Dear Healthcare Professional

This letter addresses the correct and safe use of the product REVATIO® (sildenafil citrate) 20 mg tablets for the treatment of pulmonary arterial hypertension (PAH).

The approved indication in the EU is:

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.

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension. In case of clinical deterioration in spite of Revatio treatment, alternative therapies should be considered.

The use of REVATIO and organic nitrates in any form, at any time is contraindicated.

REVATIO contains sildenafil citrate, the same active ingredient found in Viagra.

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.

Important Safety Information

The efficacy and safety of sildenafil co-administered with other treatments for pulmonary arterial hypertension (eg. bosentan, epoprostenol, iloprost) has not been studied in controlled clinical trials. Therefore, caution is recommended in case of co-administration.

The safety and efficacy of Revatio when co-administered with other PDE5 inhibitors has not been studied in pulmonary arterial hypertension patients.

Co-administration of potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) with sildenafil for pulmonary arterial hypertension is contraindicated.

Please see accompanying full prescribing information

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: severe hepatic impairment, recent history of stroke or myocardial infarction, severe hypotension (blood pressure < 90/50 mmHg) at initiation.

The efficacy of Revatio has not been established in patients with severe pulmonary arterial hypertension (functional class IV). If the clinical situation deteriorates, therapies that are recommended at the severe stage of the disease (e.g. epoprostenol) should be considered.

The benefit-risk balance of sildenafil has not been established in patients with class I functional classification of pulmonary arterial hypertension. No studies have been performed in related forms of pulmonary arterial hypertension other than related to connective tissue disease and surgical repair.

The safety of sildenafil has not been studied in patients with known hereditary degenerative retinal disorders such as *Retinitis pigmentosa* (a minority of these patients have genetic disorders of retinal phosphodiesterases) and therefore its use is not recommended.

In general, any dose adjustment should be administered only after a careful benefit-risk assessment.A downward dose adjustment to 20 mg twice daily should be considered when sildenafil is co-administered to patients already receiving medium potency CYP3A4 inhibitors like erythromycin or saquinavir. A downward dose adjustment to 20 mg once daily is recommended in case of co-administration with CYP3A4 inhibitors of intermediate potency like clarithromycin, telithromycin and nefazodone. Co-administration of potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) with sildenafil for pulmonary arterial hypertension is contraindicated. Dose adjustments of sildenafil may be required when co-administered with CYP3A4 inducers.

When prescribing sildenafil, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by sildenafil's mild to moderate vasodilatory effects, for example patients with hypotension, patients with fluid depletion, severe left ventricular outflow obstruction or autonomic dysfunction.

Caution is advised when sildenafil is administered to patients taking an alpha-blocker as the co-administration may lead to symptomatic hypotension in susceptible individuals. In order to minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Physicians should advise patients what to do in the event of postural hypotensive symptoms.

Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside *in vitro*. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore sildenafil should be administered to these patients only after careful benefit-risk assessment.

In pulmonary arterial hypertension patients, there may be a potential for increased risk of bleeding when sildenafil is initiated in patients already using a Vitamin K antagonist,

particularly in patients with pulmonary arterial hypertension secondary to connective tissue disease.

No data are available with sildenafil in patients with pulmonary hypertension associated with pulmonary veno-occlusive disease. However, cases of life threatening pulmonary oedema have been reported with vasodilators (mainly prostacyclin) when used in those patients. Consequently, should signs of pulmonary oedema occur when sildenafil is administered in patients with pulmonary hypertension, the possibility of associated veno-occlusive disease should be considered.

Lactose monohydrate is present in the tablet film coat. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Background information

Although rare, PAH is a devastating illness; left untreated, median survival time is less than 3 years (1,2). Symptoms of PAH include dyspnoea, fatigue, syncope, and chest pain (3,4). The nonspecificity of these symptoms often delays the diagnosis of PAH (3,4). The mean age at diagnosis is 36, with women generally affected more often that men (1,3).

The efficacy of REVATIO was demonstrated in the SUPER-1 (Sildenafil Use in Pulmonary Arterial HypERtension) Study, a 12-week, multinational, double-blind, placebo-controlled, randomised study in which 277 patients with PAH received placebo or REVATIO 20mg, 40 mg or 80 mg tid (5). Included in the study were patients with primary PAH (63%), PAH associated with connective disease (30%) and PAH following surgical repair of congenital heart lesions (7%). Thirty-nine percent of the patients were functional class II and 58% were functional class III (5). No differences were observed among the REVATIO doses studied – therefore, the approved dosage is 20 mg tid.

In this study, REVATIO 20 mg increased 6-minute-walk distance by 45 metres vs a decrease of 4 metres with placebo (P<.0001) (5) and reduced mean pulmonary arterial pressure by – 2.7 mm Hg (P=.04 vs placebo). The most commonly reported adverse reactions that occurred (greater or equal to 10 %) on Revatio compared to placebo were headache, facial flushing, indigestion, back pain, diarrhoea and limb pain. Adverse events with REVATIO were generally mild to moderate in nature.

Pfizer is committed to providing healthcare professionals, patients and regulatory authorities worldwide with additional information as soon as possible. If you have any enquiries or want additional information, please contact Pfizer Ltd. on freephone 1800 633 363 and ask for Medical Information.

Any suspected adverse drug reactions should be reported to the drug safety group at Pfizer Ltd., and the Irish Medicines Board in the usual way. The contact details for Pfizer are Pfizer ltd., Walton Oaks, Dorking Road, Tadworth, Surrey, UK, KT20 7NS, or by using freephone 1800 633 363 and asking for the Drug Safety Group.

Yours sincerely,

Dr John Farrell
Medical director
Pfizer Healthcare Ireland

References:

1. Galie N, Manes A, Uguccioni L, Serafini F, De Rosa M, Branzi A, Magnani B. Primary pulmonary hypertension: insights into pathogenesis from epidemiology. Chest. 1998 Sep;114(3 Suppl):184S-194S.

2. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al.Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991 Sep 1;115(5):343-9.

3. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK, et al. Primary pulmonary hypertension. A national prospective study.
Ann Intern Med. 1987 Aug;107(2):216-23.

4. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, Loyd JE; American College of Chest Physicians.Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines.
Chest. 2004 Jul;126(1 Suppl):14S-34S

5. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia, T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005; 353:2148-57

Please see accompanying full prescribing information

A NEW OPTION IN THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Dear Healthcare Professional,

I am please to announce the availability of REVATIO® (sildenafil citrate) 20mg tablets for the treatment of pulmonary arterial hypertension (PAH). REVATIO® is indicated for:

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.

Recent evidence published in the New England Journal of Medicine has shown that REVATIO® 20mg taken three times daily (tid) after 12 weeks can significantly improve exercise capacity, reduce mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) in patients with PAH[1].

Reimbursement Protocol

REVATIO® is GMS reimbursable from **1st June 2006** under the General Medical Services and Community Drugs Schemes. Reimbursement will be approved through community pharmacies for the named-patient use of REVATIO® for PAH in the following circumstances:

- Consultant-initiated (limited to named consultants and hospitals)
  - Dr Sean Gaine, Mater Hospital, Dr Kevin Walsh, Mater and Crumlin, Dr Jim Egan Mater Hospital, Dr Paul Oslizlok, Crumlin, Dr Desmond Duff, Crumlin, Dr David Coleman, Crumlin and Dr Anita Dumitrescu, Crumlin
- Specifically prescribed for treatment of PAH
- Patient criteria met
  - Each patient must have PFTs, ECHO, V-Q scan and chest x-ray as a minimum to confirm PAH.
- Each patient approval has a maximum duration of three months
- Patient re-evaluation every three months, including re-prescribing where treatment is to continue
- Details of the hospital prescription must be recorded on the Patient Approval Form made available for this purpose

- Where a patient holds a GMS card, the prescription must be dispensed under the GMS scheme (ie patient takes prescription to own GP, who then prescribes on a GMS form)
- Prescribing consultant to notify GMS Payments Board on cessation of patient's treatment

Product Detail

Formulation/Strength	Pack Size	Trade Price	Wholesale Price
20mg tablet	90	€553.95	€470.86

PAH Background and Referral Process

Although rare, PAH is a devastating illness. If left untreated, median survival time is less than three years[2,3]. The symptoms of PAH include dysonoea, fatigue, syncope and chest pain[4,5]. Often the non-specificity of these symptoms delays correct diagnosis[4,5]. PAH generally affects more women then men and the mean age of diagnosis is 36[2,4].

Once PAH is suspected, prompt referral to the Pulmonary Hypertension Unit at the Mater Misericordiae University Hospital in Dublin should not be delayed. Referrals to the Pulmonary Hypertension Unit can be made by a patient's Consultant or GP.

REVATIO® is an exciting new medicine that represents a genuine advance in the treatment of patients with PAH. For further information about REVATIO® please refer to the enclosed Summary of Product Characteristics or contact _____.
If you have any enquiries or want additional information, please contact Pfizer Ltd. on freephone 1800 633 363 and ask for Medical Information.

Yours Sincerely,

Jay Cusack,
Brand Manager
Pfizer Healthcare Ireland.

References:

1. Gaile N, Ghofrani HA, Torbicki A, Barst RJ, Rublin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, et al, for the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. *N Eng J Med.* 2005 Nov;353:38-47.

2. Gaile N, Manes A, Uguccioni L, Serafini F, De Rosa M, Branzi A, Magnani B. Primary pulmonary hypertension: insights into pathogenesis from epidemiology. *Chest.* 1998 Sept;114(3 Suppl):184S-194S.

3. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991 Sept;115(5):343-9.

4. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med.* 1987 Aug;107(2):216-23.

5. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, Loyd JE; American College of Chest Physicians. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004 July;126 (1 Suppl):14S-34S

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Revatio ® 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg of sildenafil (as citrate).
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconvex film-coated tablets marked "PFIZER" on one side and "RVT 20"on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Revatio is intended for oral use.

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension. In case of clinical deterioration in spite of Revatio treatment, alternative therapies should be considered.

Use in adults (≥ 18 years):
The recommended dose is 20 mg three times a day. Tablets should be taken approximately 6 to 8 hours apart with or without food.

Use in the elderly (≥ 65 years):
Dosage adjustments are not required in elderly patients. Clinical efficacy as measured by 6-minute walk distance could be less in elderly patients.

Use in patients with impaired renal function:
Initial dose adjustments are not required in patients with renal impairment, including severe renal impairment (creatinine clearance < 30 ml/min). A downward dose adjustment to 20 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.

Use in patients with impaired hepatic function:
Initial dose adjustments are not required in patients with hepatic impairment (Child-Pugh class A and B). A downward dose adjustment to 20 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.
Revatio is contraindicated in patients with severe hepatic impairment (Child-Pugh class C), (see section 4.3).

Use in children and adolescents (< 18 years):
The safety and efficacy in children and adolescents have not been studied in large controlled clinical trials. Therefore, the use of sildenafil is not recommended in these patients.

Discontinuation of treatment:
Limited data suggests that the abrupt discontinuation of Revatio is not associated with rebound worsening of pulmonary arterial hypertension. However to avoid the possible occurrence of sudden clinical deterioration during withdrawal, a gradual dose reduction should be considered. Intensified monitoring is recommended during the discontinuation period.

Use in patients using other medicines:
The efficacy and safety of sildenafil co-administered with other treatments for pulmonary arterial hypertension (eg. bosentan, epoprostenol, iloprost) has not been studied in controlled clinical trials. Therefore the concomitant use of sildenafil with these medicinal products cannot be recommended.

The safety and efficacy of Revatio when co-administered with other PDE5 inhibitors has not been studied in pulmonary arterial hypertension patients.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway (see section 5.1), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.

Combination with potent CYP3A4 inhibitors (eg. ketoconazole, itraconazole, ritonavir) (see section 4.5).

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: severe hepatic impairment, recent history of stroke or myocardial infarction, severe hypotension (blood pressure < 90/50 mmHg) at initiation.

4.4 Special warnings and special precautions for use

The efficacy of Revatio has not been established in patients with severe pulmonary arterial hypertension (functional class IV). If the clinical situation deteriorates, therapies that are recommended at the severe stage of the disease (e.g. epoprostenol) should be considered (see section 4.2).

The benefit-risk balance of sildenafil has not been established in patients with class I functional classification of pulmonary arterial hypertension. No studies have been performed

in related forms of pulmonary arterial hypertension other than related to connective tissue disease and surgical repair.

The safety of sildenafil has not been studied in patients with known hereditary degenerative retinal disorders such as *Retinitis pigmentosa* (a minority of these patients have genetic disorders of retinal phosphodiesterases) and therefore its use is not recommended.

In general, any dose adjustment should be administered only after a careful benefit-risk assessment.
A downward dose adjustment to 20 mg twice daily should be considered when sildenafil is co-administered to patients already receiving medium potency CYP3A4 inhibitors like erythromycin or saquinavir. A downward dose adjustment to 20 mg once daily is recommended in case of co-administration with CYP3A4 inhibitors of intermediate potency like clarithromycin, telithromycin and nefazodone. Co-administration of potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) with sildenafil for pulmonary arterial hypertension is contraindicated (see section 4.3). Dose adjustments of sildenafil may be required when co-administered with CYP3A4 inducers (see section 4.5).

When prescribing sildenafil, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by sildenafil's mild to moderate vasodilatory effects, for example patients with hypotension, patients with fluid depletion, severe left ventricular outflow obstruction or autonomic dysfunction (see section 4.4).

Sildenafil potentiates the hypotensive effect of nitrates therefore concomitant use of Revatio with nitrates is contraindicated (see section 4.3).

In post-marketing experience with sildenafil for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

Sildenafil should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

Caution is advised when sildenafil is administered to patients taking an alpha-blocker as the co-administration may lead to symptomatic hypotension in susceptible individuals (see section 4.5). In order to minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Physicians should advise patients what to do in the event of postural hypotensive symptoms.

Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside *in vitro*. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore sildenafil should be administered to these patients only after careful benefit-risk assessment.

In pulmonary arterial hypertension patients, there may be a potential for increased risk of bleeding when sildenafil is initiated in patients already using a Vitamin K antagonist,

particularly in patients with pulmonary arterial hypertension secondary to connective tissue disease.

No data are available with sildenafil in patients with pulmonary hypertension associated with pulmonary veno-occlusive disease. However, cases of life threatening pulmonary oedema have been reported with vasodilators (mainly prostacyclin) when used in those patients. Consequently, should signs of pulmonary oedema occur when sildenafil is administered in patients with pulmonary hypertension, the possibility of associated veno-occlusive disease should be considered.

Lactose monohydrate is present in the tablet film coat. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sildenafil
In vitro studies:
Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

In vivo studies:
Population pharmacokinetic analysis of pulmonary arterial hypertension clinical trial data indicated a reduction in sildenafil clearance and/or an increase of oral bioavailability when co-administered with CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers. These were the only factors with a statistically significant impact on sildenafil pharmacokinetics in patients with pulmonary arterial hypertension. The exposure to sildenafil in patients on CYP3A4 substrates and CYP3A4 substrates plus beta-blockers was 43 % and 66 % higher, respectively, compared to patients not receiving these classes of medicines. Sildenafil exposure was 5-fold higher at a dose of 80 mg three times a day compared to the exposure at a dose of 20 mg three times a day. This concentration range covers the increase in sildenafil exposure observed in specifically designed drug interaction studies with CYP3A4 inhibitors (except more potent CYP3A4 inhibitors e.g. ketoconazole, itraconazole, ritonavir).

CYP3A4 inducers seemed to have a substantial impact on the pharmacokinetics of sildenafil in pulmonary arterial hypertension patients, which was confirmed in the in-vivo interaction study with CYP3A4 inducer bosentan.

In a study of healthy male volunteers co-administration of the endothelin antagonist bosentan, which is a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19, at steady state (125 mg twice a day) with sildenafil at steady state (80 mg three times a day) resulted in a 62.6 % decrease of sildenafil AUC and a 55.4 % decrease in sildenafil C_{max}. The combination of both drugs did not lead to clinically significant changes of blood pressure (supine and standing). Efficacy of sildenafil should be closely monitored in patients using concomitant potent CYP3A4 inducers, such as carbamazepine, phenytoin, phenobarbital, St John's wort and rifamipicine.

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300 % (4-fold) increase in sildenafil C_{max} and a 1,000 % (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/ml, compared to approximately 5 ng/ml when sildenafil was administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Based on these

pharmacokinetic results co-administration of sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension patients (see section 4.3).

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) with sildenafil (100 mg single dose) resulted in a 140 % increase in sildenafil C_{max} and a 210 % increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics.

When a single 100 mg dose of sildenafil was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg twice daily for 5 days), there was a 182 % increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC, C_{max}, T_{max}, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite. Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56 % increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers.

Potent CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have effects similar to ritonavir (see section 4.3). CYP3A4 inhibitors of intermediate potency (e.g. clarithromycin, telithromycin and nefazodone) are expected to have an effect in between that of ritonavir and CYP3A4 inhibitors of medium potency (e.g. saquinavir/erythromycin), a seven-fold increase in exposure is assumed. Therefore dose adjustments are recommended when using CYP3A4 inhibitors of intermediate potency (see section 4.4).

The population pharmacokinetic analysis in pulmonary arterial hypertension patients suggested that co-administration of beta-blockers in combination with CYP3A4 substrates might result in an additional increase in sildenafil exposure compared with administration of CYP3A4 substrates alone.

Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.

Co-administration of oral contraceptives (ethinyloestradiol 30 µg and levonorgestrel 150 µg) did not affect the pharmacokinetics of sildenafil.

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to have serious interaction with sildenafil.

Effects of sildenafil on other medicinal products
In vitro studies:
Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50} >150 µM).

There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies:
No significant interactions were shown when sildenafil (50 mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

Sildenafil had no significant effect on atorvastatin exposure (AUC increased 11%), suggesting that sildenafil does not have a clinically relevant effect on CYP3A4.

No interactions were observed between sildenafil (100 mg single dose) and acenocoumarol.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150 mg).

Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.

In a study of healthy volunteers sildenafil at steady state (80 mg three times a day) resulted in a 49.8 % increase in bosentan AUC and a 42 % increase in bosentan C_{max} (125 mg twice daily).

In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers.

In three specific drug-drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and lightheadedness, but not syncope. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in susceptible individuals (see section 4.4).

Sildenafil (100 mg single dose) did not affect the steady state pharmacokinetics of the HIV protease inhibitor saquinavir, which is a CYP3A4 substrate/inhibitor.

Consistent with its known effects on the nitric oxide/cGMP pathway (see section 5.1), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated (see section 4.3).

Sildenafil had no clinically significant impact on the plasma levels of oral contraceptives (ethinyloestradiol 30 µg and levonorgestrel 150 µg).

4.6 Pregnancy and lactation

There are no data from the use of sildenafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy and embryonal/foetal development. Studies in animals have shown toxicity with respect to postnatal development (see section 5.3).

Due to lack of data, Revatio should not be used in pregnant women unless strictly necessary. It is not known whether sildenafil enters the breast milk. Revatio should not be administered to breast-feeding mothers.

4.7 Effects on ability to drive and use machines

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they might be affected by Revatio, before driving or operating machinery. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In the pivotal placebo-controlled study of Revatio in pulmonary arterial hypertension, a total of 207 patients were treated with Revatio at daily doses ranging from 20 mg to 80 mg three times a day and 70 patients were treated with placebo. The duration of treatment was 12 weeks. 259 subjects who completed the pivotal study entered a long-term extension study. Doses up to 80 mg three times a day (4 times the recommended dose of 20 mg three times a day) were studied (N=149 patients treated for at least 1 year, 101 on 80 mg three times a day).

Adverse events were generally mild to moderate in severity. The most commonly reported adverse reactions that occurred (greater or equal to 10 %) on Revatio compared to placebo were headache, flushing, dyspepsia, back pain, diarrhoea and limb pain.

The adverse reactions that occurred in ≥3 % of Revatio-treated patients and were more common (≥1 % difference) on Revatio in the pivotal placebo-controlled trial in pulmonary arterial hypertension at doses of 20, 40 or 80 mg three times a day are shown in Table 1:

Table 1: Adverse reactions occurring in ≥3 % of patients, and more frequently in patients on Revatio (20, 40 or 80 mg three times a day), in the pivotal placebo-controlled trial in pulmonary arterial hypertension

MedDRA System Organ Class / Adverse reaction	**Placebo N=70 %**	**REVATIO (all) N= 207 %**
Nervous system disorders		
Headache	39	46
Vascular disorders		
Flushing	4	12
Musculoskeletal and connective tissue disorders		
Limb Pain	6	10
Myalgia	4	9
Gastrointestinal disorders		
Dyspepsia	7	11
Diarrhoea	6	10
Respiratory, thoracic and mediastinal disorders		
Cough	6	7
Epistaxis	1	7
Psychiatric disorder		
Insomnia	1	6
General disorders and administration site conditions		
Pyrexia	3	6
Infections and infestations		

Influenza	3	5
Eye disorders Visual disturbance not otherwise specified (NOS)	0	4

The overall frequency of discontinuation in sildenafil treated patients at the recommended daily dose of 20 mg three times a day (2.9 %) was low and the same as placebo (2.9 %). The adverse reactions that occurred in ≥1% and <3% and more frequently with Revatio than with placebo were the following.

Blood and lymphatic disorders:
Anaemia NOS
Ear:
Vertigo
Eye disorders:
Abnormal sensation in eye, chromatopsia, cyanopsia, diplopia, eye irritation, photophobia, retinal haemorrhage, visual acuity reduced.
Gastrointestinal disorders:
Abdominal distension, gastritis (not otherwise specified, NOS), gastroenteritis NOS, gastroesophageal reflux disease, haemorrhoids.
Infections and infestations:
Sinusitis NOS, cellulitus.
Investigations:
Weight increased

Metabolism disorders:
Fluid retention
Nervous system disorders:
Paraesthesia, tremor, burning sensation NOS, migraine NOS, hypoaesthesia.
Psychiatric disorders:
Anxiety
Respiratory, thoracic and mediastinal disorders:
Bronchitis NOS, rhinitis NOS
Reproductive system disorders:
Gynaecomastia
Skin and subcutaneous tissue disorders:
Alopecia, erythema

In post marketing surveillance of PDE5 inhibitors in the treatment of male erectile dysfunction (MED), there have been rare reports of the following visual adverse events: non-arteritic anterior ischaemic optic neuropathy (NAION), retinal vein occlusion and visual field defect.

4.9 Overdose

In single dose volunteer studies of doses up to 800 mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. At single doses of 200 mg the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction, ATC code: G04B E03

Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), the enzyme that is responsible for degradation of cGMP. Apart from the presence of this enzyme in the corpus cavernosum of the penis, PDE5 is also present in the pulmonary vasculature. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary arterial hypertension this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. There is an 80-fold selectivity over PDE1, and over 700-fold over PDE 2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

Sildenafil causes mild and transient decreases in systemic blood pressure which, in the majority of cases, do not translate into clinical effects. After chronic dosing of 80 mg three times a day to patients with systemic hypertension the mean change from baseline in systolic and diastolic blood pressure was a decrease of 9.4 mmHg and 9.1 mm Hg respectively. After chronic dosing of 80 mg three times a day to patients with pulmonary arterial hypertension lesser effects in blood pressure reduction were observed (a reduction in both systolic and diastolic pressure of 2 mmHg). At the recommended dose of 20 mg three times a day no reductions in systolic or diastolic pressure were seen.

Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. After chronic dosing of 80 mg three times a day to patients with pulmonary arterial hypertension no clinically relevant effects on the ECG were reported.

In a study of the hemodynamic effects of a single oral 100 mg dose of sildenafil in 14 patients with severe coronary artery disease (CAD) (>70 % stenosis of at least one coronary artery), the mean resting systolic and diastolic blood pressures decreased by 7 % and 6 % respectively compared to baseline. Mean pulmonary systolic blood pressure decreased by 9 %. Sildenafil showed no effect on cardiac output, and did not impair blood flow through the stenosed coronary arteries.

Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100 mg dose, with no effects evident after 2 hours post-dose. The postulated mechanism for this change in colour discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. Sildenafil has no effect on visual acuity or contrast sensitivity. In a small size placebo-controlled study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100 mg) demonstrated no

significant changes in visual tests conducted (visual acuity, Amsler grid, colour discrimination simulated traffic light, Humphrey perimeter and photostress).

Efficacy in adult patients with pulmonary arterial hypertension (PAH)
A randomised, double-blind, placebo-controlled study was conducted in 278 patients with primary pulmonary hypertension, PAH associated with connective tissue disease (CTD), and PAH following surgical repair of congenital heart lesions. Patients were randomised to one of four treatment groups: placebo, sildenafil 20 mg, sildenafil 40 mg or sildenafil 80 mg, three times a day. Of the 278 patients randomised, 277 patients received at least 1 dose of study drug. The study population consisted of 68 (25 %) men and 209 (75 %) women with a mean age of 49 years (range: 18-81 years) and baseline 6-minute walk test distance between 100 and 450 metres inclusive (mean: 344 metres). 175 patients (63%) included were diagnosed with primary pulmonary hypertension, 84 (30%) were diagnosed with PAH associated with connective tissue disease (CTD) and 18 (7%) of the patients were diagnosed with PAH following surgical repair of congenital heart lesions. Most patients were WHO Functional Class II (107/277, 39%) or III (160/277, 58%) with a mean baseline 6 minute walking distance of 378 meters and 326 meters respectively; fewer patients were Class I (1/277, 0.4%) or IV (9/277, 3%) at baseline. Patients with left ventricular ejection fraction <45 % or left ventricular shortening fraction <0.2 were not studied.

Sildenafil (or placebo) was added to patients' background therapy which could have included a combination of anticoagulation, digoxin, calcium channel blockers, diuretics or oxygen. The use of prostacyclin, prostacyclin analogues and endothelin receptor antagonists was not permitted as add-on therapy, and neither was arginine supplementation. Patients who previously failed bosentan therapy were excluded from the study.

The primary efficacy endpoint was the change from baseline at week 12 in 6-minute walk distance. A statistically significant increase in 6-minute walk distance was observed in all 3 sildenafil dose groups compared to those on placebo. Placebo corrected increases in walk distance were 45 metres ($p < 0.0001$), 46 metres ($p < 0.0001$) and 50 metres ($p < 0.0001$) for sildenafil 20 mg, 40 mg and 80 mg respectively. There was no significant difference in effect between sildenafil doses.

The improvement in walk distance was apparent after 4 weeks of treatment and this effect was maintained at weeks 8 and 12. Results were generally consistent in subgroups according to baseline walking distance, aetiology (primary and CTD-associated PAH), WHO functional class, gender, race, location, mean PAP and PVRI.

Patients on all sildenafil doses achieved a statistically significant reduction in mean pulmonary arterial pressure (mPAP) compared to those on placebo. The placebo-corrected treatment was –2.7 mmHg ($p=0.04$) for sildenafil 20 mg three times a day. There was no evidence of a difference in effect between sildenafil 20 mg and the higher doses tested. The mean change from baseline in pulmonary vascular resistance (PVR) was –122 dyne.sec/cm^5 for sildenafil 20 mg three times a day. The percent reduction at 12 weeks for sildenafil 20 mg in PVR (11.2%) was proportionally greater than the reduction in systemic vascular resistance (SVR) (7.2%). The effect of sildenafil on mortality is unknown.

5.2 Pharmacokinetic properties

Absorption:
Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 41 % (range 25-63 %). After oral three times a day dosing of sildenafil,

AUC and C_{max} increase in proportion with dose over the dose range of 20-40 mg. After oral doses of 80 mg three times a day a more than dose proportional increase in sildenafil plasma levels has been observed. In pulmonary arterial hypertension patients, the oral bioavailability of sildenafil after 80 mg three times a day was on average 43 % (90 % CI: 27% - 60%) higher compared to the lower doses.

When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29 % however, the extent of absorption was not significantly affected (AUC decreased by 11%).

Distribution:
The mean steady state volume of distribution (V_d) for sildenafil is 105 l, indicating distribution into the tissues. After oral doses of 20 mg three times a day, the mean maximum total plasma concentration of sildenafil at steady state is approximately 113 ng/ml. Sildenafil and its major circulating N-desmethyl metabolite are approximately 96 % bound to plasma proteins. Protein binding is independent of total drug concentrations.

Metabolism:
Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50 % that of the parent drug. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 h. In patients with pulmonary arterial hypertension, plasma concentrations of N-desmethyl metabolite are approximately 72 % those of sildenafil after 20 mg three times a day dosing (translating into a 36 % contribution to sildenafil's pharmacological effects). The subsequent effect on efficacy is unknown.

Elimination:
The total body clearance of sildenafil is 41 l/h with a resultant terminal phase half-life of 3-5 h. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80 % of administered oral dose) and to a lesser extent in the urine (approximately 13 % of administered oral dose).

Pharmacokinetics in special patient groups
Elderly:
Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 90 % higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40 %.

Renal insufficiency:
In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 ml/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. In volunteers with severe renal impairment (creatinine clearance <30 ml/min), sildenafil clearance was reduced, resulting in mean increases in AUC and C_{max} of 100 % and 88 % respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased 200 % and 79 % respectively in subjects with severe renal impairment compared to subjects with normal renal function.

Hepatic insufficiency:

In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh class A and B) sildenafil clearance was reduced, resulting in increases in AUC (85 %) and C_{max} (47 %) compared to age-matched volunteers with no hepatic impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased by 154 % and 87 %, respectively in cirrhotic subjects compared to subjects with normal hepatic function. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

Population pharmacokinetics:
In patients with pulmonary arterial hypertension, the average steady state concentrations were 20 – 50 % higher over the investigated dose range of 20–80 mg three times a day compared to healthy volunteers. There was a doubling of the C_{min} compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with pulmonary arterial hypertension compared to healthy volunteers.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential, fertility and embryonal/foetal development.
In pups of rats which were pre- and postnatally treated with 60 mg/kg sildenafil, a decreased litter size, a lower pup weight on day 1 and a decreased 4-day survival were seen at exposures which were approximately fifty times the expected human exposure at 20 mg three times a day. These effects were observed at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
microcrystalline cellulose
calcium hydrogen phosphate (anhydrous)
croscarmellose sodium
magnesium stearate

Film coat:
hypromellose
titanium dioxide (E171)
lactose monohydrate
glycerol triacetate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/Aluminium blisters of 90 tablets (15 tablets per blister strip) in a carton.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited, Sandwich, Kent CT13 9NJ, United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/318/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 October 2005

10. DATE OF REVISION OF THE TEXT

28 October 2005

11. LEGAL CATEGORY

POM

Ref: RV1_0