Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sildenafil Clonmel 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg of sildenafil (as citrate).

Excipient with known effect
Each tablet also contains 58.31 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Round, biconvex, white film-coated tablets with approx. diameter of 7.1 mm and approx. thickness of 3.4 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Treatment of adult 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.

Paediatric population
Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease (see section 5.1).

4.2 Posology and method of administration

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 Sildenafil Clonmel treatment, alternative therapies should be considered.

Posology

Adults
The recommended dose is 20 mg three times a day (TID). Physicians should advise patients who forget to take Sildenafil Clonmel to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

Paediatric population (1 year to 17 years)
For paediatric patients aged 1 year to 17 years old, the recommended dose in patients ≤ 20 kg is 10 mg three times a day and for patients > 20 kg is 20 mg three times a day. Higher than recommended doses should not be used in paediatric patients with PAH (see also sections 4.4 and 5.1). The 20 mg tablet should not be used in cases where 10 mg TID should be administered in younger patients. Other pharmaceutical forms are available for administration to patients ≤ 20 kg and other younger patients who are not able to swallow tablets.

Patients using other medicinal products
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 CYP3A4

inhibitors like erythromycin or saquinavir. A downward dose adjustment to 20 mg once daily is recommended in case of co-administration with more potent CYP3A4 inhibitors clarithromycin, telithromycin and nefazodone. For the use of sildenafil with the most potent CYP3A4 inhibitors, see section 4.3. Dose adjustments for sildenafil may be required when co-administered with CYP3A4 inducers (see section 4.5).

Special populations

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

Renal impairment
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.

Hepatic impairment
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.

Sildenafil Clonmel is contraindicated in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.3).

Paediatric population (children less than 1 year and neonates)
Outside its authorised indications, sildenafil should not be used in neonates with persistent pulmonary hypertension of the newborn as risks outweigh the benefits (see section 5.1). The safety and efficacy of sildenafil in other conditions in children below 1 year of age has not been established. No data are available.

Discontinuation of treatment
Limited data suggest that the abrupt discontinuation of sildenafil 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.

Method of administration

Sildenafil Clonmel is for oral use only. Tablets should be taken approximately 6 to 8 hours apart with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form due to the hypotensive effects of nitrates (see section 5.1).

The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

Combination with the most potent of the CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) (see section 4.5).

Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

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 precautions for use

The efficacy of sildenafil 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 assessed to be at WHO functional class I pulmonary arterial hypertension.

Studies with sildenafil have been performed in forms of pulmonary arterial hypertension related to primary (idiopathic), connective tissue disease associated or congenital heart disease associated forms of PAH (see section 5.1). The use of sildenafil in other forms of PAH is not recommended.

In the long term paediatric extension study, an increase in deaths was observed in patients administered doses higher than the recommended dose. Therefore, doses higher than the recommended doses should not be used in paediatric patients with PAH (see also sections 4.2 and 5.1).

Retinitis pigmentosa
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.

Vasodilatory action
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).

Cardiovascular risk factors
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.

Priapism
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).

Prolonged erections and priapism have been reported with sildenafil in post-marketing experience. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result (see section 4.8).

Vaso-occlusive crises in patients with sickle cell anaemia
Sildenafil should not be used in patients with pulmonary hypertension secondary to sickle cell anaemia. In a clinical study events of vaso-occlusive crises requiring hospitalisation were reported more commonly by patients receiving sildenafil than those receiving placebo leading to the premature termination of this study.

Visual events
Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors. Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors (see section 4.8). In the event of any sudden visual defect, the treatment should be stopped immediately and alternative treatment should be considered (see section 4.3).

Alpha-blockers
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 minimise the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Physicians should advise patients what to do in the event of postural hypotensive symptoms.

Bleeding disorders

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.

Vitamin K antagonists
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.

Veno-occlusive 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.

Use of sildenafil with bosentan
The efficacy of sildenafil in patients already on bosentan therapy has not been conclusively demonstrated (see sections 4.5 and 5.1).

Concomitant use with other PDE5 inhibitors
The safety and efficacy of sildenafil when co-administered with other PDE5 inhibitor products, including sildenafil indicated for erectile dysfunction, has not been studied in PAH patients and such concomitant use is not recommended (see section 4.5).

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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. For dose recommendations, see sections 4.2 and 4.3.
In vivo studies
Co-administration of oral sildenafil and intravenous epoprostenol has been evaluated (see sections 4.8 and 5.1).

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

The safety and efficacy of sildenafil when co-administered with other PDE5 inhibitors has not been studied in pulmonary arterial hypertension patients (see section 4.4).

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 with the most potent of the 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.

Co-administration of bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19) 125 mg twice daily with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63 % decrease of sildenafil AUC. A population pharmacokinetic analysis of sildenafil data from adult PAH patients in clinical trials including a 12 week study to assess the efficacy and safety of oral sildenafil 20 mg three times a day when added to a stable dose of bosentan (62.5 mg – 125 mg twice a day) indicated a decrease in sildenafil exposure with bosentan co-administration, similar to that observed in healthy volunteers (see sections 4.4 and 5.1).

Efficacy of sildenafil should be closely monitored in patients using concomitant potent CYP3A4 inducers, such as carbamazepine, phenytoin, phenobarbital, St John's wort and rifampicin.

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 (1 200 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. For dose recommendations, see section 4.2.
When a single 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg twice daily for 5 days), there was a 182 % increase in sildenafil systemic exposure (AUC). For dose recommendations, see section 4.2. In 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. No dose adjustment is required. Cimetidine (800 mg), a cytochrome P450 inhibitor and a non-specific CYP3A4 inhibitor, caused a 56 % increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers. No dose adjustment is required.

The most potent of the CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have effects similar to ritonavir (see section 4.3). CYP3A4 inhibitors like clarithromycin, telithromycin and nefazodone are expected to have an effect in between that of ritonavir and CYP3A4 inhibitors like saquinavir or erythromycin, a seven-fold increase in exposure is assumed. Therefore dose adjustments are recommended when using CYP3A4 inhibitors (see section 4.2).

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. No dose adjustment is required but the concomitant use of sildenafil and grapefruit juice is not recommended.

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 (see section 4.3).

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 50 % increase in bosentan AUC (125 mg twice daily). A population pharmacokinetic analysis of data from a study of adult PAH patients on background bosentan therapy (62.5 mg - 125 mg twice a day) indicated an increase (20 % (95 % CI: 9.8 - 30.8)) of bosentan AUC with co-administration of steady-state sildenafil (20 mg three times a day) of a smaller magnitude than seen in healthy volunteers when co-administered with 80 mg sildenafil three times a day (see sections 4.4 and 5.1).

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) stabilised 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 stabilised 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).

Riociguat: Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is 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).

Addition of a single dose of sildenafil to sacubitril/valsartan at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of sacubitril/valsartan alone. Therefore, caution should be exercised when sildenafil is initiated in patients treated with sacubitril/valsartan.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and contraception in males and females
Due to lack of data on effects of sildenafil in pregnant women, sildenafil is not recommended for women of childbearing potential unless also using appropriate contraceptive measures.

Pregnancy

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, sildenafil should not be used in pregnant women unless strictly necessary.

Breast-feeding

There are no adequate and well controlled studies in lactating women. Data from one lactating woman indicate that sildenafil and its active metabolite N-desmethylsildenafil are excreted into breast milk at very low levels. No clinical data are available regarding adverse events in breast-fed infants, but amounts ingested would not be expected to cause any adverse effects. Prescribers should carefully assess the mother's clinical need for sildenafil and any potential adverse effects on the breast-fed child.

Fertility

Non-clinical data revealed no special hazard for humans based on conventional studies of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Sildenafil has moderate influence on the 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 sildenafil, before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In the pivotal placebo-controlled study of sildenafil in pulmonary arterial hypertension, a total of 207 patients were randomised to and treated with 20 mg, 40 mg, or 80 mg TID doses of sildenafil and 70 patients were randomised to placebo. The duration of treatment was 12 weeks. The overall frequency of discontinuation in sildenafil treated patients at doses of 20 mg, 40 mg and 80 mg TID was 2.9 %, 3.0 % and 8.5 % respectively, compared to 2.9 % with placebo. Of the 277 subjects treated in the pivotal study, 259 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 administered and after 3 years 87 % of 183 patients on study treatment were receiving sildenafil 80 mg TID.

In a placebo-controlled study of sildenafil as an adjunct to intravenous epoprostenol in pulmonary arterial hypertension, a total of 134 patients were treated with sildenafil (in a fixed titration starting from 20 mg, to 40 mg and then 80 mg, three times a day, as tolerated) and epoprostenol, and 131 patients were treated with placebo and epoprostenol. The duration of treatment was 16 weeks. The overall frequency of discontinuations in sildenafil/epoprostenol treated patients due to adverse events was 5.2 % compared to 10.7 % in the placebo/epoprostenol treated patients. Newly reported adverse reactions, which occurred more frequently in the sildenafil/ epoprostenol group, were ocular hyperaemia, vision blurred, nasal congestion, night sweats, back pain and dry mouth. The known adverse reactions headache, flushing, pain in extremity and oedema were noted in a higher frequency in sildenafil/epoprostenol treated patients compared to placebo/epoprostenol treated patients. Of the subjects who completed the initial study, 242 entered a long-term extension study. Doses up to 80 mg TID were administered and after 3 years 68 % of 133 patients on study treatment were receiving sildenafil 80 mg TID.

In the two-placebo-controlled studies adverse events were generally mild to moderate in severity. The most commonly reported adverse reactions that occurred (greater or equal to 10 %) on sildenafil compared to placebo were headache, flushing, dyspepsia, diarrhoea and pain in extremity.

Tabulated list of adverse reactions

Adverse reactions which occurred in > 1 % of sildenafil-treated patients and were more frequent (> 1 % difference) on sildenafil in the pivotal study or in the sildenafil combined data set of both the placebo-controlled studies in pulmonary arterial hypertension, at doses of 20, 40 or 80 mg TID are listed in the table below by class and frequency grouping (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Reports from post-marketing experience are included in italics.

MedDRA system organ class (V.14.0)	Adverse reaction

Infections and infestations	
Common	cellulitis, influenza, bronchitis, sinusitis, rhinitis, gastroenteritis
Blood and lymphatic system disorders	
Common	anaemia
Metabolism and nutrition disorders	
Common	fluid retention
Psychiatric disorders	
Common	insomnia, anxiety
Nervous system disorders	
Very common	headache
Common	migraine, tremor, paraesthesia, burning sensation, hypoaesthesia
Eye disorders	
Common	retinal haemorrhage, visual impairment, vision blurred, photophobia, chromatopsia, cyanopsia, eye irritation, ocular hyperaemia
Uncommon	visual acuity reduced, diplopia, abnormal sensation in eye
Not known	*Non-arteritic anterior ischaemic optic neuropathy (NAION) *, Retinal vascular occlusion *, Visual field defect **
Ear and labyrinth disorders	
Common	vertigo
Not known	*sudden hearing loss*
Vascular disorders	
Very common	flushing
Not Known	*hypotension*
Respiratory, thoracic and mediastinal disorders	
Common	epistaxis, cough, nasal congestion
Gastrointestinal disorders	
Very common	diarrhoea, dyspepsia
Common	gastritis, gastrooesophageal reflux disease, haemorrhoids, abdominal distension, dry mouth
Skin and subcutaneous tissue disorders	
Common	alopecia, erythema, night sweats
Not known	*rash*
Musculoskeletal and connective tissue disorders	
Very common	pain in extremity
Common	myalgia, back pain
Renal and urinary disorders	
Uncommon	haematuria
Reproductive system and breast disorders	
Uncommon	penile haemorrhage, haematospermia, gynaecomastia
Not known	*priapism, erection increased*
General disorders and administration site conditions	
Common	pyrexia

* These adverse events/reactions have been reported in patients taking sildenafil for the treatment of male erectile dysfunction (MED).

Paediatric population

In the placebo-controlled study of sildenafil in patients 1 to 17 years of age with pulmonary arterial hypertension, a total of 174 patients were treated three times a day with either low (10 mg in patients > 20 kg; no patients ≤ 20 kg received the low dose), medium (10 mg in patients ≥ 8-20 kg; 20 mg in patients ≥ 20-45 kg; 40 mg in patients > 45 kg) or high dose (20 mg in patients ≥ 8-20 kg; 40 mg in patients ≥ 20-45 kg; 80 mg in patients > 45 kg) regimens of sildenafil and 60 were treated with placebo.

The adverse reactions profile seen in this paediatric study was generally consistent with that in adults (see table above). The most common adverse reactions that occurred (with a frequency ≥ 1 %) in sildenafil patients (combined doses) and with a frequency > 1 % over placebo patients were pyrexia, upper respiratory tract infection (each 11.5 %), vomiting (10.9 %), erection increased (including spontaneous penile erections in male subjects) (9.0 %), nausea, bronchitis (each 4.6 %), pharyngitis (4.0 %), rhinorrhoea (3.4 %), and pneumonia, rhinitis (each 2.9 %).

Of the 234 paediatric subjects treated in the short-term, placebo-controlled study, 220 subjects entered the long-term extension study. Subjects on active sildenafil therapy continued on the same treatment regimen, while those in the placebo group in the short-term study were randomly reassigned to sildenafil treatment.

The most common adverse reactions reported across the duration of the short-term and long-term studies were generally similar to those observed in the short-term study. Adverse reactions reported in > 10 % of 229 subjects treated with sildenafil (combined dose group, including 9 patients that did not continue into the long-term study) were upper respiratory infection (31 %), headache (26 %), vomiting (22 %), bronchitis (20 %), pharyngitis (18 %), pyrexia (17 %), diarrhoea (15 %), and influenza, epistaxis (12 % each). Most of these adverse reactions were considered mild to moderate in severity.

Serious adverse events were reported in 94 (41 %) of the 229 subjects receiving sildenafil. Of the 94 subjects reporting a serious adverse event, 14/55 (25.5 %) subjects were in the low dose group, 35/74 (47.3 %) in the medium dose group, and 45/100 (45 %) in the high dose group. The most common serious adverse events that occurred with a frequency ≥ 1 % in sildenafil patients (combined doses) were pneumonia (7.4 %), cardiac failure, pulmonary hypertension (each 5.2 %), upper respiratory tract infection (3.1 %), right ventricular failure, gastroenteritis (each 2.6 %), syncope, bronchitis, bronchopneumonia, pulmonary arterial hypertension (each 2.2 %), chest pain, dental caries (each 1.7 %), and cardiogenic shock, gastroenteritis viral, urinary tract infection (each 1.3%).

The following serious adverse events were considered to be treatment related, enterocolitis, convulsion, hypersensitivity, stridor, hypoxia, neurosensory deafness and ventricular arrhythmia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms
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, and altered vision) was increased.
Management
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: Urologicals, Drugs used in erectile dysfunction, ATC code: G04BE03

Mechanism of action
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.

Pharmacodynamic effects
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 mmHg 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 haemodynamic 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).

Clinical efficacy and safety

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, 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 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 (6MWD). A statistically significant increase in 6MWD was observed in all 3 sildenafil dose groups compared to those on placebo. Placebo corrected increases in 6MWD 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 TID respectively. There was no significant difference in effect between sildenafil doses. For patients with a baseline 6MWD < 325 m improved efficacy was observed with higher doses (placebo-corrected improvements of 58 metres, 65 metres and 87 metres for 20 mg, 40 mg and 80 mg doses TID, respectively).

When analysed by WHO functional class, a statistically significant increase in 6MWD was observed in the 20 mg dose group. For class II and class III, placebo corrected increases of 49 metres (p = 0.0007) and 45 metres (p = 0.0031) were observed respectively.

The improvement in 6MWD 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 aetiology (primary and connective tissue disease-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) and pulmonary vascular resistance (PVR) compared to those on placebo. Placebo-corrected treatment effects with mPAP were –2.7 mmHg (p = 0.04), -3.0 mmHg (p = 0.01) and -5.1 mmHg (p < 0.0001) for sildenafil 20 mg , 40 mg and 80 mg TID respectively. Placebo-corrected treatment effects with PVR were -178 dyne.sec/cm^5 (p = 0.0051), -195 dyne.sec/cm^5 (p = 0.0017) and -320 dyne.sec/cm^5 (p < 0.0001) for sildenafil 20 mg, 40 mg and 80 mg TID, respectively. The percent reduction at 12 weeks for sildenafil 20 mg, 40 mg and 80 mg TID in PVR (11.2 %, 12.9 %, 23.3 %) was proportionally greater than the reduction in systemic vascular resistance (SVR) (7.2 %, 5.9 %, 14.4 %). The effect of sildenafil on mortality is unknown.

A greater percentage of patients on each of the sildenafil doses (i.e. 28 %, 36 % and 42 % of subjects who received sildenafil 20 mg, 40 mg and 80 mg TID doses, respectively) showed an improvement by at least one WHO functional class at week 12 compared to placebo (7 %). The respective odds ratios were 2.92 (p = 0.0087), 4.32 (p = 0.0004) and 5.75 (p < 0.0001).

Long-term survival data in naive population
Patients enrolled into the pivotal study were eligible to enter a long term open label extension study. At 3 years 87 % of the patients were receiving a dose of 80 mg TID. A total of 207 patients were treated with sildenafil in the pivotal study, and their long term survival status was assessed for a minimum of 3 years. In this population, Kaplan-Meier estimates of 1, 2 and 3 year survival were 96 %, 91 % and 82 %, respectively. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 99 %, 91 %, and 84 % respectively, and for patients of WHO functional class III at baseline was 94 %, 90 %, and 81 %, respectively.

Efficacy in adult patients with PAH (when used in combination with epoprostenol)
A randomised, double-blind, placebo controlled study was conducted in 267 patients with PAH who were stabilised on intravenous epoprostenol. The PAH patients included those with Primary Pulmonary Arterial Hypertension (212/267, 79 %) and PAH associated with connective tissue disease (55/267, 21 %). Most patients were WHO Functional Class II (68/267, 26 %) or III (175/267, 66 %); fewer patients were Class I (3/267, 1 %) or IV (16/267, 6 %) at baseline; for a few patients (5/267, 2 %), the WHO Functional Class was unknown. Patients were randomised to placebo or sildenafil (in a fixed titration starting from 20 mg, to 40 mg and then 80 mg, three times a day as tolerated) when used in combination with intravenous epoprostenol.

The primary efficacy endpoint was the change from baseline at week 16 in 6-minute walk distance. There was a statistically significant benefit of sildenafil compared to placebo in 6-minute walk distance. A mean placebo corrected increase in walk distance of 26 metres was observed in favour of sildenafil (95 % CI: 10.8, 41.2) (p = 0.0009). For patients with a baseline walking distance ≥ 325 metres, the treatment effect was 38.4 metres in favour of sildenafil; for patients with a baseline walking distance < 325 metres, the treatment effect was 2.3 metres in favour of placebo. For patients with primary PAH, the treatment effect was 31.1 metres compared to 7.7 metres for patients with PAH associated with connective tissue disease. The difference in results between these randomisation subgroups may have arisen by chance in view of their limited sample size.

Patients on sildenafil achieved a statistically significant reduction in mean Pulmonary Arterial Pressure (mPAP) compared to those on placebo. A mean placebo-corrected treatment effect of -3.9 mmHg was observed in favour of sildenafil (95 % CI: -5.7, -2.1) (p = 0.00003). Time to clinical worsening was a secondary endpoint as defined as the time from randomisation to the first occurrence of a clinical worsening event (death, lung transplantation, initiation of bosentan therapy, or clinical deterioration requiring a change in epoprostenol therapy). Treatment with sildenafil significantly delayed the time to clinical worsening of PAH compared to placebo (p = 0.0074). 23 subjects experienced clinical worsening events in the placebo group (17.6 %) compared with 8 subjects in the sildenafil group (6.0 %).

Long-term Survival Data in the background epoprostenol study
Patients enrolled into the epoprostenol add-on therapy study were eligible to enter a long term open label extension study. At 3 years 68 % of the patients were receiving a dose of 80 mg TID. A total of 134 patients were treated with sildenafil in the initial study, and their long term survival status was assessed for a minimum of 3 years. In this population, Kaplan-Meier estimates of 1, 2 and 3 year survival were 92 %, 81 % and 74 %, respectively.

Efficacy and safety in adult patients with PAH (when used in combination with bosentan)
A randomised, double-blind, placebo controlled study was conducted in 103 clinically stable subjects with PAH (WHO FC II and III) who were on bosentan therapy for a minimum of three months. The PAH patients included those with primary PAH, and PAH associated with connective tissue disease. Patients were randomised to placebo or sildenafil (20 mg three times a day) in combination with bosentan (62.5-125 mg twice a day). The primary efficacy endpoint was the change from baseline at Week 12 in 6MWD. The results indicate that there is no significant difference in mean change from baseline on 6MWD observed between sildenafil (20 mg three times a day) and placebo (13.62 m (95 % CI: -3.89 to 31.12) and 14.08 m (95 % CI: -1.78 to 29.95), respectively).

Differences in 6MWD were observed between patients with primary PAH and PAH associated with connective tissue disease. For subjects with primary PAH (67 subjects), mean changes from baseline were 26.39 m (95 % CI: 10.70 to 42.08) and 11.84 m (95 % CI: -8.83 to 32.52) for the sildenafil and placebo groups, respectively. However, for subjects with PAH associated with connective tissue disease (36 subjects) mean changes from baseline were -18.32 m (95 % CI: -65.66 to 29.02) and 17.50 m (95 % CI: -9.41 to 44.41) for the sildenafil and placebo groups, respectively.

Overall, the adverse events were generally similar between the two treatment groups (sildenafil plus bosentan vs. bosentan alone), and consistent with the known safety profile of sildenafil when used as monotherapy (see sections 4.4 and 4.5).

Paediatric population

Pulmonary arterial hypertension

A total of 234 subjects aged 1 to 17 years were treated in a randomised, double-blind, multi-centre, placebo controlled parallel group, dose ranging study. Subjects (38 % male and 62 % female) had a body weight ≥ 8 kg, and had primary pulmonary hypertension (PPH) [33 %], or PAH secondary to congenital heart disease [systemic-to-pulmonary shunt 37 %, surgical repair 30 %]. In this trial, 63 of 234 (27 %) patients were < 7 years old (sildenafil low dose = 2; medium dose = 17; high dose = 28; placebo = 16) and 171 of 234 (73 %) patients were 7 years or older (sildenafil low dose = 40; medium dose = 38; and high dose = 49; placebo = 44). Most subjects were WHO Functional Class I (75/234, 32 %) or II (120/234, 51 %) at baseline; fewer patients were Class III (35/234, 15 %) or IV (1/234, 0.4%); for a few patients (3/234, 1.3 %), the WHO Functional Class was unknown.

Patients were naïve for specific PAH therapy and the use of prostacyclin, prostacyclin analogues and endothelin receptor antagonists was not permitted in the study, and neither was arginine supplementation, nitrates, alpha-blockers and potent CYP450 3A4 inhibitors.

The primary objective of the study was to assess the efficacy of 16 weeks of chronic treatment with oral sildenafil in paediatric subjects to improve exercise capacity as measured by the Cardiopulmonary Exercise Test (CPET) in subjects who were developmentally able to perform the test, n = 115). Secondary endpoints included haemodynamic monitoring, symptom assessment, WHO functional class, change in background treatment, and quality of life measurements.

Subjects were allocated to one of three sildenafil treatment groups, low (10 mg), medium (10-40 mg) or high dose (20-80 mg) regimens of sildenafil given three times a day, or placebo. Actual doses administered within a group were dependent on body weight (see Section 4.8). The proportion of subjects receiving supportive medicinal products at baseline (anticoagulants, digoxin, calcium channel blockers, diuretics and/or oxygen) was similar in the combined sildenafil treatment group (47.7%) and the placebo treatment group (41.7 %).

The primary endpoint was the placebo-corrected percentage change in peak VO_2 from baseline to week 16 assessed by CPET testing in the combined dose groups (Table 2). A total of 106 out of 234 (45 %) subjects were evaluable for CPET, which comprised those children ≥ 7 years old and developmentally able to perform the test. Children < 7 years (sildenafil combined dose = 47; placebo = 16) were evaluable only for the secondary endpoints. Mean baseline peak volume of oxygen consumed (VO_2) values were comparable across the sildenafil treatment groups (17.37 to 18.03 ml/kg/min), and slightly higher for the placebo treatment group (20.02 ml/kg/min). The results of the main analysis (combined dose groups versus placebo) were not statistically significant (p = 0.056) (see Table 2). The estimated difference between the medium sildenafil dose and placebo was 11.33 % (95 % CI: 1.72 to 20.94) (see Table 2).

Table 2: Placebo Corrected % Change from Baseline in Peak VO_2 by Active Treatment Group

Treatment group	Estimated difference	95 % confidence interval
Low dose (n = 24)	3.81	-6.11, 13.73
Medium dose (n = 26)	11.33	1.72, 20.94
High dose (n = 27)	7.98	-1.64, 17.60
Combined dose groups (n = 77)	7.71 (p = 0.056)	-0.19, 15.60

n = 29 for placebo group

Estimates based on ANCOVA with adjustments for the covariates baseline peak VO$_2$, aetiology and weight group

Dose related improvements were observed with pulmonary vascular resistance index (PVRI) and mean pulmonary arterial pressure (mPAP). The sildenafil medium and high dose groups both showed PVRI reductions compared to placebo, of 18 % (95% CI: 2 % to 32 %) and 27 % (95 % CI: 14 % to 39 %), respectively; whilst the low dose group showed no significant difference from placebo (difference of 2 %). The sildenafil medium and high dose groups displayed mPAP changes from baseline compared to placebo, of -3.5 mmHg (95 %CI: -8.9, 1.9) and -7.3 mmHg (95 %CI: -12.4, -2.1), respectively; whilst the low dose group showed little difference from placebo (difference of 1.6 mmHg). Improvements were observed with cardiac index with all three sildenafil groups over placebo, 10 %, 4 % and 15 % for the low, medium and high dose groups respectively.

Significant improvements in functional class were demonstrated only in subjects on sildenafil high dose compared to placebo. Odds ratios for the sildenafil low, medium and high dose groups compared to placebo were 0.6 (95 % CI: 0.18, 2.01), 2.25 (95 % CI: 0.75, 6.69) and 4.52 (95 % CI: 1.56, 13.10), respectively.

Long term extension data

Of the 234 paediatric subjects treated in the short-term, placebo-controlled study, 220 subjects entered the long-term extension study. Subjects who had been in the placebo group in the short-term study were randomly reassigned to sildenafil treatment; subjects weighing ≤ 20 kg entered the medium or high dose groups (1:1), while subjects weighing > 20 kg entered the low, medium or high dose groups (1:1:1). Of the total 229 subjects who received sildenafil, there were 55, 74, and 100 subjects in the low, medium and high dose groups, respectively. Across the short-term and long-term studies, the overall duration of treatment from start of double-blind for individual subjects ranged from 3 to 3 129 days. By sildenafil treatment group, median duration of sildenafil treatment was 1 696 days (excluding the 5 subjects who received placebo in double-blind and were not treated in the long-term extension study).

Kaplan-Meier estimates of survival at 3 years in patients > 20 kg in weight at baseline were 94 %, 93 % and 85 % in the low, medium and high dose groups, respectively; for patients ≤ 20 kg in weight at baseline, the survival estimates were 94 % and 93 % for subjects in the medium and high dose groups respectively (see sections 4.4 and 4.8).

During the conduct of the study, there were a total of 42 deaths reported, whether on treatment or reported as part of the survival follow-up. 37 deaths occurred prior to a decision taken by the Data Monitoring Committee to down titrate subjects to a lower dosage, based on an observed mortality imbalance with increasing sildenafil doses. Among these 37 deaths, the number (%) of deaths was 5/55 (9.1 %), 10/74 (13.5 %), and 22/100 (22 %) in the sildenafil low, medium, and high dose groups, respectively. An additional 5 deaths were reported subsequently. The causes of deaths were related to PAH. Higher than recommended doses should not be used in paediatric patients with PAH (see sections 4.2 and 4.4).

Peak VO$_2$ was assessed 1 year after the start of the placebo-controlled study. Of those sildenafil treated subjects developmentally able to perform the CPET 59/114 subjects (52 %) had not shown any deterioration in Peak VO$_2$ from start of sildenafil. Similarly 191 of 229 subjects (83 %) who had received sildenafil had either maintained or improved their WHO Functional Class at 1 year assessment.

Persistent pulmonary hypertension of the newborn

A randomised, double-blind, two-arm, parallel-group, placebo-controlled study was conducted in 59 neonates with persistent pulmonary hypertension of the newborn (PPHN), or hypoxic respiratory failure (HRF) and at risk for PPHN with oxygenation index (OI) > 15 and < 60. The primary objective was to evaluate the efficacy and safety of IV sildenafil when added to inhaled nitric oxide (iNO) compared with iNO alone.

The co-primary endpoints were treatment failure rate, defined as need for additional treatment targeting PPHN, need for extracorporeal membrane oxygenation (ECMO), or death during the study; and time on iNO treatment after initiation of IV study drug for patients without treatment failure. The difference in treatment failure rates was not statistically significant between the two treatment groups (27.6 % and 20.0 % in the iNO + IV sildenafil group and iNO + placebo group, respectively). For patients without treatment failure, the mean time on iNO treatment after initiation of IV study drug was the same, approximately 4.1 days, for the two treatment groups.

Treatment-emergent adverse events and serious adverse events were reported in 22 (75.9 %) and 7 (24.1 %) subjects in the iNO + IV sildenafil treatment group, respectively, and in 19 (63.3 %) and 2 (6.7 %) subjects in the iNO + placebo group, respectively. The most commonly reported treatment-emergent adverse events were hypotension (8 [27.6 %] subjects),

hypokalaemia (7 [24.1 %] subjects), anaemia and drug withdrawal syndrome (4 [13.8 %] subjects each) and bradycardia (3 [10.3%] subjects) in the iNO + IV sildenafil treatment group and pneumothorax (4 [13.3 %] subjects), anaemia, oedema, hyperbilirubinaemia, C-reactive protein increased, and hypotension (3 [10.0 %] subjects each) in the iNO + placebo treatment group (see section 4.2).

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 (Vss) 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.

Biotransformation
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 impairment
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 by 200 % and 79 % respectively in subjects with severe renal impairment compared to subjects with normal renal function.

Hepatic impairment
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.

Paediatric population
From the analysis of the pharmacokinetic profile of sildenafil in patients involved in the paediatric clinical trials, body weight was shown to be a good predictor of drug exposure in children. Sildenafil plasma concentration half-life values were estimated to range from 4.2 to 4.4 hours for a range of 10 to 70 kg of body weight and did not show any differences that would appear as clinically relevant. C^{max} after a single 20 mg sildenafil dose administered PO was estimated at 49, 104 and 165 ng/ml for 70, 20 and 10 kg patients, respectively. C^{max} after a single 10 mg sildenafil dose administered PO was estimated at 24, 53 and 85 ng/ml for 70, 20 and 10 kg patients, respectively. $T_{max}$was estimated at approximately 1 hour and was almost independent from body weight.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential, toxicity to reproduction and 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. Effects in non-clinical studies were observed at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

There were no adverse reactions, with possible relevance to clinical use, seen in animals at clinically relevant exposure levels which were not also observed in clinical studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose (E460)
Hydroxypropylcellulose (E463)
Croscarmellose sodium (E468)
Silica, colloidal anhydrous (E551)
sodium stearyl fumarate (E485)

Film coat:
Opadry II White (consisting of hypromellose 2910 (E464)
Titanium dioxide (E171)
Polydextrose FCC (E1200)
Talc (E553b)
Maltodextrin
Triglycerides, medium chain

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVdC // Al blisters packs

Packs size of 90 or 300 (3x100) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/199/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd December 2016
Date of last renewal: 19th September 2021

10 DATE OF REVISION OF THE TEXT

August 2022