Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Sildenafil 50mg film-coated tablets

Public Consultation

Proposal to make available from Pharmacies

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency responsible for regulating medicines and medical devices. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public reclassification reports. Suspected side-effects to any drug or vaccine can be reported to MHRA by both healthcare professionals and members of the public via the Yellow Card Scheme (http://www.mhra.gov.uk/yellowcard)

Ref: ARM94

Sildenafil 50mg film-coated tablets

Proposal to make available from Pharmacies without prescription

We want to know what you think

- Sildenafil 50mg tablets are used to treat erectile dysfunction in adult men aged 18 years or over.
- Sildenafil 50mg tablets are only at the moment available on prescription.
- We propose to make it available in pharmacies.
- We consider that this product can be available as a Pharmacy medicine.
- We want to know what you think about this change.

Please tell us your views – please use the form at the end of this document.

The deadline for comments is **18 April 2017**.

In this document there is:

- A summary of the proposed change and the background
- A copy of the patient information leaflet and label proposed if the change goes ahead
- A form for your response

The full name of the medicine is Sildenafil 50mg film-coated tablets – in this document, we will call it ‘sildenafil.’

Contents:

Product details:

Product name: Sildenafil 50mg film-coated tablets

Active substances: Sildenafil citrate

Licence holder: Pfizer Consumer Healthcare

Route of sale/supply: Current – on prescription (POM); Proposed – Pharmacy (P)

Indication: For adult men (aged 18 years and older) with erectile dysfunction
Marketing Authorisation Number: PL 00165/0392
Consultation is open from: 28 March 2017 – 18 April 2017

Reference: ARM94

Contact: reclassification@mhra.gsi.gov.uk

1. Background on deciding where medicines are available

The role of MHRA

MHRA regulates medicines and medical devices in the UK, on behalf of the UK Licensing Authority. This means that MHRA decides whether medicines are available:

- on prescription only - 'prescription only medicine' (POM)
- bought from pharmacies - 'pharmacy medicine' (P)
- bought from other shops - 'general sales list medicine' (GSL)

What is re-classification of a medicine?

Making a change on where a medicine is available is called 'reclassification'. This is sometimes referred to as 'switching'. To decide on this change, MHRA may:

- take advice from its committees of external experts
- take advice from a group ('stakeholder group') of health professionals and representatives of people affected by the classification change
- run a public consultation

To be reclassified from POM to P, a medicine must:

- be unlikely to be a direct or indirect danger to human health when used without the supervision of a doctor, even if used correctly
- be generally used correctly (ie not frequently or to a wide extent used incorrectly)
- not contain substances or preparations of substances where the activity of the product or its side effects require further investigation
- not normally be prescribed by a doctor for injection (parenteral administration)

What evidence is needed?

A company or organisation can ask MHRA for a medicine to be available as a pharmacy medicine or a general sale medicine. To do this, they need to get together evidence to show that the medicine

a) is likely to be used appropriately, and
b) with relatively little danger to the public.

This evidence needs to focus on the risk to the public. This includes evidence on the possible abuse or misuse of the medicine. The evidence may include:

- clinical studies
- evidence showing acceptable level of side effects
- advice of experts
- views of relevant health professionals and their professional bodies
- views of relevant public associations and individuals with an interest in the medicine under consideration.

Who makes the final decision?

The final decision on whether to approve a change is made by the MHRA, on behalf of the UK Licensing Authority.

2. About sildenafil

Sildenafil tablets are a treatment for adult men (aged 18 years and older) with erectile dysfunction (also known as impotence). This is when a man cannot get or keep an erection hard enough for satisfactory sexual activity.

Erections depend on proper blood flow to the penis. If blood cannot flow adequately to the penis, it can cause erectile dysfunction. Erectile dysfunction is a common problem and can

affect men differently. Some men cannot get an erection, other men can get an erection but it may not be hard enough for sex, or they may lose their erection before or during sex.

Sildenafil belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors. It works by blocking the phosphodiesterase enzyme, which normally breaks down a substance known as cyclic guanosine monophosphate (cGMP). During normal sexual stimulation, cGMP is produced in the penis, where it causes the muscle in the spongy tissue of the penis (the *corpora cavernosa*) to relax, allowing the flow of blood into the *corpora*, producing the erection. By blocking the breakdown of cGMP, sildenafil improves erectile function. Sexual stimulation is still needed to produce an erection.

The MHRA considers that this product is safe enough to be made available as a Pharmacy medicine in certain circumstances. This report outlines the background to this decision. Please tell us your views by using the response form at the end of this document (Annex 1). The deadline for comments is **18 April 2017**.

The patient information leaflet, label and summary of product characteristics are provided in Annex 2, 3 and 4. The pharmacy checklist is provided in Annex 5.

This is the first application for a sildenafil product to be available as a Pharmacy medicine.

This report relates specifically to the proposal to reclassify sildenafil from a prescription to pharmacy medicine. If you want more information on sildenafil as a prescription medicine then please refer to sildenafil Public Assessment Reports that are available here:
http://www.mhra.gov.uk/public-assessment-reports/

NHS Choices provides health advice about erectile dysfunction:
http://www.nhs.uk/conditions/Erectile-dysfunction/Pages/Introduction.aspx

3. Proposal to make sildenafil available as a Pharmacy medicine

Who has made the proposal?

The licence-holder for sildenafil tablets (Pfizer Consumer Healthcare) has applied to make this product available as a Pharmacy Medicine. Pharmacy medicines can be supplied without prescription only from pharmacies by or under the supervision of a pharmacist.

Pfizer Consumer Healthcare are referred to as ‘the applicant’ throughout this document.

What are the details of this change?

The application proposes to make sildenafil available through Pharmacy outlets in the following circumstances:

- For oral use
- Strength: 50mg sildenafil citrate
- For adult men with erectile dysfunction
- Dose: 50mg tablet to be taken as needed with water approximately one hour before sexual activity
- Maximum dose: 50mg
- Maximum daily dose: 50mg
- Maximum pack size: 8 tablets

This proposal does not change any of the conditions of supply of the currently available prescription products for erectile dysfunction – which will remain available on prescription.

4. How was the proposal assessed for sildenafil being available on as a Pharmacy medicine?

A medicine will be non-prescription unless it fulfills the criteria for prescription control as set out below. Prescription only status will apply where:

- a direct or indirect danger exists to human health, even when used correctly, if used without medical supervision
- there is frequently incorrect use which could lead to direct or indirect danger to human health
- further investigation of activity and/or side-effects is required
- the product is normally prescribed for parenteral administration (by injection)

In the UK these criteria are laid down in the Human Medicines Regulations 2012, regulation 62(3). The MHRA assessed the application against the criteria for prescription control to assess the suitability for Pharmacy availability.

The company has produced a checklist (Annex 5) that pharmacists can choose to use when supplying the medicine. This checklist can be used to determine whether the medicine is suitable for a patient by asking a series of questions around cardiovascular health, other medicines and other conditions. The patient will have the patient information leaflet (Annex 2) and packaging (Annex 3) to refer to.

The Summary of Product Characteristics is provided in Annex 4. This document is a description of a medicine's properties and the conditions attached to its use. It is used as a reference by healthcare professionals.

4.1 Criterion 1 – "It is likely to present a direct or indirect danger to human health, even when used correctly, if used without medical supervision"

The main criterion that must be considered in the reclassification of sildenafil to Pharmacy status is that it does not present a direct or indirect danger to human health if used, even correctly, without the supervision of a doctor.

A direct danger may be present if the product causes adverse reactions that are important because of their seriousness, severity or frequency or because the reaction is one for which there is no suitable preventative action such as being able to identify the group of patients who are at risk if they use the product without medical supervision so that they can be excluded from using the Pharmacy product. Direct danger may arise from drug interactions with commonly used medicines. For the product to be suitable for Pharmacy status the drug interactions would need to be prevented

4.1.1 Direct danger to human health

The safety profile of sildenafil is favourable and well known when used under medical supervision, especially the adverse events and interactions. Overall there are no identified concerns related to how it works, interactions with other medicines and side effects that are not already well documented. The main known or potential adverse effects of sildenafil relate to its pharmacological effects arising from the elevation of cGMP in other tissues such as systemic vascular smooth muscle, the retina, platelets and gastrointestinal smooth muscle. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia (indigestion), nasal (nose) congestion, dizziness, nausea (feeling sick), hot flush, visual disturbance, cyanopsia (vision tinted blue) and blurred vision.

The particular areas that could potentially lead to direct danger are;

- Use with nitrates
- Use with certain other medications (CYP3A4 inhibitors, alpha-blockers, guanylate cyclase stimulators)
- Previous episodes of non-arteritic anterior ischaemic optic neuropathy (NAION)
- Priapism

Nitrates
Use at the same time with nitrates or nitric oxide donors (such as glyceryl trinitrate, isosorbide mononitrate, nicorandil, or amyl nitrate (also known as “poppers”), which are used for angina (chest pain) or heart failure, can lead to a dangerous fall in blood pressure. Therefore sildenafil cannot be used at the same time as nitrates or nitric oxide donors.

CYP3A4 inhibitors, guanylate cyclase stimulators, alpha-blockers
Ritonavir (a CYP3A4 inhibitor) increases the concentration of sildenafil in the blood by four times. Therefore sildenafil cannot be used at the same time.

Use of PDE5 inhibitors, including sildenafil, must not be used at the same time with guanylate cyclase stimulators, such as riociguat (used to treat high blood pressure in the lungs), as it may potentially lead to symptomatic hypotension (low blood pressure causing dizziness).

Clinical trial data indicates a reduction in sildenafil clearance when taken with other CYP3A4 inhibitors (with the exception of ritonavir). This means that if sildenafil is taken with these types of medicines it stays longer in the blood stream. Although no increased incidence of adverse events was observed in these patients the prescription only product recommends a starting dose of 25mg sildenafil for these patients.

Use of sildenafil at the same time as alpha-blocker medicines may lead to symptomatic hypotension in a few susceptible individuals. To minimise the potential of developing postural hypotension (a sudden fall in blood pressure when standing up, which can lead to dizziness or fainting) in patients receiving alpha-blocker treatment the prescription only product recommends a starting dose of 25mg sildenafil.

As it is not practical to reduce the dose to 25mg in the pharmacy model of supply, and to simplify the model, the Pharmacy product must not be supplied to men taking CYP3A4 inhibitors and alpha-blockers.

NAION
Non-arteritic anterior ischaemic optic neuropathy (NAION; a loss of vision because of damage to the optic nerve) has been rarely reported post-marketing in temporal association with the use of all PDE5 inhibitors, including sildenafil. Therefore sildenafil must not be used in any patient with a history of vision loss or in anyone with an inherited eye disease (such as retinitis pigmentosa).

Priapism
Prolonged and sometimes painful erections lasting longer than four hours (priapism) have been occasionally reported with sildenafil in post-marketing experience. The product information advises patients who have conditions that may expose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia) to consult a doctor before using sildenafil, and that after using, if an erection persists longer than 4 hours that patient should seek immediate medical assistance.

Renal Impairment
No dosage adjustments are required for patients with mild to moderate renal (kidney) impairment. However, since sildenafil clearance is reduced in individuals with severe renal impairment (creatinine clearance <30ml/min), individuals previously diagnosed with severe renal impairment must be advised to consult their doctor before taking this product, since the 25 mg prescription dose may be more suitable for them.

Hepatic Impairment
Sildenafil clearance is reduced in individuals with hepatic (liver) impairment (e.g. cirrhosis). Individuals previously diagnosed with hepatic impairment must be advised to consult their doctor before taking sildenafil tablets, since the 25 mg prescription dose may be more suitable for them.

Can direct risk be minimised as a Pharmacy medicine?
It is essential for pharmacists to be aware of the above issues relating to interacting medicines, renal and hepatic impairment, NAION, and priapism. It is considered that pharmacists can question patients on the medicines that they are currently taking, and on their medical history, and pharmacies in England have access to Summary Care Records. This will assist the pharmacist in identifying patients with renal and hepatic impairment and those on interacting medicines, and these patients will be signposted to a medical professional. The pharmacist will also question patients to identify if they have suffered from any eye problems, or any conditions that predispose them to priapism. Additionally, the product information (including the patient information leaflet and label) has been strengthened for Pharmacy supply to clearly state that these men should not take Pharmacy sildenafil.

The counselling points available on the checklist for pharmacists remind the patient to seek medical attention immediately if they develop an erection that lasts more than four hours, or experience any sudden visual impairment. These points are also clearly included in the patient information leaflet provided with the product, which the patient can refer to.

The MHRA considers that the direct risks can be minimised to an acceptable level for Pharmacy supply of sildenafil 50mg tablets.

4.1.2 Indirect danger to human health
Treatments may present an indirect danger when particular symptoms are caused by range of different conditions. If the patient cannot easily self-diagnose the cause of such symptoms it may be inappropriate to provide a product to treat the symptoms without also treating and managing the underlying disease.

An important example of an indirect danger is when treating the symptoms might mask an underlying condition requiring medical attention. Consideration should be given to whether an indirect danger might exist and if so, whether the risk, its frequency and the seriousness of the consequences would make reclassification unacceptable. Additional warnings such as a recommendation to seek medical advice if symptoms continue beyond a stated time period may be necessary in such instances.

Erectile dysfunction is a symptom of cardiovascular disease, and may also be caused by psychological factors or alcohol use. If these are not identified by the pharmacist an indirect danger to health may exist.

Cardiovascular disease and risks
Several medical conditions are associated with erectile dysfunction, most notably cardiovascular disease and diabetes mellitus, and there is generally low awareness amongst both the public and healthcare professionals of these established links. The applicant states that Pharmacy availability of sildenafil is likely to increase the number of men with erectile dysfunction who seek treatment. This should lead to an increase and/or earlier diagnosis of

erectile dysfunction by a healthcare professional along with earlier diagnosis of potential underlying conditions such as cardiovascular disease or diabetes, by increasing patient-awareness of the association of erectile dysfunction with other more chronic conditions, and facilitating dialogue with a healthcare professional.

For the Pharmacy sildenafil product it is proposed that patients with certain cardiovascular conditions and risk factors that are not suitable to be supplied this product will be provided with clear instructions to consult a doctor. These patients are those:

(a) With severe cardiovascular disorders such as a recent acute myocardial infarction (heart attack) or stroke (within the last 6 months), unstable angina or severe cardiac failure.
(b) With uncontrolled hypertension (high blood pressure), moderate to severe valvular disease (problems with heart valves), left ventricular dysfunction, hypertrophic obstructive and other cardiomyopathies (inflammation of the heart muscle), or significant arrhythmias (irregular heart beat).
(c) With increased susceptibility to vasodilators including those with left ventricular outflow obstruction, aortic narrowing (heart problems causing blood flow issues), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.
(d) Who feel very breathless or experience chest pain after light or moderate physical activity, such as walking briskly for 20 minutes or climbing 2 flights of stairs.

The following patients are considered to be at low cardiovascular risk and will be able to use the product, providing they are considered to be fit for sex (in response to questioning on (d) above):
(e) patients who have been successfully revascularised (e.g. via coronary artery bypass grafting, stenting, or angioplasty), patients with asymptomatic controlled hypertension, and those with mild valvular disease.

The applicant will be supplying a checklist with this product that enables a pharmacist to perform a basic screening for cardiovascular health. It is considered that the patients in categories (a) to (c) can be identified by the pharmacist asking a series of questions around cardiovascular health history, and the medicines they are taking. Those patients who are not suitable for supply would be referred to a doctor.

The more nuanced area is category (e) – those patients who are considered at low cardiovascular risk from sexual activity. It is considered that patients who have been successfully vascularised, those with asymptomatic controlled hypertension and those with mild valvular disease are considered suitable to take the product *if* they are fit for sex. It is proposed that cardiovascular fitness for sex is assessed by a simple question (i.e. can you walk briskly for 20minutes or climb 2 flights of stairs without getting breathless?). It is considered that, whilst it is difficult to quantify this question, it is a simple and practical way to determine fitness considering that there is a low risk of cardiovascular events with the use of sildenafil.

In addition to the checklist the company will be providing training material which provides background information and covers the management of erectile dysfunction, misconceptions around the condition and how Pharmacy sildenafil should be supplied. The pharmacy training materials and checklist will assist pharmacists in identifying these patients appropriately. In addition, the leaflet and label will also clearly warn patients, using patient friendly terminology, that they should not take the product if they suffer from certain cardiovascular conditions.

Erectile dysfunction with a psychological cause
Difficulties with erections can sometimes develop because of depression or anxiety. Psychological causes account for 1 in 10 cases of erectile dysfunction. Psychological causes can occur for a wide range of reasons. These include issues such as performance anxiety in relation to erectile dysfunction and the fear this will keep occurring, lack of sexual knowledge, past sexual problems or life stress.

Erectile dysfunction can often have both physical and psychological causes. For example, erectile dysfunction may be a symptom of depression and/or in men with erectile dysfunction, the emotional stress commonly associated with loss of sexual function may lead to depression. Additionally, antidepressant drugs can also cause ED.

It will be important for the pharmacist to look out for signs of untreated depression, which may have not been picked up before. There is no reason why sildenafil should not be supplied for those men with erectile dysfunction with a psychological origin. However as per the European Association of Urology guidelines lifestyle advice should also be provided in conjunction with supply of the product. This could be generic lifestyle advice and stress reducing tips, whilst others may need to be referred to the doctor or supported by counselling. Details relating to this will be provided in the pharmacy training materials and the checklist advise the pharmacist to check for signs of concern from a psychological perspective and how to guide the patient accordingly.

Alcohol use
Alcohol is a depressant, and using it heavily can dampen mood, decrease sexual desire, and make it difficult for a man to achieve erections or reach an orgasm while under the influence. Drinking alcohol to excess in both the short term and long terms can cause erectile dysfunction. As such, there may be patients with erectile dysfunction, who wish to take sildenafil, which may have underlying issues with alcohol use.

It is acceptable for sildenafil to be used in these patients, although it would be advisable that the pharmacist advises the patient about moderating alcohol intake and the possible effect excess alcohol may have on sexual performance, even if they are using sildenafil. The pharmacist should also look at the consultation as an opportunity to help guide the patient to make lifestyle changes. The pharmacy training guide emphasises the actions patients can take for themselves in relation to erectile dysfunction. This includes reference to the reducing alcohol intake to help to prevent the erectile dysfunction in the first place. Furthermore, if the pharmacist believes that the man has an issue with short or long term alcohol intake they can refer to him to his GP or other relevant supportive services.

Can indirect danger be minimised as a Pharmacy medicine?
The information provided to the pharmacist (the pharmacy training, and the checklist) and the information for the patient (leaflet, label) help to identify those patients who have certain cardiovascular problems, and help to inform the patient that the product is not suitable them so they should see their doctor.

The training and checklist also help pharmacists to recognise patients who may be suffering from depression, anxiety and alcohol use, and to counsel, support, and refer these patients appropriately.

There is a low risk of masking underlying disease (an ‘indirect danger’ under criterion 1). However, this is considered to be minimised by the supply model provided and also outweighed by the benefits of patients being able to access a legitimate supply from a pharmacist who can provide healthcare advice and signpost the patient to their GP if appropriate.

4.2 Criterion 2 – " It is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health"

Addiction, dependence, recreational use, and misuse can be considered to be incorrect use.

There is no indication from the controlled clinical trial or post-marketing data that patients develop dependence or addiction to sildenafil. There are no underlying pharmacological mechanisms, or neural or behavioural signs and symptoms that suggest that sildenafil would induce drug-seeking behaviour. There have been no reports of drug abuse or drug dependence associated with the use of sildenafil in clinical trials.

There is evidence that sildenafil, often obtained illegally, is used with the recreational use of other drugs (e.g. methamphetamine, methylenedioxy-N-methylamphetamine, amyl nitrite ('poppers') and opioids) in people who do not normally suffer from erectile dysfunction. This appears to mainly be in healthy men who use erectile dysfunction medicines to counteract effects of recreational drugs. It is unknown whether these users would purchase sildenafil from a Pharmacy if that option was available, so it is not known whether reclassification would have any effect on this group. However, there appears to be little evidence of harm from this intentional incorrect use that leads to a direct or indirect danger to health and it is considered that the second POM criteria is not fulfilled.

The concurrent use with amyl nitrate causing blood vessel dilation and blood pressure drop leading to myocardial infarction is a well-established concern. Use with amyl nitrate is contraindicated in the product information, and it is considered that this is an acceptable risk minimisation measure.

It is proposed that Pharmacy sildenafil cannot be supplied to men without erectile dysfunction, women and children/adolescents under 18 years old.

4.3 *Criterion 3 – "It contains substances or preparations of substances of which the activity requires, or the side effects require, further investigation"*

The safety profile of sildenafil is well known. It has been available in the UK as a prescription only medicine for 18 years and it is widely used, so this criterion is not considered to be applicable to the non-prescription application. There is no indication that any issue requires further investigation. Therefore, sildenafil does not meet the requirements for medical prescription in relation to this criterion.

4.4 *Criterion 4 – "It is normally prescribed by a doctor for parenteral administration (that is, by injection)."*

This product is a tablet, so this criterion does not apply.

5. Further details on the application

5.1 Risk Management Plan

As is required for all new marketing authorisations applications, the application contains a risk management plan (RMP) which documents the following:

- the known safety profile of the medicine including any important identified and potential risks
- what is not known about the safety profile ('missing information')
- how the safety profile will be monitored after the medicine is licensed, including any plans for further studies to actively gain more knowledge about the safety of the medicine ('additional pharmacovigilance activities')
- how any important risks will be prevented or minimised in patients ('risk minimisation measures') and how the utility and effectiveness of the risk minimisation measures will be assessed

The RMP for this product has detailed the important identified and potential risks based on the known safety profile of sildenafil which has been established through 18 years of use in the POM setting. In addition, the RMP for this product includes the important potential risk "Serious cardiovascular events associated with sexual activity in men with pre-existing or undiagnosed cardiovascular disease and/or risk factors". This relates specifically to the Pharmacy supply of sildenafil and the possibility that men won't be assessed by their GP for underlying cardiovascular (or other) causes of their erectile dysfunction and an opportunity to diagnose and treat underlying cardiovascular disease may be missed. Sildenafil should also not be given to men in whom sexual activity is not advised. To address this potential risk the applicant has proposed to provide Pharmacy training materials and a checklist. This will be supplied in addition to the routine risk minimisation measures (SPC, labelling and patient information leaflet). The Pharmacy training material will be designed to ensure that only men who are fit for sex are supplied sildenafil in the Pharmacy setting and that all men (including those who are supplied sildenafil in the Pharmacy setting) are advised to see their GP for a health check.

In addition, the applicant has been requested to undertake a questionnaire or survey based study to assess the utility and effectiveness of the proposed Pharmacy risk minimisation material in conveying the key messages to both patients and pharmacists and their impact on self-reported patient behaviour (i.e. did or did not attend GP for health check) and pharmacy practice (i.e. sildenafil was supplied to only men in whom its use is appropriate and/or appropriate advice issued).

The applicant has proposed for routine pharmacovigilance activities to take place; no additional safety studies are planned. This is in general accepted given the well-established safety profile of sildenafil and the difficulties associated with conducting a post-authorisation safety study in the over the counter setting in this instance.

5.2 Checklist

The checklist that pharmacists can use to assist in supply of this product is provided in Annex 5.

5.3 Label and leaflet

The patient information leaflet and label that patients will have when they buy this product are provided in Annex 2 and 3.

5.4 Summary of Product Characteristics

The Summary of Product Characteristics is provided in Annex 4. This document is a description of Pharmacy sildenafil's properties and the conditions attached to its use. It is used as a reference by healthcare professionals.

6. Advice from the Commission on Human Medicines

The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products. CHM is an advisory non-departmental public body, sponsored by the Department of Health.

The CHM advised in favour of Pharmacy availability of sildenafil 50mg tablets under the circumstances outlined above i.e. for adult men with erectile dysfunction with a maximum dose of one tablet each day, and a maximum pack size of 8 tablets.

7. Summary

Pharmacy availability of sildenafil tablets would be of value to men who suffer from erectile dysfunction. Patients can be assessed for suitability by a pharmacist and made aware of the risks, situations where supply is not appropriate and potential interactions with other drugs. The risks of indirect danger arising from missed diagnosis of underlying disease is

minimised through the pharmacist using their professional judgement and the checklist to identify patients for whom the product is not suitable, and referring these patients to a doctor.

It is also considered that there is a low risk of direct danger and of intentional abuse that will lead to a danger to human health. Furthermore this low risk are outweighed by the benefits that this route of supply can bring – by bringing a hard to reach group into healthcare environment with the potential to increase earlier identification of heart disease and also reducing the risks associated with use of counterfeits obtained via the internet.

8. What do you think?

- Sildenafil 50mg tablets are used to treat erectile dysfunction in adult men aged 18 years or over.
- Sildenafil 50mg tablets are only at the moment available on prescription.
- We propose to make it available in pharmacies.
- We consider that this product can be available as a Pharmacy medicine.
- We want to know what you think about this change.

Please tell us your views – please use the form on the next page in Annex 1. Please respond by 18 April 2017.

Response document for MHRA public consultation on the proposal to make Sildenafil 50mg Tablets available in Pharmacies
Ref: ARM94

ANNEX 1

Your details

Name:

Position (if applicable):

Organisation (if applicable):

Email:

a. Do you consider that Sildenafil 50mg Tablets should be available as a Pharmacy medicine?

Yes ☐ No ☐ Not sure ☐

Please provide any comments or evidence to support your response:

b. Do you have any specific comments on the checklist, leaflet or the label provided in the public reclassification report? In particular:

- **If you are a potential patient, do you find the patient information leaflet (Annex 2) and the label (Annex 3) understandable?**
- **If you are a pharmacist or healthcare professional, do you find the checklist (Annex 5) useful?**

c. Do you have any other comments on the reclassification?

d. The MHRA may publish consultation responses. Do you want your response to remain confidential?

Yes ☐ Partially* ☐ No ☐

*If partially, please indicate which parts you wish to remain confidential. In line with the Freedom of Information Act 2000, if we receive a request for disclosure of the information we will take full account of your explanation, but we cannot give an assurance that confidentiality can be maintained in all circumstances. Responses to consultation will not normally be released under FOI until the regulatory process is complete.

Responses can be continued onto a separate page if required. This form should be returned by email (reclassification@mhra.gsi.gov.uk) to arrive by **18 April 2017.** Contributions received after that date cannot be included in the exercise.

Annex 2 - Patient information leaflet

Package Leaflet: Information for the User

SILDENAFIL 50 mg

film-coated tablets
sildenafil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

Always take this medicine exactly as described in this leaflet or as your pharmacist has told you.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects, talk to your pharmacist or doctor. This includes any possible side effects not listed in this leaflet. See section 4.
- If you have taken Sildenafil 50 mg as directed and were NOT able to get or keep an erection hard enough for satisfactory sex, you should talk to your pharmacist or doctor.

What is in this leaflet?

1. What SILDENAFIL 50 mg is and what it is used for

✓ **Sildenafil 50 mg is a treatment for adult men (aged 18 years and older) with erectile dysfunction (also known as impotence).** This is when a man cannot get or keep an erection hard enough for satisfactory sexual activity.

Erections depend on proper blood flow to the penis. If blood cannot flow adequately to the penis, it can cause erectile dysfunction. Erectile dysfunction is a common problem and can affect men differently. Some men cannot get an erection, other men can get an erection but it may not be hard enough for sex, or they may lose their erection before or during sex.

Sildenafil 50 mg contains the active ingredient sildenafil. It belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors. It works by relaxing the blood vessels in your penis, allowing blood to flow into your penis when you get sexually excited and causing an erection. Sildenafil 50 mg will only help you to get an erection if you are sexually excited (stimulated).

2. What you need to know before you take SILDENAFIL 50 mg

✗ Do NOT take Sildenafil 50 mg if you:

- **do not have an erection problem, as this medicine will not provide any benefit to you;**
- **take any medicines called nitrates** or nitric oxide donors, (such as glyceryl trinitrate, isosorbide mononitrate, isosorbide dinitrate or amyl nitrite also known as “poppers”) for the relief of chest pain, or heart failure, as the combination may lead to a dangerous fall in blood pressure;
- are allergic to sildenafil or any of the other ingredients of this medicine (listed in section 6);
- take riociguat. This medicine is used to treat high blood pressure in the lungs;
- take ritonavir for the treatment of HIV infection;
- have been advised by your doctor to **avoid sexual activity** because of a problem with your heart or blood vessels, such as a recent heart attack or stroke (within the last 6 months), unstable angina or severe cardiac failure;
- have ever had loss of vision because of damage to the optic nerve [such as non-arteritic anterior ischaemic optic neuropathy (NAION)] or have an inherited eye disease (such as retinitis pigmentosa);
- **have low blood pressure** (which can cause symptoms such as tiredness, dizziness, lightheadedness, feeling sick, clammy skin, depression, loss of consciousness, or blurry vision) or high blood pressure that is not controlled;
- have a severe liver problem;
- have any disease or deformity of your penis (such as Peyronie’s Disease);
- are a woman;
- are under 18 years of age.

Warnings and precautions

Sexual activity can put extra strain on your heart. If you have a heart problem or think you might have a heart problem you should tell your pharmacist.

! It is important to have a check-up with your doctor within the first 6 months of using Sildenafil 50 mg to ensure that your erection problems are not caused by another serious health condition.

Even if you feel healthy, your erection problems may be linked to other serious health conditions. Erectile dysfunction may be an early sign of:
- heart and blood vessel problems
- diabetes
- high blood pressure
- high cholesterol

You should discuss your symptoms and these conditions with your doctor if you have not already done so.

Before taking Sildenafil 50 mg, in order to ensure this medicine is suitable for you and that you are fit enough to have sex, tell your pharmacist or doctor if you:

! • **get very breathless or feel any pain in the chest with light or moderate activity (e.g. walking briskly for 20 minutes or climbing two flights of stairs). Your pharmacist may recommend that your doctor check whether your heart can take the additional strain of having sex;**
- have a problem with one of the valves in your heart (valvular heart disease);
- have a disease in which the heart muscle becomes inflamed and does not work as well as it should (cardiomyopathy);
- have an irregular heart beat (arrhythmia)
- you have had surgery to improve blood flow to your heart, or you have high blood pressure which is now under control;
- have ever had an erection that lasted more than 4 hours even without any physical or psychological stimulation; (called priapism) or have any condition which can cause priapism. Conditions which can cause priapism include sickle cell anaemia (an abnormality of red blood cells), leukaemia (cancer of blood cells), or multiple myeloma (cancer of bone marrow).
- take any other medicines listed in this leaflet. Please refer to section 2 ‘Other medicines and Sildenafil 50 mg’;
- have a stomach ulcer or a bleeding disorder (such as haemophilia);
- have previously diagnosed mild to moderate liver disease, or severe kidney problems. Sildenafil 50 mg may not be suitable for you.

Children and adolescents

This medicine should not be given to children or adolescents under the age of 18 years.

Other medicines and Sildenafil 50 mg

Tell your pharmacist or doctor if you are taking, have recently taken or might take any other medicines. Some medicines may be affected by Sildenafil 50 mg or they may affect how well Sildenafil 50 mg will work.

✗ **NITRATE medicines: Do NOT take Sildenafil 50 mg if you are taking nitrate medicines (such as glyceryl trinitrate, isosorbide mononitrate, isosorbide dinitrate) or nitric oxide donors (such as amyl nitrite (“poppers”), nicorandil or sodium nitroprusside).** These are often used for the relief of chest pain *(angina pectoris),* or heart failure. Using Sildenafil 50 mg with any of these medicines may lead to a dangerous fall in blood pressure.

Do not take Sildenafil 50 mg if you are taking a medicine called riociguat, used to treat high blood pressure in the lungs. In addition, do not take Sildenafil 50 mg if you are taking a medicine called ritonavir, for the treatment for HIV infection.

Tell your pharmacist or doctor before using Sildenafil 50 mg if you are taking:
- any other treatment for erectile dysfunction;
- alpha-blockers such as alfuzosin, doxazosin or tamsulosin, which are medicines used to treat urinary problems due to an enlarged prostate (benign prostatic hyperplasia) or occasionally high blood pressure, as Sildenafil 50 mg may not be suitable for you;
- medicines known as CYP3A4 inhibitors, such as protease inhibitors (saquinavir) to treat HIV infections and the heartburn treatment cimetidine; Sildenafil 50 mg may not be suitable for you;
- medicines to treat fungal infections called itraconazole or ketoconazole, and an antibiotic called erythromycin.

FRONT

Sildenafil 50 mg with food and drink

Sildenafil 50 mg can be taken with or without food. When this medicine is taken after a high-fat meal, it may take a little longer to start working. Do not take Sildenafil 50 mg with grapefruit or grapefruit juice, because this can affect how the medicine works.

Drinking excessive alcohol can temporarily reduce your ability to get an erection. To get the maximum benefit from your medicine, you are advised not to drink large amounts of alcohol before sexual activity.

Pregnancy and breast-feeding

This medicine should not be used by women.

Driving and using machines

Sildenafil 50 mg can cause dizziness and can affect your vision. Do not drive or use machines if you suffer from these side effects after taking this medicine.

Important information about some of the ingredients of Sildenafil 50 mg

If you have been told by your doctor that you have intolerance to some sugars, such as lactose, speak to your pharmacist or doctor before taking this medicine.

Other important information

You can improve your erectile function by making lifestyle changes; these include exercising regularly, reducing stress, giving up smoking and avoiding excessive alcohol use. If you are feeling depressed or anxious, talk to your pharmacist or doctor, who will be able to provide you with further advice.

3. How to take SILDENAFIL 50 mg

Always take Sildenafil 50 mg exactly as described in this leaflet or as your pharmacist or doctor has told you. Check with your pharmacist or doctor if you are not sure.

- take one tablet, as needed, approximately 1 hour before sexual activity;
- swallow the tablet whole with water;
- **do not take more than one tablet a day.**

You will not get an erection just by taking Sildenafil 50 mg. This medicine will only help you get an erection if you are sexually aroused. You and your partner should engage in foreplay just as you would if you were not taking a medicine for erectile dysfunction.

The amount of time this medicine takes to work varies from person to person, but it normally takes between 30 to 60 minutes to work. You may take it up to 4 hours before sexual activity.

Remember to relax and be patient. There is no rush. If you are not successful the first time, try to have sex again, but remember **you can only take 1 tablet a day.** For most men, Sildenafil 50 mg will work the first or second time they try it. If it has been some time since you were able to get or keep an erection, it may take a couple of attempts before you are able to achieve an erection. If you feel the effect of Sildenafil 50 mg is too strong or too weak, talk to your pharmacist or doctor.

! **Talk to your doctor or pharmacist if you have taken Sildenafil 50 mg as directed and are still not able to get and keep an erection.**

If you take more Sildenafil 50 mg than you should

If you take more tablets than recommended, contact your pharmacist or doctor immediately. Taking more than the recommended dose may result in an increase in side effects and/or their severity.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them. These side effects are usually mild to moderate and of a short duration.

STOP TAKING Sildenafil 50 mg and seek medical attention IMMEDIATELY if you experience any of the following SERIOUS side effects:

- **Chest pains:** this occurs uncommonly. If this occurs before, during or after intercourse get in a semi-sitting position and try to relax. Do **NOT** use nitrates to treat your chest pain.
- **A persistent and sometimes painful erection lasting longer than 4 hours:** this rarely occurs.
- **A sudden decrease or loss of vision:** this occurs rarely.
- **An allergic reaction:** this occurs uncommonly. Symptoms include sudden wheeziness, difficulty breathing or dizziness, swelling of the eyelids, face, lips or throat.
- **Serious skin reactions** such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Syndrome (TEN): this occurs rarely. Symptoms may include severe peeling and swelling of the skin, blistering of the mouth, genitals and around the eyes, fever.
- **Seizures or fits:** this occurs rarely.

Other side effects that have been reported

Very common (may affect more than 1 in 10 people): headache.

Common (may affect up to 1 in 10 people):
- nausea, indigestion, stuffy nose, dizziness
- facial flushing, hot flush (symptoms include a sudden feeling of heat in your upper body)
- colour tinge to vision, blurred vision, visual disturbance

Uncommon (may affect up to 1 in 100 people):
- vomiting, upper abdominal pain, gastro-oesophageal reflux disease (symptoms include heartburn)
- skin rash, pain in the arms or legs, nosebleed, feeling hot, feeling tired
- eye irritation, bloodshot eyes /red eyes, eye pain, seeing flashes of light, visual brightness, light sensitivity, watery eyes
- pounding heartbeat, rapid heartbeat, high blood pressure, low blood pressure
- muscle pain, feeling sleepy, reduced sense of touch, vertigo, ringing in the ears
- dry mouth, blocked or stuffy sinuses, inflammation of the lining of the nose (symptoms include runny nose, sneezing and stuffy nose)
- presence of blood in urine

Rare (may affect up to 1 in 1,000 people):
- fainting, dry nose, swelling of the inside of the nose, feeling irritable and sudden decrease or loss of hearing
- stroke, heart attack, irregular heartbeat, temporary decreased blood flow to parts of the brain
- feeling of tightening of the throat, numb mouth
- bleeding at the back of the eye, double vision, reduced sharpness of vision, abnormal sensation in the eye, swelling of the eye or eyelid, small particles or spots in your vision, seeing halos around lights, dilation of the pupil of the eye, discolouration of the white of the eye
- penile bleeding, presence of blood in semen

Cases of unstable angina (a heart condition) and sudden death have been reported rarely. Of note, most, but not all, of the men who experienced these side effects had heart problems before taking this medicine. It is not possible to determine whether these events were directly related to this medicine.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store SILDENAFIL 50 mg

Keep out of the sight and reach of children.

Do not store above 30°C.

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

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Sildenafil 50 mg contains

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

What Sildenafil 50 mg looks like and contents of the pack

The tablets are provided in blister packs containing 2, 4 or 8 tablets within a carton. Some pack sizes may not be marketed in your country.

Marketing Authorisation Holder and Manufacturer
[To be completed nationally]

Company Contact Address
[To be completed nationally]

This medicinal product is authorized in the Member States of the EEA under the following names:
<{Name of the Member Sate}> <{Name of the medicinal product}>

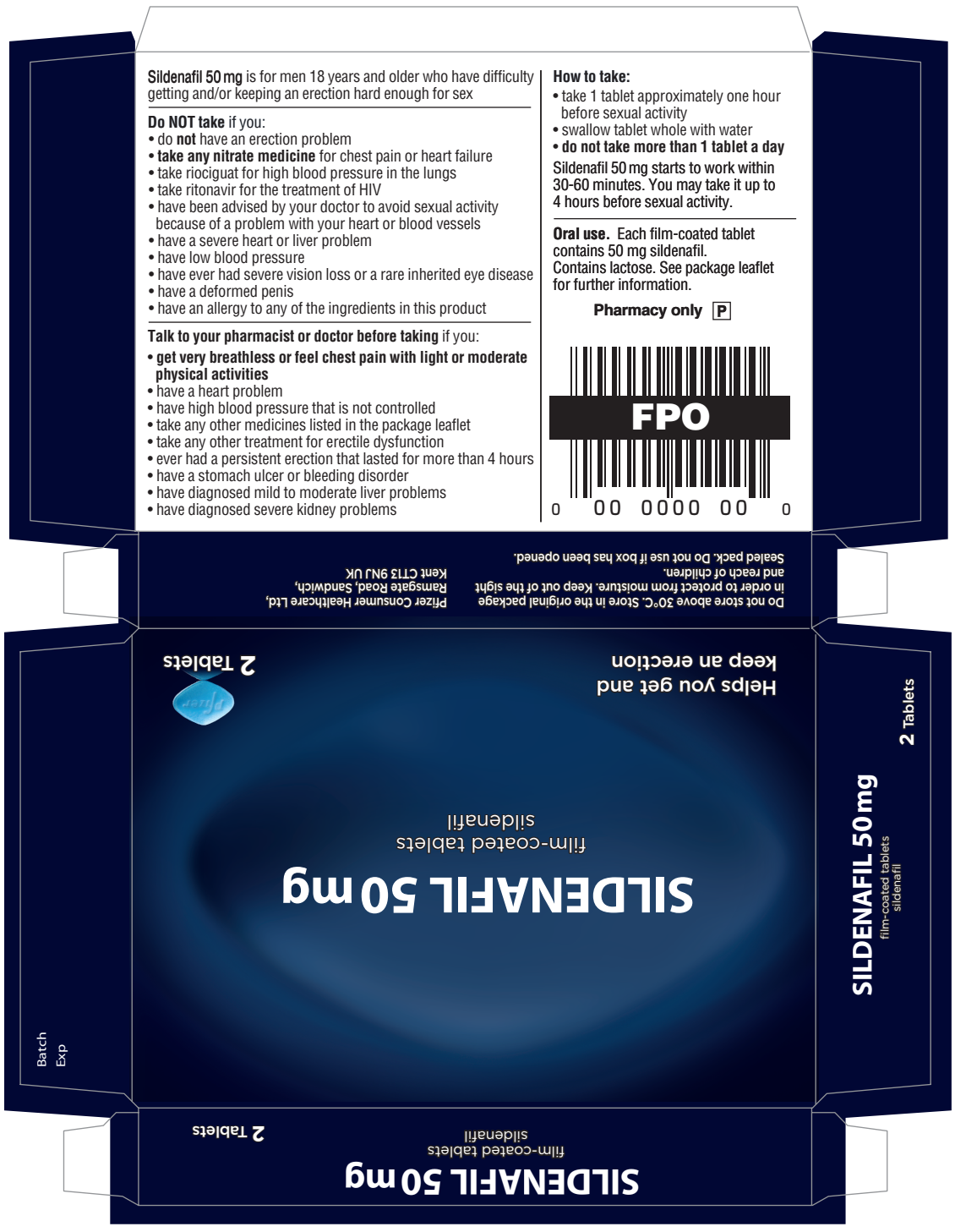
For the most recent product information, visit www.xxxx.com
[To be completed nationally]

This leaflet was last revised in <month YYY>

Pfizer Consumer Healthcare Ltd

PAA000000

BACK



Annex 3 - Label

Annex 4 - Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Sildenafil 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains sildenafil citrate equivalent to 50 mg of sildenafil.

Excipient(s) with known effect:.
Each 50 mg tablet contains 1.667 mg lactose (as monohydrate).

For the 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 "V50" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sildenafil 50 mg is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Sildenafil 50 mg to be effective, sexual stimulation is required.

4.2 Posology and method of administration

Posology

Use in adults
The recommended dose is one 50 mg tablet taken as needed with water approximately one hour before sexual activity.
The maximum recommended dosing frequency is once per day. If Sildenafil 50 mg is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2).

Patients should be advised that they may need to take Sildenafil 50 mg a number of times on different occasions (a maximum of one 50 mg tablet per day), before they can achieve a penile erection satisfactory for sexual activity. If after several attempts on different dosing occasions patients are still not able to achieve a penile erection sufficient for satisfactory sexual activity, they should be advised to consult a doctor.

Special populations

Elderly
Dosage adjustments are not required in elderly patients (≥ 65 years old).

Renal Impairment
No dosage adjustments are required for patients with mild to moderate renal impairment. However, since sildenafil clearance is reduced in individuals with severe renal impairment (creatinine clearance <30ml/min), individuals previously diagnosed with severe renal impairment must be advised to consult their doctor before taking Sildenafil 50 mg, since the 25 mg prescription dose may be more suitable for them (see section 4.4 for further information).

Hepatic Impairment
Sildenafil clearance is reduced in individuals with hepatic impairment (e.g. cirrhosis). Individuals previously diagnosed with mild to moderate hepatic impairment must be advised to consult their doctor before taking Sildenafil 50 mg, since the 25 mg prescription dose may be more suitable for them (see section 4.4 for further information).
The safety of sildenafil has not been studied in patients with severe hepatic impairment, and its use is therefore contraindicated (see section 4.3).

Paediatric population
Sildenafil 50 mg is not indicated for individuals below 18 years of age.

Use in patients taking other medicinal products
Pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, erythromycin, cimetidine).

With the exception of ritonavir, for which co-administration with sildenafil is contraindicated (see section 4.3), individuals receiving concomitant treatment with CYP3A4 inhibitors must be advised to consult their doctor before taking Sildenafil 50 mg, since the 25 mg prescription dose may be more suitable for them (see section 4.4 for further information).

In order to minimise the potential of developing postural hypotension in patients receiving alpha blocker treatment, patients should be stabilised on alpha blocker therapy prior to initiating sildenafil treatment. Thus, patients taking alpha blockers must be advised to consult their doctor before taking Sildenafil 50 mg since the 25 mg prescription dose may be more suitable for them (see sections 4.4 and 4.5).

Method of administration

For oral use.

4.3 Contraindications

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

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.

Co-administration of Sildenafil 50 mg with ritonavir (a highly potent P450 enzyme inhibitor) is contraindicated (see section 4.5).

The co-administration of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used by those men for whom sexual activity may be inadvisable, and these patients should be referred to their doctor. This includes patients with severe cardiovascular disorders such as a recent acute myocardial infarction (AMI) or stroke (6 months), unstable angina or severe cardiac failure.

Sildenafil should not be used in patients with severe hepatic impairment, hypotension (blood pressure < 90/50 mmHg) and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a

minority of these patients have genetic disorders of retinal phosphodiesterases). This is because the safety of sildenafil has not been studied in these sub-groups of patients, and its use is therefore contraindicated.

Sildenafil 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).

Sildenafil 50 mg should not be used in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).

Sildenafil 50 mg is not indicated for use by women.

The product is not intended for men without erectile dysfunction.

This product is not intended for men under 18 years of age.

4.4 Special warnings and precautions for use

Erectile dysfunction can be associated with a number of contributing conditions, e.g. hypertension, diabetes mellitus, hypercholesterolemia or cardiovascular disease. As a result, all men with erectile dysfunction should be advised to consult their doctor within 6 months for a clinical review of potential underlying conditions and risk factors associated with erectile dysfunction (ED). If symptoms of ED have not improved after taking Sildenafil 50 mg on several consecutive occasions, or if their erectile dysfunction worsens, the patient should be advised to consult their doctor.

Cardiovascular risk factors

Since there is a degree of cardiac risk associated with sexual activity, the cardiovascular status of men should be considered prior to initiation of therapy.

Agents for the treatment of erectile dysfunction, including sildenafil, are not recommended to be used by those men who with light or moderate physical activity, such as walking briskly for 20 minutes or climbing 2 flights of stairs, feel very breathless or experience chest pain.

The following patients are considered at low cardiovascular risk from sexual activity : patients who have been successfully revascularised (e.g. via coronary artery bypass grafting, stenting, or angioplasty), patients with asymptomatic controlled hypertension, and those with mild valvular disease. These patients may be suitable for treatment but should consult a pharmacist or doctor before resuming sexual activity.

Patients previously diagnosed with the following must be advised to consult with their doctor before resuming sexual activity: uncontrolled hypertension, moderate to severe valvular disease, left ventricular dysfunction, hypertrophic obstructive and other cardiomyopathies, or significant arrhythmias.

Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure. Men with these conditions must not use the product without consulting a doctor.

Sildenafil 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 sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

Priapism
Patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia), should consult a doctor before using agents for the treatment of erectile dysfunction, including sildenafil.

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

Concomitant use with other treatments for erectile dysfunction
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.

Effects on vision
Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors (see section 4.8). Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors (see section 4.8). Patients should be advised that in the event of any sudden visual defect, they should stop taking Sildenafil 50 mg and consult a physician immediately (see section 4.3).

Concomitant use with CYP3A4 inhibitors
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, they should be advised to consult a doctor before taking Sildenafil 50 mg as the 25 mg prescription dose may be more suitable for them (see section 4.5 for further information).

Concomitant use with alpha-blockers
Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration may lead to symptomatic hypotension in 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. Thus, patients taking alpha blockers should be advised to consult their doctor before taking Sildenafil 50 mg as the 25 mg prescription dose may be more suitable for them. Treatment should be stopped if symptoms of postural hypotension occur, and patients should seek advice from their pharmacist or doctor on what to do.

Effect on bleeding
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 the use of sildenafil is not recommended in those patients with history of bleeding disorders or active peptic ulceration, and should only be administered after consultation with a doctor.

Hepatic impairment

Patients with hepatic impairment must be advised to consult their doctor before taking Sildenafil 50 mg, since the 25 mg prescription dose may be more suitable for them (see section 4.2 and 5.2 for further information).

Renal impairment
Patients with severe renal impairment (creatinine clearance <30 mL/min), must be advised to consult their doctor before taking Sildenafil 50 mg, since the 25 mg prescription dose may be more suitable for them (see section 4.2 and 5.2 for further information).

Lactose
The film coating of the tablet contains lactose. Sildenafil 50 mg should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Use with alcohol
Drinking excessive alcohol can temporarily reduce a man's ability to get an erection. Men should be advised not to drink large amounts of alcohol before sexual activity.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sildenafil

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

In vivo studies
Pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, with the exception of individuals taking ritonavir for which co-administration with sildenafil is contraindicated, individuals must be advised to consult their doctor before taking Sildenafil 50 mg, since the 25 mg prescription dose may be more suitable for them.

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 Cmax and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200ng/mL, compared to approximately 5ng/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 sildenafil should not be co-administered with ritonavir (see section 4.3).

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil Cmax 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, Cmax, Tmax, 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, pharmacokinetic analysis showed no effect of concomitant treatment 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). In a study of healthy male volunteers, co-administration of the endothelin antagonist, bosentan, (an inducer of CYP3A4 [moderate], CYP2C9 and possibly of CYP2C19) at steady state (125 mg twice a day) with sildenafil at steady state (80 mg three times a day) resulted in 62.6% and 55.4% decrease in sildenafil AUC and Cmax, respectively. Therefore, concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of sildenafil.

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to result in a 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 (IC50 >150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after 100mg of sildenafil, it is unlikely that Sildenafil 50 mg 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).

Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is contraindicated (see section 4.3).

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.

In healthy male volunteers sildenafil at steady state (80mg tid) resulted in a 49.8% increase in bosentan AUC and a 42% increase in bosentan Cmax (125mg bid).

4.6 Pregnancy and lactation

Sildenafil 50 mg is not indicated for use by women.

There are no adequate and well-controlled studies in pregnant or breast-feeding women.
No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers (see section 5.1).

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 this medicine, before driving or operating machinery.

4.8 Undesirable effects

The safety profile of Sildenafil 50 mg is based on > 9,000 patients in > 70 double-blind placebo-controlled clinical studies. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, hot flush, visual disturbance, cyanopsia and vision blurred.

Adverse reactions from post-marketing surveillance has been gathered covering an estimated period >10 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.

Tabulated list of adverse reactions

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). 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	**Very common** ***(≥1/10)***	**Common** ***(≥1/100 and <1/10)***	**Uncommon** ***(≥1/1,000 and <1/100)***	**Rare** ***(≥1/10,000 and <1/1,000)***
Infections and infestations			Rhinitis	
Immune system disorders			Hypersensitivity	
Nervous system disorders	Headache	Dizziness	Somnolence, Hypoaesthesia	Cerebrovascular accident, Transient ischaemic attack, Seizure,* Seizure recurrence,* Syncope
Eye disorders		Visual colour distortions**, Visual disturbance, Vision blurred	Lacrimation disorders***, Eye pain, Photophobia, Photopsia, Ocular hyperaemia, Visual brightness, Conjunctivitis	Non-arteritic anterior ischaemic optic neuropathy (NAION)*, Retinal vascular occlusion*, Retinal haemorrhage, Arteriosclerotic retinopathy, Retinal disorder, Glaucoma, Visual field defect, Diplopia, Visual acuity reduced, Myopia, Asthenopia, Vitreous floaters, Iris disorder, Mydriasis, Halo vision, Eye oedema, Eye swelling, Eye disorder, Conjunctival hyperaemia, Eye irritation, Abnormal sensation in eye, Eyelid oedema, Scleral discoloration
Ear and labyrinth disorders			Vertigo, Tinnitus	Deafness

System Organ Class	**Very common** ***(≥ 1/10)***	**Common** ***(≥ 1/100 and <1/10)***	**Uncommon** ***(≥ 1/1,000 and <1/100)***	**Rare** ***(≥ 1/10,000 and <1/1,000)***
Cardiac disorders			Tachycardia, Palpitations	Sudden cardiac death*, Myocardial infarction, Ventricular arrhythmia*, Atrial fibrillation, Unstable angina
Vascular disorders		Flushing, Hot flush	Hypertension, Hypotension	
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Epistaxis, Sinus congestion	Throat tightness, Nasal oedema, Nasal dryness
Gastrointestinal disorders		Nausea, Dyspepsia	Gastro oesophagael reflux disease, Vomiting, Abdominal pain upper, Dry mouth	Hypoaesthesia oral
Skin and subcutaneous tissue disorders			Rash	Stevens-Johnson Syndrome (SJS)*, Toxic Epidermal Necrolysis (TEN)*
Musculoskeletal and connective tissue disorders			Myalgia, Pain in extremity	
Renal and urinary disorders			Haematuria	
Reproductive system and breast disorders				Penile haemorrhage, Priapism*, Haematospermia, Erection increased
General disorders and administration site conditions			Chest pain, Fatigue, Feeling hot	Irritability
Investigations			Heart rate increased	

*****Reported during post-marketing surveillance only
**Visual colour distortions: Chloropsia, Chromatopsia, Cyanopsia, Erythropsia and Xanthopsia
***Lacrimation disorders: Dry eye, Lacrimal disorder and Lacrimation increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: Urologicals; Drugs used in erectile dysfunction. ATC Code: G04B E03.

Mechanism of action
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.

Pharmacodynamic 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 100 mg doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE 2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

Clinical efficacy and safety
A clinical study was 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 Sildenafil 50mg in 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.

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

A double-blind, placebo-controlled exercise stress trial evaluated 144 patients with erectile dysfunction and chronic stable angina who regularly received anti-anginal medicinal products (except nitrates). The results, following a 100 mg dose, demonstrated no clinically relevant differences between sildenafil and placebo in time to limiting angina.

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 the 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 (see section 4.6).

Further information on clinical trials

In clinical trials sildenafil (doses 25 to 100 mg) 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.

Four clinical trials (148-102, 148-364 and 101/101B and A1481239) each directly compared the efficacy of fixed 50 mg doses of sildenafil and double-blind placebo, each taken approximately 1 hour prior to sexual activity by men with ED for treatment periods lasting 8-24 weeks. Efficacy was assessed by means of diaries used to capture details of each sexual event, and a sexual function questionnaire (now known as the International Index of Erectile Function) IIEF. Men were told that sexual stimulation was necessary for efficacy to occur, and that erections would not occur in absence of sexual stimulation. Compared to placebo, sildenafil 50 mg caused clinically and statistically

significant improvements in proportions of erections hard enough for sexual intercourse and erections lasting long enough to complete sexual intercourse. All the following results with sildenafil 50 mg were also clinically and statistically significantly different from placebo unless otherwise stated. Sildenafil 50 mg improved the men's confidence to get and keep an erection. Sildenafil 50 mg also improved men's satisfaction with sexual intercourse, orgasm, sexual relationship with partner and overall sex life. Sildenafil 50 mg had no clinically significant effect on sexual desire. Men (in whom sildenafil 50 mg was effective) reported improved function (increased hardness of erection with duration long enough to complete intercourse) after the first dose (40.8% for 50 mg and 14.6% for placebo). However some men only reported improvements after several (up to 8) doses (78.4% for 50 mg and 46.7% for placebo). Sildenafil 50 mg was effective at various times post-dose from less than 1 hour to up to 4 hours after administration. In the two studies that included assessment of quality of life (148-102, 148-364), men treated with sildenafil reported less distress associated with erection problems than men receiving placebo. One study (A1481239) used additional questionnaires to evaluate the effect of sildenafil on sexual performance and relationship with partner. In this study men taking sildenafil 50 mg 30 minutes to one hour prior to sexual activity reported improved quality of erections and satisfaction with sexual experience, improved relationship with partner, improved confidence and self–esteem and less anxiety about attempting sexual intercourse than men taking placebo. Effectiveness and satisfaction with treatment is maintained during follow on long-term treatment (one year and longer) (study 148-101C). In the study (148-101B) assessing partner satisfaction with intercourse, female partners of men treated with sildenafil 50mg reported improved satisfaction with sexual intercourse compared to partners of men treated with placebo.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Sildenafil 50 mg in all subsets of the paediatric population for the treatment of erectile dysfunction. See section 4.2 for information on paediatric use.

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.

Biotransformation
Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% that of the parent drug. 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 200% and 79% 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 (85%) 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 and development.

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°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 or 8 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Annex 5 - Checklist

Sildenafil 50mg Film-coated Tablets Pharmacy Checklist

The checklist can be used to help determine whether your patient is suitable for Sildenafil 50mg or whether he should be seen by a doctor for further advice. The Pharmacy Training Guide provides additional background information in relation to the supply of this product.

If the patient has previously been supplied with Sildenafil 50mg, he should be asked if anything has changed with respect to his health status or medicines usage. If there are no changes, there is no need to repeat this checklist prior to supply. Remind him to follow up with his doctor within the first 6 months of use. If any factors have changed, sections 2 - 4 of the checklist should be reviewed again.

1. Who is Sildenafil 50mg for?

Sildenafil 50mg is only intended for use by men over 18 years of age who are experiencing erectile dysfunction (ED) (i.e. difficulty in getting and/or maintaining an erection satisfactory for sexual performance). This product must not be supplied to men who do not have an erection problem.

It is important to confirm if the man is already receiving treatment for the condition. Men currently prescribed 50 mg of sildenafil can be supplied this product provided they do not take more than 50 mg daily. If the man is using a different dose of sildenafil or another ED treatment, he should be referred to his doctor.

2 .Check patient's cardiovascular (CV) health

If the patient answers **YES** to any of the following: **do not supply the product** and refer to the doctor. If you have any reason to consider, based on physical status, the patient should not be using this product, refer to the doctor.

Y N Has your doctor advised that you are not fit enough for any physical and/or sexual activity?

Y N Do you feel very breathless or experience chest pain with light or moderate physical activity, such as walking briskly for 20 minutes or climbing two flights of stairs?

Y N Have you had a heart attack or stroke within the last 6 months?

Y N Do you have any other heart problems or are you under a doctor's care for any of the following;

- uncontrolled high blood pressure, or low blood pressure
- unstable angina (chest pain) irregular heart beat or palpitations (arrhythmia)
- a problem with one of the valves in your heart (valvular heart disease)
- a problem where the heart muscle becomes inflamed and does not work as well as it should (cardiomyopathy)
- heart problems causing blood flow issues (e.g. left ventricular outflow obstruction, aortic narrowing) or severe cardiac failure

3. Check concomitant medication use

Please check what other medicines the man is taking.

If the patient answers **YES** to any of the following: **do not supply the product** and refer to the doctor

Y N Are you taking nitrates for chest pain?

Y N Are you using drugs called "poppers" for recreational purposes (e.g. amyl nitrite)?

Y N Are you taking riociguat for lung problems?

Y N Are you taking ritonavir for HIV infection?

Y N Are you taking any CYP3A4 inhibitors (e.g. erythromycin, saquinavir, cimetidine, diltiazem, fluconazole.)?

Y N Are you taking any Alpha-blockers (e.g. doxazosin, tamsulosin)?

4. Check concomitant conditions

Men answering **YES** to any of the following: **do not supply the product** and refer to the doctor

Y N Do you have Peyronie's disease or any other deformation of the penis?

Y N Have ever had loss of vision because of damage to the optic nerve (such as non-arteritic anterior ischaemic optic neuropathy (NAION)) or have an inherited eye disease (such as retinitis pigmentosa)?

Y N Do you have galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption?

Y N Do you have previously diagnosed hepatic (liver) disease (including cirrhosis of the liver) or severe renal (kidney) impairment?

Y N Do you have any of the following; sickle cell anaemia, multiple myeloma or leukaemia?

Y N Do you have any bleeding issues (e.g. haemophilia) or have active stomach ulcers?

Additional Advice

You should consider possible causes of erectile dysfunction such as undiagnosed depression, anxiety, excessive alcohol use and taking certain medicines. Examples of classes of medicines that cause ED include diuretics, anti-hypertensives, corticosteroids, anticonvulsants and recreational drugs. Whilst it may be appropriate to supply the product, you should provide lifestyle advice and/or recommend a follow up with a doctor.

Points for counselling and other information

Having ascertained that your patient is suitable for Sildenafil 50mg, this information will help ensure the product is used optimally. Please refer patients to the in-pack patient information leaflet.

Using Sildenafil 50mg

- The recommended dose is one 50 mg tablet taken as needed with water, approximately one hour before sexual activity. Avoid taking with a heavy meal.
- The maximum recommended dosing frequency is once per day. If Sildenafil 50mg is taken with food, the onset of activity may be delayed compared to the fasted state.
- Men should be advised that they may need to take Sildenafil 50mg a number of times on different occasions (a maximum of one 50 mg tablet per day), before they can achieve a penile erection satisfactory for sexual activity. If after several attempts on different dosing occasions patients are still not able to achieve a penile erection sufficient for satisfactory sexual activity, they should be advised to consult a doctor.
- Remind patients that Sildenafil 50mg is only intended for men over 18 who have ED. Men who do not have ED will not benefit from using this product.
- Remind patients about common side effects. These include headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, visual disturbance, cyanopsia (blue tinted vision) and blurred vision.

  If any of these become a concern, advise the patient to talk with a pharmacist or doctor.

Men should be advised to STOP TAKING Sildenafil 50mg and seek medical attention IMMEDIATELY if they experience any of the following SERIOUS side effects

- Chest pains: If this occurs before, during or after intercourse get in a semi-sitting position and try to relax.
- Do NOT use nitrates to treat your chest pain.
- A persistent and sometimes painful erection lasting longer than 4 hours
- A sudden decrease or loss of vision
- An allergic reaction; Symptoms include sudden wheeziness, difficulty breathing or dizziness, swelling of the eyelids, face, lips or throat.
- Serious skin reactions such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Syndrome (TEN): Symptoms may include severe peeling and swelling of the skin, blistering of the mouth, genitals and around the eyes, fever.
- Seizures or fits.

Follow up advice for all men

- Erectile dysfunction (ED) can be associated with a number of contributing conditions, e.g. hypertension, diabetes mellitus, hypercholesterolemia or cardiovascular disease. As a result, all men with ED should be advised to consult their doctor within 6 months for a clinical review of potential underlying conditions and risk factors associated with ED.
- Provide appropriate advice on lifestyle factors and general healthy living
  – losing weight,
  – giving up smoking,
  – cutting back on alcohol/recreational drugs,
  – exercising regularly,
  – reducing stress.
- You may also want to check if the man is buying products from unregulated sources. It is important to explain these products are not tested for their safety or effectiveness and may not contain the ingredients listed within them and are therefore potentially dangerous, unlike product sourced from a pharmacy and medicines obtained via prescription from the doctor.

Advice for Men who have not been given the product

Most men who are not suitable to be given this product should go to their doctor for a review as their erectile dysfunction might be caused by another condition such as high blood pressure or heart disease. You can provide these men with a record of the discussion to take to their doctor.