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Pfizer Healthcare Ireland

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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.
The information in this letter has been agreed with the European Medicines Agency and the Irish Medicines Board.

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 to lower study- specific dose groups was observed.
- Therefore, prescribers are reminded that higher doses of Revatio than those recommended in the SmPC should not be used.
- 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.
- The dosing recommended in the SmPC in patients ≤ 20 kg is 10 mg three times a day and for patients > 20 kg is 20 mg 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

Further information on the safety concern:

Paediatric patients with PAH who completed the 16-week placebo-controlled trial (Study A1481131)[1] were eligible to enter the long-term randomised extension trial (Study A1481156) [2] with an initial blinded phase followed by open label administration of sildenafil using low, medium and high dose 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 dose groups for each of the three weight categories in the pivotal and extension studies are presented in the following table:

Body Weight	Low Dose	Medium Dose	High Dose
≥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.

When participating subjects had completed 3 years and some as long as 7 years, more deaths were observed in the high dose group. The incidence of deaths in the high, medium and low dose 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 to 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 patient 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 revised SmPC, approved by the European Medicines Agency, is set out in the attached Annex.

Call for reporting:
You can assist us with monitoring the safety of Revatio by reporting suspected adverse reactions to Pfizer Medical Information on 1800 633363. Alternatively, this information may be reported to the Irish Medicines Board (IMB) by calling: (01) 6764971, using on-line reporting forms at: www.imb.ie or using post-paid Report Cards (Yellow Cards) e-mail: imbpharmacovigilance@imb.ie

Communication information:
If you have any questions about this letter , please contact Pfizer Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS or Tel: 1800 633363 and ask for Medical Information. You may also request a member of the medical team to contact you for a more in-depth discussion.

Yours sincerely,

Dr. Declan O'Callaghan
Director of Medical Affairs, Specialty Care Business Unit
Pfizer Healthcare Ireland

References

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