



Worldwide Biopharmaceutical Businesses

30 September 2011

Important Safety Information:

Increased risk of mortality in paediatric patients with pulmonary arterial hypertension with the use of higher than recommended doses of Revatio (sildenafil citrate)

Dear Healthcare Professional,

Pfizer is writing to inform you of important new safety information regarding Revatio (sildenafil citrate) tablets for the treatment of pulmonary arterial hypertension (PAH) in paediatric patients.

Summary:

- In a clinical study of Revatio for the treatment of PAH in paediatric patients with doses in the range of 10-80 mg three times a day, a higher risk of mortality among patients in the higher compared with lower study-specific dose groups was observed.
- Therefore, prescribers are reminded that doses of Revatio higher than those recommended in the SmPC should not be used. For patients who weigh ≤ 20 kg the dose is 10 mg three times a day and for patients > 20 kg the dose is 20 mg three times a day.
- If your patients are currently being prescribed doses that are higher than recommended in the SmPC, these doses should be titrated down to the recommended dose in a timely manner in accordance with your medical judgment of the patient's condition.

Further information on the safety concern:

Paediatric patients with PAH who completed the 16-week placebo-controlled randomised blinded trial (Study A1481131) [1] were eligible to enter the long-term extension study (Study A1481156) [2] with open label administration of sildenafil using low, medium and high level dosing groups (range 10–80 mg sildenafil). Doses were allocated according to weight category and dose titrations were permitted throughout the course of the long-term extension study.

The doses (three times a day) corresponding to the low, medium, and high level sildenafil for each of the three weight categories in the pivotal and extension studies are presented in the following table:

Body Weight	Low level	Medium level	High level
$\geq 8-20$ kg	NA	10 mg	20 mg*
$> 20-45$ kg	10 mg	20 mg	40 mg*
> 45 kg	10 mg	40 mg*	80 mg*

*Represents a dose that is higher than the approved dose in the EU SmPC. NA = not applicable

When participating subjects had completed 3 years and some as long as 7 years, more deaths were observed in the high level dosing group. The incidence of deaths in the high, medium and low level dosing groups was 20% (20 of 100), 14% (10 of 74) and 9% (5 of 55), respectively.

The Data Monitoring Committee (DMC) concluded that the high dose of sildenafil in this clinical trial was associated with a harmful effect on survival when compared with the low dose. The DMC

also expressed concern about the potential dose-response relationship between increasing dose and mortality. Hence, the DMC recommended that patients in the study on the higher doses be down-titrated.

Based on the information available, Revatio remains a safe and effective medicine for the treatment of PAH in paediatric patients, when used in accordance with the dosing recommendations in the SmPC.

If your patients are currently being prescribed doses that are higher than the dosing described in the SmPC, these doses should be titrated down to the recommended dose as noted below, in a timely manner in accordance with your medical judgment of the patient's condition. The recommended doses of Revatio for the treatment of paediatric PAH have not changed.

The posology for paediatric patients included in the SmPC of Revatio is:

For paediatric patients aged 1 year to 17 years old, the recommended dose in patients ≤ 20 kg is 10 mg (1 ml of compounded suspension) three times a day and for patients > 20 kg is 20 mg (2 ml of compounded suspension or 1 tablet) three times a day.

The SmPC is updated to include a warning that Revatio doses higher than the recommended doses in the SmPC should not be used in paediatric patients with PAH.

The revised SmPC, approved by the European Medicines Agency, is set out in the attached Annex. The information in this letter has been agreed with the European Medicines Agency and National Competent Authorities.

Call for reporting:

Please report suspected adverse reactions with any medicine or vaccine to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme online at <http://yellowcard.mhra.gov.uk/>

Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail: "FREEPOST YELLOW CARD"
- at the back of the British National Formulary (BNF)
- by telephoning the Commission of Human Medicines (CHM) free phone line: 0800-731-6789
- or by electronic download through the MHRA website (<http://yellowcard.mhra.gov.uk/downloads/>)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Suspected adverse drug reactions may also be reported to Pfizer Medical Information on 01304 616161.

Communication information:

If you have any questions about this letter or for more information about Revatio, please contact Pfizer Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS or Telephone: 01304 616161. You may also request a member of the medical team to contact you for a more in-depth discussion.

Yours sincerely,



Jonathan Jones
Medical Director, Specialty Care Business Unit
Pfizer UK Ltd

References

1. <http://clinicaltrials.gov/ct2/show/NCT00159913?term=A1481131&rank=2>
2. <http://clinicaltrials.gov/ct2/show/NCT00159874?term=a1481156&rank=1>