ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of sildenafil (as citrate)

Excipient: Lactose

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue rounded diamond-shaped tablets, marked “PFIZER” on one side and “VGR 25” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for VIAGRA to be effective, sexual stimulation is required.

4.2 Posology and method of administration

For oral use.

Use in adults:
The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If VIAGRA is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2).

Use in the elderly:
Dosage adjustments are not required in elderly patients.

Use in patients with impaired renal function:
The dosing recommendations described in ‘Use in adults’ apply to patients with mild to moderate renal impairment (creatinine clearance = 30 - 80 ml/min).

Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 ml/min) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in patients with impaired hepatic function:
Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in children and adolescents:
VIAGRA is not indicated for individuals below 18 years of age.

Use in patients using other:
With the exception of ritonavir for which co-administration with sildenafil is not advised (see section 4.4) a starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors (see section 4.5).

In order to minimise the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered (see sections 4.4 and 4.5).

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.

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).

VIAGRA is contraindicated in 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, hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as *retinitis pigmentosa* (a minority of these patients have genetic disorders of retinal phosphodiesterases).

4.4 Special warnings and precautions for use

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

VIAGRA potentiates the hypotensive effect of nitrates (see section 4.3).

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of VIAGRA. 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 VIAGRA without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

Agents for the treatment of erectile dysfunction, including 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).

The safety and efficacy of combinations of sildenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

Visual defects and cases of non-arteritic anterior ischaemic optic neuropathy have been reported in connection with the intake of sildenafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking VIAGRA and consult a physician immediately (see section 4.3).

Co-administration of sildenafil with ritonavir is not advised (see section 4.5).

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the coadministration may lead to symptomatic hypotension in a few susceptible individuals (see section 4.5). This is most likely to occur within 4 hours post sildenafil dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered (see section 4.2). In addition, 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.

The film coating of the VIAGRA tablet contains lactose. VIAGRA should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

VIAGRA is not indicated for use by women.

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.

In vivo studies:
Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25 mg should be considered.

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. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised (see section 4.4) and in any event the maximum dose of sildenafil should under no circumstances exceed 25 mg within 48 hours.

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 (see section 4.2). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

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.

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.

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).

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). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

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

In vivo studies:
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).

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing (see sections 4.2 and 4.4). 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 blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, 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 light-headedness, but not syncope.

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 (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.

Pooling of the following classes of antihypertensive medication: diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. 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 (see section 5.1).

Sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

4.6 Pregnancy and lactation

VIAGRA is not indicated for use by women.

No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to VIAGRA, before driving or operating machinery.

4.8 Undesirable effects

The safety profile of VIAGRA is based on 8691 patients who received the recommended dosing regimen in 67 placebo-controlled clinical studies. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, visual disorders, nasal congestion, dizziness and visual colour distortion.

Adverse reactions from post-marketing surveillance has been gathered covering an estimated period >9 years. Because not all adverse reactions are reported to the Marketing Authorisation Holder and included in the safety database, the frequencies of these reactions cannot be reliably determined.

In the table below all medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and frequency (very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000). In addition, the frequency of medically important adverse reactions reported from post-marketing experience is included as not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Medically important adverse reactions reported at an incidence greater than placebo in controlled clinical studies and medically important adverse reactions reported through post-marketing surveillance

System Organ Class	Adverse Reactions
Immune system disorders	
Rare	Hypersensitivity reactions
Nervous system disorders	
Very common	Headache
Common	Dizziness
Uncommon	Somnolence, Hypoaesthesia
Rare	Cerebrovascular accident, Syncope
Not known	Transient ischaemic attack, Seizure, Seizure recurrence
Eye disorders	
Common	Visual disorders, Visual colour distortion
Uncommon	Conjunctival disorders, Eye Disorders, Lacrimation Disorders, Other Eye Disorders
Not known	Non-arteritic anterior ischaemic optic neuropathy (NAION), Retinal vascular occlusion, Visual field defect
Ear and labyrinth disorders	
Uncommon	Vertigo, Tinnitus
Rare	Deafness*
Vascular disorders	
Common	Flushing
Rare	Hypertension, Hypotension
Cardiac disorders	
Uncommon	Palpitations, Tachycardia
Rare	Myocardial infarction, Atrial fibrillation
Not known	Ventricular arrhythmia, Unstable angina, Sudden cardiac death
Respiratory, thoracic and mediastinal disorders	
Common	Nasal congestion
Rare	Epistaxis
Gastrointestinal disorders	
Common	Dyspepsia
Uncommon	Vomiting, Nausea, Dry mouth
Skin, subcutaneous and soft tissue disorders	
Uncommon	Skin rash
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Reproductive system and breast disorders	
Not known	Priapism, Prolonged erection
General disorders and administration site conditions	
Uncommon	Chest pain, Fatigue

System Organ Class	Adverse Reactions
Investigations	
Uncommon	Heart rate increased

* Ear disorders: Sudden deafness. Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil.

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. Doses of 200 mg did not result in increased efficacy but 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 an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

Studies *in vitro* have shown that sildenafil is selective for PDE5, which is involved in the erection process. 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. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE2, 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.

Two clinical studies were specifically designed to assess the time window after dosing during which sildenafil could produce an erection in response to sexual stimulation. In a penile plethysmography (RigiScan) study of fasted patients, the median time to onset for those who obtained erections of 60% rigidity (sufficient for sexual intercourse) was 25 minutes (range 12-37 minutes) on sildenafil. In a separate RigiScan study, sildenafil was still able to produce an erection in response to sexual stimulation 4-5 hours post-dose.

Sildenafil causes mild and transient decreases in blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 100 mg oral dosing of sildenafil was 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg. These decreases in blood pressure are consistent with the vasodilatory effects of sildenafil, probably due to increased cGMP levels in vascular smooth muscle. Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG.

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.

No clinical relevant differences were demonstrated in time to limiting angina for sildenafil when compared with placebo in a double blind, placebo controlled exercise stress trial in 144 patients with erectile dysfunction and chronic stable angina, who were taking on a regular basis anti-anginal medications (except nitrates).

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).

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers.

Further information on clinical trials
In clinical trials sildenafil was administered to more than 8000 patients aged 19-87. The following patient groups were represented: elderly (19.9%), patients with hypertension (30.9%), diabetes mellitus (20.3%), ischaemic heart disease (5.8%), hyperlipidaemia (19.8%), spinal cord injury (0.6%), depression (5.2%), transurethral resection of the prostate (3.7%), radical prostatectomy (3.3%). The following groups were not well represented or excluded from clinical trials: patients with pelvic surgery, patients post-radiotherapy, patients with severe renal or hepatic impairment and patients with certain cardiovascular conditions (see section 4.3).

In fixed dose studies, the proportions of patients reporting that treatment improved their erections were 62% (25 mg), 74% (50 mg) and 82% (100 mg) compared to 25% on placebo. In controlled clinical trials, the discontinuation rate due to sildenafil was low and similar to placebo.
Across all trials, the proportion of patients reporting improvement on sildenafil were as follows: psychogenic erectile dysfunction (84%), mixed erectile dysfunction (77%), organic erectile dysfunction (68%), elderly (67%), diabetes mellitus (59%), ischaemic heart disease (69%), hypertension (68%), TURP (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%). The safety and efficacy of sildenafil was maintained in long-term studies.

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 dosing of sildenafil AUC and C_{max} increase in proportion with dose over the recommended dose range (25-100 mg).

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%.

Distribution:
The mean steady state volume of distribution (V_d) for sildenafil is 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/ml (CV 40%). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/ml (38 nM). Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil (100 mg single dose), less than 0.0002% (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

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. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 h.

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. The mean AUC and C_{max} of the N-desmethyl metabolite increased 126% and 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. 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 79% and 200% respectively.

Hepatic insufficiency:
In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

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, carcinogenic potential, and toxicity to reproduction.

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
triacetin
indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30^{o}C.
Store in the original package, in order to protect from moisture.

6.5 Nature and content of container

PVC/Aluminium foil blisters in cartons of 2, 4, 8 or 12 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/98/077/002-004
EU/1/98/077/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 September 1998
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of sildenafil (as citrate)

Excipient: Lactose

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue, rounded diamond-shaped tablets, marked “PFIZER” on one side and “VGR 50” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for VIAGRA to be effective, sexual stimulation is required.

4.2 Posology and method of administration

For oral use.

Use in adults:
The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If VIAGRA is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2).

Use in the elderly:
Dosage adjustments are not required in elderly patients.

Use in patients with impaired renal function:
The dosing recommendations described in ‘Use in adults’ apply to patients with mild to moderate renal impairment (creatinine clearance = 30 - 80 ml/min).

Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 ml/min) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in patients with impaired hepatic function:
Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in children and adolescents:
VIAGRA is not indicated for individuals below 18 years of age.

Use in patients using other medicines:
With the exception of ritonavir for which co-administration with sildenafil is not advised (see section 4.4) a starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors (see section 4.5).

In order to minimise the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered (see sections 4.4 and 4.5).

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.

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).

VIAGRA is contraindicated in 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, hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as *retinitis pigmentosa* (a minority of these patients have genetic disorders of retinal phosphodiesterases).

4.4 Special warnings and precautions for use

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

VIAGRA potentiates the hypotensive effect of nitrates (see section 4.3).

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of VIAGRA. 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 VIAGRA without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

Agents for the treatment of erectile dysfunction, including 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).

The safety and efficacy of combinations of sildenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

Visual defects and cases of non-arteritic anterior ischaemic optic neuropathy have been reported in connection with the intake of sildenafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking VIAGRA and consult a physician immediately (see section 4.3).

Co-administration of sildenafil with ritonavir is not advised (see section 4.5).

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the coadministration may lead to symptomatic hypotension in a few susceptible individuals (see section 4.5). This is most likely to occur within 4 hours post sildenafil dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered (see section 4.2). In addition, 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.

The film coating of the VIAGRA tablet contains lactose. VIAGRA should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

VIAGRA is not indicated for use by women.

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.

In vivo studies:
Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25 mg should be considered.

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. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised (see section 4.4) and in any event the maximum dose of sildenafil should under no circumstances exceed 25 mg within 48 hours.

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 (see section 4.2). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

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.

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.

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).

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). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

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

In vivo studies:
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).

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing (see sections 4.2 and 4.4). 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 blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, 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 light-headedness, but not syncope.

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 (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.

Pooling of the following classes of antihypertensive medication: diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. 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 (see section 5.1).

Sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

4.6 Pregnancy and lactation

VIAGRA is not indicated for use by women.

No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to VIAGRA, before driving or operating machinery.

4.8 Undesirable effects

The safety profile of VIAGRA is based on 8691 patients who received the recommended dosing regimen in 67 placebo-controlled clinical studies. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, visual disorders, nasal congestion, dizziness and visual colour distortion.
Adverse reactions from post-marketing surveillance has been gathered covering an estimated period >9 years. Because not all adverse reactions are reported to the Marketing Authorisation Holder and included in the safety database, the frequencies of these reactions cannot be reliably determined.

In the table below all medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and frequency (very common (≥1/10),

common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000). In addition, the frequency of medically important adverse reactions reported from post-marketing experience is included as not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Medically important adverse reactions reported at an incidence greater than placebo in controlled clinical studies and medically important adverse reactions reported through post-marketing surveillance

System Organ Class	Adverse Reactions
Immune system disorders	
Rare	Hypersensitivity reactions
Nervous system disorders	
Very common	Headache
Common	Dizziness
Uncommon	Somnolence, Hypoaesthesia
Rare	Cerebrovascular accident, Syncope
Not known	Transient ischaemic attack, Seizure, Seizure recurrence
Eye disorders	
Common	Visual disorders, Visual colour distortion
Uncommon	Conjunctival disorders, Eye Disorders, Lacrimation Disorders, Other Eye Disorders
Not known	Non-arteritic anterior ischaemic optic neuropathy (NAION), Retinal vascular occlusion, Visual field defect
Ear and labyrinth disorders	
Uncommon	Vertigo, Tinnitus
Rare	Deafness*
Vascular disorders	
Common	Flushing
Rare	Hypertension, Hypotension
Cardiac disorders	
Uncommon	Palpitations, Tachycardia
Rare	Myocardial infarction, Atrial fibrillation
Not known	Ventricular arrhythmia, Unstable angina, Sudden cardiac death
Respiratory, thoracic and mediastinal disorders	
Common	Nasal congestion
Rare	Epistaxis
Gastrointestinal disorders	
Common	Dyspepsia
Uncommon	Vomiting, Nausea, Dry mouth
Skin, subcutaneous and soft tissue disorders	
Uncommon	Skin rash
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Reproductive system and breast disorders	
Not known	Priapism, Prolonged erection
General disorders and administration site conditions	
Uncommon	Chest pain, Fatigue
Investigations	
Uncommon	Heart rate increased

* Ear disorders: Sudden deafness. Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil.

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. Doses of 200 mg did not result in increased efficacy but 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 an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

Studies *in vitro* have shown that sildenafil is selective for PDE5, which is involved in the erection process. 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. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE2, 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.

Two clinical studies were specifically designed to assess the time window after dosing during which sildenafil could produce an erection in response to sexual stimulation. In a penile plethysmography (RigiScan) study of fasted patients, the median time to onset for those who obtained erections of 60% rigidity (sufficient for sexual intercourse) was 25 minutes (range 12-37 minutes) on sildenafil. In a separate RigiScan study, sildenafil was still able to produce an erection in response to sexual stimulation 4-5 hours post-dose.

Sildenafil causes mild and transient decreases in blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 100 mg oral dosing of sildenafil was 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg. These decreases in blood pressure are consistent with the vasodilatory effects of sildenafil, probably due to increased cGMP levels in vascular smooth muscle. Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG.

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.

No clinical relevant differences were demonstrated in time to limiting angina for sildenafil when compared with placebo in a double blind, placebo controlled exercise stress trial in 144 patients with erectile dysfunction and chronic stable angina, who were taking on a regular basis anti-anginal medications (except nitrates).

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).

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers.

Further information on clinical trials
In clinical trials sildenafil was administered to more than 8000 patients aged 19-87. The following patient groups were represented: elderly (19.9%), patients with hypertension (30.9%), diabetes mellitus (20.3%), ischaemic heart disease (5.8%), hyperlipidaemia (19.8%), spinal cord injury (0.6%), depression (5.2%), transurethral resection of the prostate (3.7%), radical prostatectomy (3.3%). The following groups were not well represented or excluded from clinical trials: patients with pelvic surgery, patients post-radiotherapy, patients with severe renal or hepatic impairment and patients with certain cardiovascular conditions (see section 4.3).

In fixed dose studies, the proportions of patients reporting that treatment improved their erections were 62% (25 mg), 74% (50 mg) and 82% (100 mg) compared to 25% on placebo. In controlled clinical trials, the discontinuation rate due to sildenafil was low and similar to placebo.
Across all trials, the proportion of patients reporting improvement on sildenafil were as follows: psychogenic erectile dysfunction (84%), mixed erectile dysfunction (77%), organic erectile dysfunction (68%), elderly (67%), diabetes mellitus (59%), ischaemic heart disease (69%), hypertension (68%), TURP (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%). The safety and efficacy of sildenafil was maintained in long-term studies.

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 dosing of sildenafil AUC and C_{max} increase in proportion with dose over the recommended dose range (25-100 mg).

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%.

Distribution:
The mean steady state volume of distribution (V_d) for sildenafil is 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/ml (CV 40%). Since sildenafil (and its major circulating N-

desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/ml (38 nM). Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil (100 mg single dose), less than 0.0002% (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

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. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 h.

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. The mean AUC and C_{max} of the N-desmethyl metabolite increased 126% and 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. 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 79% and 200% respectively.

Hepatic insufficiency:
In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

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, carcinogenic potential, and toxicity to reproduction.

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
triacetin
indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30^{o}C.
Store in the original package, in order to protect from moisture.

6.5 Nature and content of container

PVC/Aluminium foil blisters in cartons or secondary heat sealed card packaging of 2, 4, 8 or 12 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/98/077/006-008
EU/1/98/077/014
EU/1/98/077/016-019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 September 1998
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of sildenafil (as citrate)

Excipient: Lactose

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue, rounded diamond-shaped tablets, marked “PFIZER” on one side and “VGR 100” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for VIAGRA to be effective, sexual stimulation is required.

4.2 Posology and method of administration

For oral use.

Use in adults:
The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If VIAGRA is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2).

Use in the elderly:
Dosage adjustments are not required in elderly patients.

Use in patients with impaired renal function:
The dosing recommendations described in ‘Use in adults’ apply to patients with mild to moderate renal impairment (creatinine clearance = 30 - 80 ml/min).

Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 ml/min) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in patients with impaired hepatic function:
Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in children and adolescents:
VIAGRA is not indicated for individuals below 18 years of age.

Use in patients using other medicines:
With the exception of ritonavir for which co-administration with sildenafil is not advised (see section 4.4) a starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors (see section 4.5)

In order to minimise the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered (see sections 4.4 and 4.5).

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.

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).

VIAGRA is contraindicated in 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, hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as *retinitis pigmentosa* (a minority of these patients have genetic disorders of retinal phosphodiesterases).

4.4 Special warnings and precautions for use

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

VIAGRA potentiates the hypotensive effect of nitrates (see section 4.3).

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of VIAGRA. 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 VIAGRA without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

Agents for the treatment of erectile dysfunction, including 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).

The safety and efficacy of combinations of sildenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

Visual defects and cases of non-arteritic anterior ischaemic optic neuropathy have been reported in connection with the intake of sildenafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking VIAGRA and consult a physician immediately (see section 4.3).

Co-administration of sildenafil with ritonavir is not advised (see section 4.5).

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the coadministration may lead to symptomatic hypotension in a few susceptible individuals (see section 4.5). This is most likely to occur within 4 hours post sildenafil dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered (see section 4.2). In addition, 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.

The film coating of the VIAGRA tablet contains lactose. VIAGRA should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

VIAGRA is not indicated for use by women.

4.5 Interaction with other medicinal products and other forms of interaction

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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.

In vivo studies:
Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25 mg should be considered.

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mgtwice 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. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised (see section 4.4) and in any event the maximum dose of sildenafil should under no circumstances exceed 25 mg within 48 hours.

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 (see section 4.2). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

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.

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.

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).

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). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

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

In vivo studies:
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).

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing (see sections 4.2 and 4.4). 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 blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, 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 light-headedness, but not syncope.

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 (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.

Pooling of the following classes of antihypertensive medication: diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. 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 (see section(see section 5.1).

Sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

4.6 Pregnancy and lactation

VIAGRA is not indicated for use by women.

No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to VIAGRA, before driving or operating machinery.

4.8 Undesirable effects

The safety profile of VIAGRA is based on 8691 patients who received the recommended dosing regimen in 67 placebo-controlled clinical studies. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, visual disorders, nasal congestion, dizziness and visual colour distortion.

Adverse reactions from post-marketing surveillance has been gathered covering an estimated period >9 years. Because not all adverse reactions are reported to the Marketing Authorisation Holder and included in the safety database, the frequencies of these reactions cannot be reliably determined.

In the table below all medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and frequency (very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000). In addition, the frequency of medically important adverse reactions reported from post-marketing experience is included as not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Medically important adverse reactions reported at an incidence greater than placebo in controlled clinical studies and medically important adverse reactions reported through post-marketing surveillance

System Organ Class	Adverse Reactions
Immune system disorders	
Rare	Hypersensitivity reactions
Nervous system disorders	
Very common	Headache
Common	Dizziness
Uncommon	Somnolence, Hypoaesthesia
Rare	Cerebrovascular accident, Syncope
Not known	Transient ischaemic attack, Seizure, Seizure recurrence
Eye disorders	
Common	Visual disorders, Visual colour distortion
Uncommon	Conjunctival disorders, Eye Disorders, Lacrimation Disorders, Other Eye Disorders
Not known	Non-arteritic anterior ischaemic optic neuropathy (NAION), Retinal vascular occlusion, Visual field defect
Ear and labyrinth disorders	
Uncommon	Vertigo, Tinnitus
Rare	Deafness*
Vascular disorders	
Common	Flushing
Rare	Hypertension, Hypotension
Cardiac disorders	
Uncommon	Palpitations, Tachycardia
Rare	Myocardial infarction, Atrial fibrillation
Not known	Ventricular arrhythmia, Unstable angina, Sudden cardiac death
Respiratory, thoracic and mediastinal disorders	
Common	Nasal congestion
Rare	Epistaxis
Gastrointestinal disorders	
Common	Dyspepsia
Uncommon	Vomiting, Nausea, Dry mouth
Skin, subcutaneous and soft tissue disorders	
Uncommon	Skin rash
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Reproductive system and breast disorders	
Not known	Priapism, Prolonged erection
General disorders and administration site conditions	
Uncommon	Chest pain, Fatigue
Investigations	
Uncommon	Heart rate increased

* Ear disorders: Sudden deafness. Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil.

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. Doses of 200 mg did not result in increased efficacy but 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 an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

Studies *in vitro* have shown that sildenafil is selective for PDE5, which is involved in the erection process. 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. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE2, 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.

Two clinical studies were specifically designed to assess the time window after dosing during which sildenafil could produce an erection in response to sexual stimulation. In a penile plethysmography (RigiScan) study of fasted patients, the median time to onset for those who obtained erections of 60% rigidity (sufficient for sexual intercourse) was 25 minutes (range 12-37 minutes) on sildenafil. In a separate RigiScan study, sildenafil was still able to produce an erection in response to sexual stimulation 4-5 hours post-dose.

Sildenafil causes mild and transient decreases in blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 100 mg oral dosing of sildenafil was 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg. These decreases in blood pressure are consistent with the

vasodilatory effects of sildenafil, probably due to increased cGMP levels in vascular smooth muscle. Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG.

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.

No clinical relevant differences were demonstrated in time to limiting angina for sildenafil when compared with placebo in a double blind, placebo controlled exercise stress trial in 144 patients with erectile dysfunction and chronic stable angina, who were taking on a regular basis anti-anginal medications (except nitrates).

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).

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers.

Further information on clinical trials
In clinical trials sildenafil was administered to more than 8000 patients aged 19-87. The following patient groups were represented: elderly (19.9%), patients with hypertension (30.9%), diabetes mellitus (20.3%), ischaemic heart disease (5.8%), hyperlipidaemia (19.8%), spinal cord injury (0.6%), depression (5.2%), transurethral resection of the prostate (3.7%), radical prostatectomy (3.3%). The following groups were not well represented or excluded from clinical trials: patients with pelvic surgery, patients post-radiotherapy, patients with severe renal or hepatic impairment and patients with certain cardiovascular conditions (see section 4.3).

In fixed dose studies, the proportions of patients reporting that treatment improved their erections were 62% (25 mg), 74% (50 mg) and 82% (100 mg) compared to 25% on placebo. In controlled clinical trials, the discontinuation rate due to sildenafil was low and similar to placebo.
Across all trials, the proportion of patients reporting improvement on sildenafil were as follows: psychogenic erectile dysfunction (84%), mixed erectile dysfunction (77%), organic erectile dysfunction (68%), elderly (67%), diabetes mellitus (59%), ischaemic heart disease (69%), hypertension (68%), TURP (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%). The safety and efficacy of sildenafil was maintained in long-term studies.

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 dosing of sildenafil AUC and C_{max} increase in proportion with dose over the recommended dose range (25-100 mg).

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%.

Distribution:
The mean steady state volume of distribution (V_d) for sildenafil is 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/ml (CV 40%). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/ml (38 nM). Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil (100 mg single dose), less than 0.0002% (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

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. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 h.

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. The mean AUC and C_{max} of the N-desmethyl metabolite increased 126% and 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. 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 79% and 200% respectively.

Hepatic insufficiency:
In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

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, carcinogenic potential, and toxicity to reproduction.

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
triacetin
indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30^{o}C.
Store in the original package, in order to protect from moisture.

6.5 Nature and content of container

PVC/Aluminium foil blisters in cartons of 2, 4, 8 or 12 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/98/077/010-012
EU/1/98/077/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 September 1998
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer PGM
Zone Industrielle,
29 route des Industries
37530 Pocé-sur-Cisse
France

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER PACKAGING /CARTON

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA 25 mg film-coated tablets
Sildenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

25 mg sildenafil (as citrate)

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated-tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed Pack
Do not use if box has been opened

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Pfizer Limited
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/077/013 (2 film-coated tablets)
EU/1/98/077/002 (4 film-coated tablets)
EU/1/98/077/003 (8 film-coated tablets)
EU/1/98/077/004 (12 film-coated tablets)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VIAGRA 25mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKAGING /CARTON

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA 50 mg film-coated tablets
Sildenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

50 mg sildenafil (as citrate)

3. LIST OF EXCIPIENTS

Contains lactose
See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed Pack
Do not use if box has been opened

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Pfizer Limited
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/077/014 (2 film-coated tablets)
EU/1/98/077/006 (4 film-coated tablets)
EU/1/98/077/007 (8 film-coated tablets)
EU/1/98/077/008 (12 film-coated tablets)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VIAGRA 50mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKAGING /SECONDARY HEAT SEALED CARD PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA 50 mg film-coated tablets
Sildenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

50 mg sildenafil (as citrate)

3. LIST OF EXCIPIENTS

Contains lactose
See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed Pack
Do not use if box has been opened

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Pfizer Limited
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/077/016 (2 film-coated tablets)
EU/1/98/077/017 (4 film-coated tablets)
EU/1/98/077/018 (8 film-coated tablets)
EU/1/98/077/019 (12 film-coated tablets)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VIAGRA 50mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKAGING /CARTON

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA 100 mg film-coated tablets
Sildenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

100 mg sildenafil (as citrate)

3. LIST OF EXCIPIENTS

Contains lactose
See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed Pack
Do not use if box has been opened

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Pfizer Limited
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/077/015 (2 film-coated tablets)
EU/1/98/077/010 (4 film-coated tablets)
EU/1/98/077/011 (8 film-coated tablets)
EU/1/98/077/012 (12 film-coated tablets)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VIAGRA 100mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PRIMARY PACKAGING/BLISTER

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA 25 mg film-coated tablets
Sildenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PRIMARY PACKAGING/BLISTER

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA 50 mg film-coated tablets
Sildenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PRIMARY PACKAGING/BLISTER

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA 100 mg film coated tablets
Sildenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

VIAGRA 25 mg film-coated tablets
Sildenafil citrate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT VIAGRA IS AND WHAT IT IS USED FOR

VIAGRA belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors. It works by helping to relax the blood vessels in your penis, allowing blood to flow into your penis when you get sexually excited. VIAGRA will only help you to get an erection if you are sexually stimulated. You should not take VIAGRA if you do not have erectile dysfunction. You should not take VIAGRA if you are a woman.

VIAGRA is a treatment for men with erectile dysfunction, sometimes known as impotence. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.

2. BEFORE YOU TAKE VIAGRA

Do not take VIAGRA

- If you are taking medicines called nitrates, as the combination may cause a potentially dangerous decrease in your blood pressure. Tell your doctor if you are taking any of these medicines which are often given for relief of angina pectoris (or "chest pain"). If you are not certain, ask your doctor or pharmacist.

- If you are using any of the drugs known as nitric oxide donors such as amyl nitrite ("poppers"), as the combination may also lead to a potentially dangerous decrease in your blood pressure.

- If you are allergic (hypersensitive) to sildenafil or any of the other ingredients of VIAGRA.

- If you have a severe heart or liver problem.

- If you have recently had a stroke or a heart attack, or if you have low blood pressure.

- If you have certain rare inherited eye diseases (such as *retinitis pigmentosa*).

- If you have ever had loss of vision due to non-arteritic anterior ischaemic optic neuropathy (NAION).

Take special care with VIAGRA

Tell your doctor
- If you have sickle cell anaemia (an abnormality of red blood cells), leukaemia (cancer of blood cells), multiple myeloma (cancer of bone marrow).

- If you have a deformity of your penis or Peyronie's Disease.

- If you have problems with your heart. Your doctor should in that case carefully check whether your heart can take the additional strain of having sex.

- If you currently have a stomach ulcer, or a bleeding problems (such as haemophilia).

- If you experience sudden decrease or loss of vision, stop taking VIAGRA and contact your doctor immediately.

You should not use VIAGRA with any other oral or local treatments for erectile dysfunction.

Special considerations for children and adolescents
VIAGRA should not be given to individuals under the age of 18.

Special considerations for patients with kidney or liver problems
You should tell your doctor if you have kidney or liver problems. Your doctor may decide on a lower dose for you.

Taking other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken other medicines, including medicines obtained without prescription.

VIAGRA tablets may interfere with some medicines, especially those used to treat chest pain. In the event of a medical emergency, you should tell any health care professional treating your condition that you have taken VIAGRA and when you did. Do not take VIAGRA with other medicines unless your doctor tells you that you can.

You should not take VIAGRA if you are taking medicines called nitrates, as the combination of these products may cause a potentially dangerous decrease in your blood pressure. Always tell your doctor or pharmacist if you are taking any of these medicines that are often used for the relief of angina pectoris (or "chest pain").

You should not take Viagra if you are using any of the drugs known as nitric oxide donors such as amyl nitrite ("poppers") as the combination may also lead to a potentially dangerous decrease in your blood pressure.

If you are taking medicines known as protease inhibitors, such as for the treatment of HIV, your doctor may start you on the lowest dose (25 mg) of VIAGRA.

Some patients who take alpha-blocker therapy for the treatment of high blood pressure or prostate enlargement may experience dizziness or light-headedness, which may be caused by low blood pressure upon sitting or standing up quickly. Certain patients have experienced these symptoms when taking VIAGRA with alpha-blockers. This is most likely to occur within 4 hours after taking VIAGRA. In order to reduce the likelihood that these symptoms occur, you should be on a regular

daily dose of your alpha-blocker before you start VIAGRA. Your doctor may start you on a lower dose (25 mg) of VIAGRA.

Taking VIAGRA with food and drink
VIAGRA can be taken with or without food. However, you may find that VIAGRA takes longer to start working if you take it with a heavy meal.

Drinking alcohol can temporarily impair your ability to get an erection. To get the maximum benefit from your medicine, you are advised not to drink excessive amounts of alcohol before taking VIAGRA.

Pregnancy and Breast feeding
VIAGRA is not indicated for use by women.

Driving and using machines
VIAGRA can cause dizziness and can affect vision. You should be aware of how you react to VIAGRA before you drive or use machinery.

Important information about some of the ingredients of VIAGRA
If you have been told by your doctor that you have an intolerance to some sugars, such as lactose, contact your doctor before taking VIAGRA.

3. HOW TO TAKE VIAGRA

Always take VIAGRA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual starting dose is 50 mg.

You should not take VIAGRA more than once a day.

You should take VIAGRA about one hour before you plan to have sex. Swallow the tablet whole with a glass of water.

If you have the impression that the effect of VIAGRA is too strong or too weak, talk to your doctor or pharmacist.

VIAGRA will only help you to get an erection if you are sexually stimulated. The amount of time VIAGRA takes to work varies from person to person, but it normally takes between half an hour and one hour. You may find that VIAGRA takes longer to work if you take it with a heavy meal.

If VIAGRA does not help you to get an erection, or if your erection does not last long enough for you to complete sexual intercourse you should tell your doctor.

If you take more VIAGRA than you should:
You may experience an increase in side effects and their severity. Doses above 100 mg do not increase the efficacy.

You should not take more tablets than your doctor tells you to.

Contact your doctor if you take more tablets than you should.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, VIAGRA can cause side effects although not everybody gets them. The side effects reported in association with the use of Viagra are usually mild to moderate and of a short duration.

If you have chest pains during or after intercourse:
- Get in a semi-sitting position and try to relax.
- **Do not use nitrates** to treat your chest pain.
- Contact your doctor immediately.

All medicines including VIAGRA can cause allergic reactions. You should contact your doctor immediately if you experience any of the following symptoms after taking VIAGRA: sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat.

Prolonged and sometimes painful erections have been reported after taking VIAGRA. If you have an erection which lasts for more than 4 hours, you should contact a doctor immediately.

If you experience a sudden decrease or loss of vision, stop taking VIAGRA and contact your doctor immediately.

A very common side effect (likely to occur in more than 1 in 10 patients) is headache.

Common side effects (likely to occur in 1 to 10 patients in 100) include: facial flushing, indigestion, effects on vision (including colour tinge to vision, light sensitivity, blurred vision or reduced sharpness of vision) stuffy nose and dizziness.

Uncommon side effects (likely to occur in 1 to 10 patients in 1000) include: vomiting, , skin rash, bleeding at the back of the eye, eye irritation, bloodshot eyes /red eyes, eye pain, double vision, abnormal sensation in the eye, irregular or rapid heartbeat, muscle pain, feeling sleepy, reduced sense of touch, vertigo, ringing in the ears, nausea, dry mouth, chest pain and feeling tired.

Rare side effects (likely to occur in 1 to 10 patients in 10000) include: high blood pressure, low blood pressure, fainting, stroke, nosebleed and sudden decrease or loss of hearing.

Additional side effects reported from post-marketing experience include: pounding heartbeat, chest pain, sudden death, heart attack or temporary decreased blood flow to parts of the brain. Most, but not all, of these men had heart problems before taking this medicine. It is not possible to determine whether these events were directly related to VIAGRA. Cases of convulsions or seizures have also been reported.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet please tell your doctor.

5. HOW TO STORE VIAGRA

Keep out of the reach and sight of children
Do not store above 30^{o}C.
Store in the original package, in order to protect from moisture.

Do not use VIAGRA after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What VIAGRA contains

- The active substance is sildenafil. Each tablet contains 25 mg of sildenafil (as the citrate salt).
- The other ingredients are:
  - Tablet core: microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate,
  - Film coat: hypromellose, titanium dioxide (E171), lactose, triacetin, indigo carmine aluminium lake (E132)

What VIAGRA looks like and contents of the pack

VIAGRA film-coated tablets are blue, with a rounded-diamond shape. They are marked "PFIZER" on one side and "VGR 25" on the other side. The tablets are provided in blister packs containing 2, 4, 8 or 12 tablets. Some pack sizes may not be marketed in your country.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder of VIAGRA is Pfizer Limited, Sandwich, Kent, CT13 9NJ, United Kingdom.

The manufacturer of VIAGRA is Pfizer PGM, Zone Industrielle, 29 route des Industries, 37530 Pocé-sur-Cisse, France.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in

Detailed information on VIAGRA is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

PACKAGE LEAFLET: INFORMATION FOR THE USER

VIAGRA 50 mg film-coated tablets
Sildenafil citrate

Read all of this leaflet carefully before you start taking this medicine.
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- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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VIAGRA belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors. It works by helping to relax the blood vessels in your penis, allowing blood to flow into your penis when you get sexually excited. VIAGRA will only help you to get an erection if you are sexually stimulated. You should not take VIAGRA if you do not have erectile dysfunction. You should not take VIAGRA if you are a woman.

VIAGRA is a treatment for men with erectile dysfunction, sometimes known as impotence. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.

2. BEFORE YOU TAKE VIAGRA

Do not take VIAGRA

- If you are taking medicines called nitrates, as the combination may cause a potentially dangerous decrease in your blood pressure. Tell your doctor if you are taking any of these medicines which are often given for relief of angina pectoris (or "chest pain"). If you are not certain, ask your doctor or pharmacist.

- If you are using any of the drugs known as nitric oxide donors such as amyl nitrite ("poppers"), as the combination may also lead to a potentially dangerous decrease in your blood pressure.

- If you are allergic (hypersensitive) to sildenafil or any of the other ingredients of VIAGRA.

- If you have a severe heart or liver problem.

- If you have recently had a stroke or a heart attack, or if you have low blood pressure.

- If you have certain rare inherited eye diseases (such as *retinitis pigmentosa*).

- If you have ever had loss of vision due to non-arteritic anterior ischaemic optic neuropathy (NAION).

Take special care with VIAGRA

Tell your doctor
- If you have sickle cell anaemia (an abnormality of red blood cells), leukaemia (cancer of blood cells), multiple myeloma (cancer of bone marrow).

- If you have a deformity of your penis or Peyronie's Disease.

- If you have problems with your heart. Your doctor should in that case carefully check whether your heart can take the additional strain of having sex.

- If you currently have a stomach ulcer, or a bleeding problems (such as haemophilia).

- If you experience sudden decrease or loss of vision, stop taking VIAGRA and contact your doctor immediately.

You should not use VIAGRA with any other oral or local treatments for erectile dysfunction.

Special considerations for children and adolescents
VIAGRA should not be given to individuals under the age of 18.

Special considerations for patients with kidney or liver problems
You should tell your doctor if you have kidney or liver problems. Your doctor may decide on a lower dose for you.

Taking other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken other medicines, including medicines obtained without prescription.

VIAGRA tablets may interfere with some medicines, especially those used to treat chest pain. In the event of a medical emergency, you should tell any health care professional treating your condition that you have taken VIAGRA and when you did. Do not take VIAGRA with other medicines unless your doctor tells you that you can.

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daily dose of your alpha-blocker before you start VIAGRA. Your doctor may start you on a lower dose (25 mg) of VIAGRA.

Taking VIAGRA with food and drink
VIAGRA can be taken with or without food. However, you may find that VIAGRA takes longer to start working if you take it with a heavy meal.

Drinking alcohol can temporarily impair your ability to get an erection. To get the maximum benefit from your medicine, you are advised not to drink excessive amounts of alcohol before taking VIAGRA.

Pregnancy and Breast feeding
VIAGRA is not indicated for use by women.

Driving and using machines
VIAGRA can cause dizziness and can affect vision. You should be aware of how you react to VIAGRA before you drive or use machinery.

Important information about some of the ingredients of VIAGRA
If you have been told by your doctor that you have an intolerance to some sugars, such as lactose, contact your doctor before taking VIAGRA.

3. HOW TO TAKE VIAGRA

Always take VIAGRA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual starting dose is 50 mg.

You should not take VIAGRA more than once a day.

You should take VIAGRA about one hour before you plan to have sex. Swallow the tablet whole with a glass of water.

If you have the impression that the effect of VIAGRA is too strong or too weak, talk to your doctor or pharmacist.

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If VIAGRA does not help you to get an erection, or if your erection does not last long enough for you to complete sexual intercourse you should tell your doctor.

If you take more VIAGRA than you should:
You may experience an increase in side effects and their severity. Doses above 100 mg do not increase the efficacy.

You should not take more tablets than your doctor tells you to.

Contact your doctor if you take more tablets than you should.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, VIAGRA can cause side effects although not everybody gets them. The side effects reported in association with the use of Viagra are usually mild to moderate and of a short duration.

If you have chest pains during or after intercourse:
- Get in a semi-sitting position and try to relax.
- **Do not use nitrates** to treat your chest pain.
- Contact your doctor immediately.

All medicines including VIAGRA can cause allergic reactions. You should contact your doctor immediately if you experience any of the following symptoms after taking VIAGRA: sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat.

Prolonged and sometimes painful erections have been reported after taking VIAGRA. If you have an erection which lasts for more than 4 hours, you should contact a doctor immediately.

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Additional side effects reported from post-marketing experience include: pounding heartbeat, chest pain, sudden death, heart attack or temporary decreased blood flow to parts of the brain. Most, but not all, of these men had heart problems before taking this medicine. It is not possible to determine whether these events were directly related to VIAGRA. Cases of convulsions or seizures have also been reported.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet please tell your doctor.

5. HOW TO STORE VIAGRA

Keep out of the reach and sight of children
Do not store above 30^{o}C.
Store in the original package, in order to protect from moisture.
Do not use VIAGRA after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What VIAGRA contains

- The active substance is sildenafil. Each tablet contains 50 mg of sildenafil (as the citrate salt).
- The other ingredients are:
  - Tablet core: microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate,
  - Film coat: hypromellose, titanium dioxide (E171), lactose, triacetin, indigo carmine aluminium lake (E132)

What VIAGRA looks like and contents of the pack

VIAGRA film-coated tablets are blue, with a rounded-diamond shape. They are marked "PFIZER" on one side and "VGR 50" on the other side. The tablets are provided in blister packs containing 2, 4, 8 or 12 tablets in a carton or card packaging. Some pack sizes may not be marketed in your country.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder of VIAGRA is Pfizer Limited, Sandwich, Kent, CT13 9NJ, United Kingdom.

The manufacturer of VIAGRA is Pfizer PGM, Zone Industrielle, 29 route des Industries, 37530 Pocé-sur-Cisse, France.

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This leaflet was last approved in

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PACKAGE LEAFLET: INFORMATION FOR THE USER

VIAGRA 100 mg film-coated tablets
Sildenafil citrate

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- If you have a severe heart or liver problem.

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VIAGRA tablets may interfere with some medicines, especially those used to treat chest pain. In the event of a medical emergency, you should tell any health care professional treating your condition that you have taken VIAGRA and when you did. Do not take VIAGRA with other medicines unless your doctor tells you that you can.

You should not take VIAGRA if you are taking medicines called nitrates, as the combination of these products may cause a potentially dangerous decrease in your blood pressure. Always tell your doctor or pharmacist if you are taking any of these medicines that are often used for the relief of angina pectoris (or "chest pain").

You should not take Viagra if you are using any of the drugs known as nitric oxide donors such as amyl nitrite ("poppers") as the combination may also lead to a potentially dangerous decrease in your blood pressure.

If you are taking medicines known as protease inhibitors, such as for the treatment of HIV, your doctor may start you on the lowest dose (25 mg) of VIAGRA.

Some patients who take alpha-blocker therapy for the treatment of high blood pressure or prostate enlargement may experience dizziness or light-headedness, which may be caused by low blood pressure upon sitting or standing up quickly. Certain patients have experienced these symptoms when taking VIAGRA with alpha-blockers. This is most likely to occur within 4 hours after taking VIAGRA. In order to reduce the likelihood that these symptoms occur, you should be on a regular

daily dose of your alpha-blocker before you start VIAGRA. Your doctor may start you on a lower dose (25 mg) of VIAGRA.

Taking VIAGRA with food and drink
VIAGRA can be taken with or without food. However, you may find that VIAGRA takes longer to start working if you take it with a heavy meal.

Drinking alcohol can temporarily impair your ability to get an erection. To get the maximum benefit from your medicine, you are advised not to drink excessive amounts of alcohol before taking VIAGRA.

Pregnancy and Breast feeding
VIAGRA is not indicated for use by women.

Driving and using machines
VIAGRA can cause dizziness and can affect vision. You should be aware of how you react to VIAGRA before you drive or use machinery.

Important information about some of the ingredients of VIAGRA
If you have been told by your doctor that you have an intolerance to some sugars, such as lactose, contact your doctor before taking VIAGRA.

3. HOW TO TAKE VIAGRA

Always take VIAGRA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual starting dose is 50 mg.

You should not take VIAGRA more than once a day.

You should take VIAGRA about one hour before you plan to have sex. Swallow the tablet whole with a glass of water.

If you have the impression that the effect of VIAGRA is too strong or too weak, talk to your doctor or pharmacist.

VIAGRA will only help you to get an erection if you are sexually stimulated. The amount of time VIAGRA takes to work varies from person to person, but it normally takes between half an hour and one hour. You may find that VIAGRA takes longer to work if you take it with a heavy meal.

Drinking alcohol can temporarily impair the ability to get an erection. To get the maximum benefit from your medicine, you are advised not to drink large amounts of alcohol before taking VIAGRA.

If VIAGRA does not help you to get an erection, or if your erection does not last long enough for you to complete sexual intercourse you should tell your doctor.

If you take more VIAGRA than you should:
You may experience an increase in side effects and their severity. Doses above 100 mg do not increase the efficacy.

You should not take more tablets than your doctor tells you to.

Contact your doctor if you take more tablets than you should.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, VIAGRA can cause side effects although not everybody gets them. The side effects reported in association with the use of Viagra are usually mild to moderate and of a short duration.

If you have chest pains during or after intercourse:
- Get in a semi-sitting position and try to relax.
- **Do not use nitrates** to treat your chest pain.
- Contact your doctor immediately.

All medicines including VIAGRA can cause allergic reactions. You should contact your doctor immediately if you experience any of the following symptoms after taking VIAGRA: sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat.

Prolonged and sometimes painful erections have been reported after taking VIAGRA. If you have an erection which lasts for more than 4 hours, you should contact a doctor immediately.

If you experience a sudden decrease or loss of vision, stop taking VIAGRA and contact your doctor immediately.

A very common side effect (likely to occur in more than 1 in 10 patients)is headache.

Common side effects (likely to occur in 1 to 10 patients in 100) include: facial flushing, indigestion, effects on vision (including colour tinge to vision, light sensitivity, blurred vision or reduced sharpness of vision) stuffy nose and dizziness.

Uncommon side effects (likely to occur in 1 to 10 patients in 1000) include: vomiting, , skin rash, bleeding at the back of the eye, eye irritation, bloodshot eyes /red eyes, eye pain, double vision, abnormal sensation in the eye, irregular or rapid heartbeat, muscle pain, feeling sleepy, reduced sense of touch, vertigo, ringing in the ears, nausea, dry mouth, chest pain and feeling tired.

Rare side effects (likely to occur in 1 to 10 patients in 10000) include: high blood pressure, low blood pressure, fainting, stroke, nosebleed and sudden decrease or loss of hearing.

Additional side effects reported from post-marketing experience include: pounding heartbeat, chest pain, sudden death, heart attack or temporary decreased blood flow to parts of the brain. Most, but not all, of these men had heart problems before taking this medicine. It is not possible to determine whether these events were directly related to VIAGRA. Cases of convulsions or seizures have also been reported.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet please tell your doctor.

5. HOW TO STORE VIAGRA

Keep out of the reach and sight of children
Do not store above 30^{o}C.
Store in the original package, in order to protect from moisture.
Do not use VIAGRA after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What VIAGRA contains

- The active substance is sildenafil. Each tablet contains 100 mg of sildenafil (as the citrate salt).
- The other ingredients are:
  - Tablet core: microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate,
  - Film coat: hypromellose, titanium dioxide (E171), lactose, triacetin, indigo carmine aluminium lake (E132)

What VIAGRA looks like and contents of the pack

VIAGRA film-coated tablets are blue, with a rounded-diamond shape. They are marked "PFIZER" on one side and "VGR 100" on the other side. The tablets are provided in blister packs containing 2, 4, 8 or 12 tablets. Some pack sizes may not be marketed in your country.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder of VIAGRA is Pfizer Limited, Sandwich, Kent, CT13 9NJ, United Kingdom.

The manufacturer of VIAGRA is Pfizer PGM, Zone Industrielle, 29 route des Industries, 37530 Pocé-sur-Cisse, France.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on VIAGRA is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/