from open label study A1481142. However, these results suggest that improvements in 6-MWT are maintained in less severe functional class II subjects after 36 months of sildenafil treatment.

– *Long-term Maintenance of Functional Class*

Long-term functional class data were also collected in Study A1481142. The majority of subjects who were baseline functional class II (62%) or functional class III (59%) improved or maintained their functional class after 3 years of sildenafil treatment.

1.2.1.2 Discussion on clinical efficacy

No new clinical studies were submitted to support the current application. The MAH re-evaluated data from the study A1481140 and its long term extension study A1481142 which were the pivotal studies submitted in the Revatio application and resulted in the registration of Revatio for WHO FC III. Ambrisentan, an endothelin receptor antagonist, is currently registered for PAH FC II based on the results of studies ARIES-1/ARIES-2. The ARIES studies were 12 week double-blind placebo-controlled multi-center studies in 394 PAH patients (both FC II and III) with 6-MWT as primary endpoint.

With the publishing of the French Registry of PAH patients (Humbert *et al*., 2006) based on data from 674 patients, lower 6-MWT values were assigned for FC II than those previously reported in the article by Miyamoto et al., 2000: 415m vs. 450 m respectively. The values reported in the French Registry are currently the accepted ones.

Adequate number of patients in FC II were recruited in the pivotal study A1481140 (n=103, compared to n=158 in FC III). The reported baseline 6-MWT for FC II in the pivotal study A1481140 (mean 379±60m) still appears lower than those reported in the French Registry (mean 415±86m); however, they are comparable to those reported in the ARIES studies (Table 1).

The submitted data supports that recruited PAH patients in study A1481140 had statistically different haemodynamic values for WHO FC II and III. The haemodynamic parameters for FC II and FC III appear comparable to those reported in the French Registry.

It can be agreed with the MAH that the submitted data show that at baseline the recruited WHO FC II patients in study A1481140 were distinguishable from WHO FC III based on their 6-MWT and haemodynamic data. This is also supported by lesser administration of background supportive medications e.g. diuretics, digoxin and oxygen. These WHO FC II patients appear comparable to those described in the French Registry and those recruited in the ARIES studies. The MAH established that the baseline characteristics in the subgroups of grade II functional status was balanced between the placebo and sildenafil groups.

Administration of the registered dose of sildenafil 20 mg t.i.d resulted in a significant increase in 6-MWT in FC II of 49.2 m (95% CI: 21.5- 76.97) which is comparable to the increase achieved in FC III (45.4 m 95% CI: 15.56-75.26).

The MAH has also analysed the change from baseline in 6MWD using different cut-off points (≤400 m, >400 m, ≤415 m and >415 m). In general, the changes observed for all cut-off points were clinically relevant for all dosages although the effect size was lower for the less severe patients (who

walked >400 and >415 m) and who took the lower dose (20 mg), for whom the change from baseline was around 25 m (24.1 and 28.6m respectively). The MAH argued that the less size effect observed with 20 mg dose in these subgroups could be the result of the variability in the data and a chance consequence. The MAH's response appears reasonable given that a number of non-pre-specified analyses have been performed and consistency is observed for most of them.

In order to assess the robustness of the previous parametric analyses, the MAH provided the changes for these different cut-off (<400 m / >400 m and <415 m / >415 m) according to a numerical and graphical non parametric approach (Hodges-Lehman, 95% CI for the median estimates by treatment group and the median difference and 95% CI in the continuous efficacy variables). The additional analyses using non-parametric methods were consistent with the previous parametric analyses.

Results of the secondary endpoints (PAP, clinical worsening events and BORG dyspnoea) in FC II were submitted at the request of the CHMP. After administration of sildenafil 20 mg, a trend for a reduction in PAP: -3.2 mmHg is noticed. Only with higher doses of sildenafil 80 mg or for the whole sildenafil group, significant reductions are shown. These results are in line with those shown for FC III. It is agreed with the MAH that the small number of clinical worsening events preclude any conclusions. Similarly, BORG dyspnoea scores did not show differences following treatment as patients were only suffering from slight breathlessness at baseline and not much improvement would have been expected. In conclusion, sildenafil 20 mg may have a pressure lowering effect on PAP, in FC II. As with other haemodynamic parameter, the clinical relevance of such effects is not clear.

The principal disease aetiology of patients with secondary pulmonary hypertension (n=100) was PAH-CTD (class II- N: 32; class III- N: 51). The number of patients in the PAH-CTD group (class II) is limited and it is difficult to draw any firm conclusions. However, the magnitude of the observed effect (63 m) is consistent with that seen for the PAH-PPH group, class II and III (52 m and 29 m, respectively), though not statistically significant.

Overall, the post hoc analysis can be regarded as globally acceptable since it may facilitate the comparison with other marketed products.

As stated by the MAH, results of the long term extension study should be reviewed cautiously considering the open label non-controlled design. Generally, the reported results are reassuring regarding maintenance of efficacy (50 m and 45 m at 36 months for baseline functional class II and functional class III subjects, respectively).

1.2.2 Clinical safety

1.2.2.1 Main studies

The safety profile, based solely on safety tables, was generally similar for baseline functional class II subjects and baseline function class III subjects in Study A1481140. As would be expected, more severe AEs, SAEs, and deaths were reported in baseline functional class III subjects with more severe PAH.

In Study A1481142 sildenafil was generally well tolerated. The AEs reported were consistent with known side effects of sildenafil. The most frequently reported treatment related AEs were headache, dyspepsia, diarrhoea and blurred vision. Most AEs (all causality and treatment related) were mild or moderate in severity.

Survival at 1, 2, and 3 Years (presented under Safety)

One year survival data from Study A1481142 were provided in the original Revatio submission. Since the original submission in 2005, the long-term survival data after 3 years of sildenafil treatment has become available.

The 1, 2 and 3 year survival data from Study A1481142 were analysed for subjects randomised to sildenafil in Study A1481140 and for baseline functional class II and functional class III subjects randomised to sildenafil in Study A1481140. The Kaplan Meier survival estimates for subjects

randomised to sildenafil in Study A1481140 were 96%, 91%, and 82% at 1, 2, and 3 years, respectively. Kaplan Meier survival estimates at 1, 2, and 3 years for baseline functional class II subjects were 99%, 91%, and 84%, respectively, and for baseline functional class III subjects were 94%, 90%, and 81%, respectively.

These data suggest that sildenafil treatment improves survival and, as would be expected, functional class II subjects treated with sildenafil have a better prognosis than functional class III subjects. Survival data for sildenafil are comparable with the results presented for ambrisentan.

Safety data in patients with FC II and III, administered the registered dose of 20 mg t.i.d.

– *Adverse Events*

Table 9 summarises treatment-emergent, all causality adverse events (AEs) by baseline FC in Study A1481140 for the 20 mg treatment group. Overall the proportion of subjects with all causality AEs and SAEs were similar for baseline FC II and baseline FC III subjects in the 20 mg treatment group of Study A1481140. Few subjects had dose reductions, temporary discontinuations, or permanently discontinued due to AEs in either group. A higher proportion of severe AEs were reported for baseline FC III subjects.

Table 9 - Summary of Treatment-Emergent, All-Causality AEs by Baseline Functional Class - Study A1481140, Sildenafil 20 mg Treatment Group

Number (%) of	Functional class II	Functional Class III
Subjects evaluable for AEs	24	40
Number of AEs	140	175
Subjects with AEs	23 (95.8)	35 (87.5)
Subjects with Serious Adverse Events	3 (12.5)	6 (15.0)
Subjects with severe AEs	1 (4.2)	9 (22.5)
Subjects discontinued due to AEs	1 (4.2)	0
Subjects with dose reduced or temporary discontinuation due to AEs	1 (4.2)	4 (10.0)

– *Treatment-related adverse events (TRAEs)*

The proportion of subjects with TRAEs and SAEs were similar for baseline FC II and baseline FC III subjects in the 20 mg treatment group of Study A1481140. Few subjects had dose reductions or temporary discontinuations, and no subjects permanently discontinued due to AEs in either group. Two subjects experienced severe AEs in the baseline functional class III group, compared with none in the baseline functional class II group.

Table 10 - Summary of Treatment-Emergent, Treatment-Related AEs by Baseline Functional Class - Study A1481140, Sildenafil 20 mg Treatment Group

Number (%) of	Functional class II	Functional Class III
Subjects evaluable for AEs	24	40
Number of AEs	36	49
Subjects with AEs	14 (58.3)	21 (52.5)
Subjects with Serious Adverse Events	1 (4.2)	1 (2.5)
Subjects with severe AEs	0	2 (5.0)
Subjects discontinued due to AEs	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	1 (4.2)	1 (2.5)

Table 11 - The most frequently reported TRAEs in FC II compared to their frequency in FC III.

Body System/Adverse Event	Sildenafil 20mg Functional Class II (%) N = 24	Placebo Functional Class II (%) N = 32	Sildenafil 20 mg Functional Class III (%) N = 40	Placebo Functional Class III (%) N = 34
Dizziness	4 (16.7)	2 (6.3)	0	2 (5.9)
Headache	10 (41.7)	7 (21.9)	12 (30.0)	9 (26.5)
Abdominal pain NOS	3 (12.5)	1 (3.1)	0	3 (8.8)

According to the MAH, these data are difficult to interpret because of the relatively small number of baseline functional class II (24) and baseline functional class III (40) subjects in the 20 mg treatment group of Study A1481140.

– *Permanent Discontinuations*

One FC II patient in the 20 mg treatment group permanently discontinued treatment because of decreased creatinine clearance on day 1 of the study. The causality was given as concomitant treatment furosemide. The subject discontinued from the study and only took study drug on Day 1.

– *Deaths*

No deaths were reported with FC II; 2 deaths were reported in FC III, none considered related to sildenafil.

– *Serious Adverse Events*

Three serious adverse events were reported in FC II administered sildenafil 20 mg table 5, whereas 7 SAEs were reported in FC III.

Table 12 - Summary of SAEs reported in Baseline Functional Class II Patients – Study A1481140, Sildenafil 20 mg Treatment Group

Baseline functional class	Gender	Age (yrs)	Event term	Action taken/ Outcome	SAE start Day	Investigator Causality
II	Female	65	Bronchial infection	No action taken/ Resolved	6	Other illness – bronchial infection
			Haemorrhagic gastritis	No action taken/ Resolved	6	Other not study drug related
			Peptic ulcer oesophagitis	No action taken/ Resolved	6	Other not study drug related
			Left ventricular dysfunction	Permanently discontinued/ Resolved	94	Study drug
II	Female	43	Respiratory infection	No action taken/ Resolved	52	Other illness – bronchial infection
II	Female	51	Epistaxis	No action taken/ Resolved	5	Other illness – recurrent epistaxis

In these three patients, 6 SAEs were reported; all except one were assessed as not related to sildenafil and did not lead to permanent study discontinuation.

In one SAE: left ventricular dysfunction was assessed as related to sildenafil and ended with permanent discontinuation of sildenafil. The haemodynamic measurements were as follows:

Test	Baseline at 11:30	Week 12 at 14:30	Week 12 at 15:30
Pulmonary Systolic	56 mmHg	72 mmHg	68 mmHg
Pulmonary Diastolic	21 mmHg	34 mmHg	33 mmHg
Pulmonary Mean	27 mmHg	46 mmHg	45 mmHg
PCWP	13 mmHg	23 mmHg	23 mmHg
Systemic Systolic	117 mmHg	105 mmHg	128 mmHg
Systemic Diastolic	74 mmHg	71 mmHg	89 mmHg
Systemic Mean	95.5 mmHg	82 mmHg	102 mmHg
Heart Rate	86 beats/minute	87 beats/minute	82 beats/minute
Mean Cardiac Output	5.6 L/min	5.6 L/min	5.31 L/min
SVO_2	66.8%	55.5%	55.2%

The investigator attributed the left ventricular dysfunction to sildenafil. In the opinion of the sponsor, the event, most likely represented a complication of disease under study; however, the contributory effect of sildenafil, a pulmonary vasodilator, in unmasking the underlying left ventricular dysfunction cannot be excluded.

1.2.2.2 Post-Marketing Safety Data

According to International Marketing Service (IMS) estimates, approximately 33,883 patient-years of exposure to sildenafil (PAH) occurred during the period second quarter of 2005 through the first quarter of 2008.

A total of 47 sildenafil (PAH) cases (containing 75 events) were identified for the period 01 June 2008 through 31 August 2008. Eleven of these 47 cases involved death in patients treated with sildenafil for PAH. In 7 cases, assessment of the cause of death was not possible because insufficient data were provided. In the remaining four cases, the reported events and the fatal outcome most likely represented complications of patients' underlying diseases or intercurrent illnesses.

In addition, review of cases involving hemorrhagic events, ocular events, nervous system disorders, skin and subcutaneous events, cardiovascular events, or hearing impairment were performed. The risk/benefit balance for sildenafil (PAH) remained unchanged upon review of these events.

1.2.2.3 Discussion on clinical safety

The reported K-M survival estimates at 1, 2, and 3 years for baseline functional class II subjects of 99%, 91%, and 84% are slightly lower than those reported with ambrisentan of 94% for 2 and 3 years, but no conclusion can be drawn.

The MAH was requested to submit safety data in patients with FC II and III, administered the registered dose of 20 mg t.i.d, in order to establish the safety profile of sildenafil in its registered dose of 20 mg tid in patients with FC II.

The number of patients recruited in FC II administered sildenafil 20 mg in study A1481140 was 24, precluding any robust conclusions. Generally it can be observed that the frequencies of treatment related AEs such as headache, dizziness and abdominal pain NOS were higher in FC II (41.7%, 16.7% and 12.5% respectively) compared to either FCIII (30%, 0, and 0 respectively, or the matching placebo (21.9%, 6.3% and 3.1% respectively). The MAH did not comment on these unexpected findings. No deaths were reported. The single case of discontinuation in FC II was not considered related to sildenafil. In one single event of SAE (left ventricular dysfunction) the investigator related the event to sildenafil.

In conclusion, the safety profile of sildenafil 20 mg in patients with FC II is limited. In future PSURs, AEs should be separately reported per FC.

With respect to post-marketing data, the MAH provided the narratives and the medical review for two cases in which the contribution of sildenafil to the fatal outcome cannot be ruled out due to direct causality, concomitant therapy (other PAH treatment) or due to the natural progression of PAH. The

MAH committed to including these cases in the seventh Revatio PSUR and updating any follow-up information received.

1.3 Orphan Medicinal Products

Sildenafil was granted an orphan designation (EU/3/03/178) by the European Commission on 12 December 2003 for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

Due to the overlap of the extension of indication in PAH WHO functional class II proposed by the MAH of Revatio with that approved for Volibris (ambrisentan) and Tracleer (bosentan), the MAH was requested to submit a critical report addressing the possible similarity with this authorised orphan medicinal product.

Having considered the arguments presented by the MAH of Revatio on 10 December 2008, it is concluded that sildenafil does not share the same principal molecular structural features as ambrisentan and bosentan and the differences in molecular structure are not only minor. Sildenafil is regarded as structurally not similar to ambrisentan and bosentan. As defined in Art. 3 of Commission Regulation (EC) No 847/2000), Revatio is considered as non-similar to Volibris and Tracleer.

Therefore, with reference to article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Volibris and Tracleer in PAH including WHO functional class II, does not prevent the granting of the extension of indication of Revatio in PAH WHO functional class II which can be considered as significantly overlapping with the indication approved for Volibris and Tracleer (see Attachment 5).

1.4 Benefit/Risk Assessment

PAH is a rare and devastating disease. Owing to the difficulties associated with the diagnosis, many patients will have progressed to WHO functional class (FC) III or even IV before treatment is offered. Nevertheless, about 25% of PAH patients seen in the clinic are classed as WHO FC II or less at the time of diagnosis. Recently, it has been recognized that PAH patients in WHO FC II may benefit from specialized PAH therapy. Ambrisentan and bosentan have been recently approved for this indication (ref. EPAR)

The MAH did not submit new clinical data. Clinical data from previously submitted studies are re-evaluated. Based on data of the French registry re-defining PAH patients FC II, it could be seen that the pivotal study A1481140 recruited an adequate number of FC II patients, who are distinguishable from FC III. Haemodynamic analysis also supported such a distinction. The enrolled patients were PAH-treatment naïve, but the administered background medications further supports a distinction in their FC. The recruited patients appear comparable to those recruited in the Ambrisentan studies. Administration of sildenafil 20 mg t.i.d in WHO FC II patients resulted in significant improvement in the 6-minute walk test 6-MWT, comparable to that shown in the whole studied population or FC III. The results are also comparable to those reported with Ambrisentan (Ambrisentan EPAR). A requested non-parametric analysis of the 6-MWT further supported the already presented parametric analysis. Of the investigated secondary endpoints, only a trend for pressure lowering in PAP was noticed with the 20 mg t.i.d sildenafil. The number of recruited patients in the PAH-CTD group (class II) is limited precluding any firm conclusions. However, the magnitude of the observed effect is in line with the general results, though not statistically significant.

No safety issues were identified with long term use of sildenafil in PAH patients FC WHO II, but the specific database for the 20 mg t.i.d sildenafil in FC II is limited. In future PSURs, AEs should be reported separately per FC.

In conclusion, the benefit risk assessment for sildenafil is considered positive for the proposed extension of indication. Consequently, the CHMP agreed for sections 4.1 and 5.1 of the SPC to be updated accordingly.

2. CONCLUSION

On 29 May 2009, the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics.