Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Sildenafil 50mg Film-coated Tablets

(sildenafil)

PL 16028/0165

Galpharm Healthcare Ltd

LAY SUMMARY

Sildenafil 50mg Film-coated Tablets

(sildenafil)

This is a summary of the Public Assessment Report (PAR) for Sildenafil 50mg Film-coated Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Sildenafil Film-coated Tablets in this lay summary for ease of reading.

For practical information about using Sildenafil Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Sildenafil Film-coated Tablets and what are they used for?
This application is the same as Sildenafil Accord 50mg Film coated Tablets (PL 20075/0199) which is already authorised.

The Company responsible for Sildenafil Accord 50mg Film coated Tablets has agreed that its scientific data can be used as the basis for the grant of an identical licence for Sildenafil Film-Coated Tablets.

Sildenafil Film-coated Tablets 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 many things, including 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 Film-coated Tablets 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 the penis, allowing blood to flow into the penis when the patient gets sexually excited and causing an erection. Sildenafil 50 mg Film-coated Tablets will only help the patient to get an erection if the patient is sexually excited (stimulated).

How do Sildenafil Film-coated Tablets work?
Sildenafil Film-coated Tablets 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 the penis, allowing blood to flow into the penis when the patient gets sexually excited and causing an erection. Sildenafil 50 mg Film-coated Tablets will only help the patient to get an erection if the patient is sexually excited (stimulated).

How are Sildenafil Film-coated Tablets used?
The pharmaceutical form of this medicine is film-coated tablets and the route of administration is oral (given by mouth).

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

The patient will not get an erection just by taking Sildenafil Film-Coated Tablets. This medicine will only help the patient get an erection if the patient is sexually aroused.

The patient and their partner should engage in foreplay just as the patient would if they 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. The patient may take it up to 4 hours before sexual activity.

The patient should remember to relax and be patient. There is no rush. If the patient is not successful the first time, they should try to have sex again, but remember that they can only take 1 tablet a day. For most men, Sildenafil Film-coated Tablets will work the first or second time they try it. If it has been some time since the patient was able to get or keep an erection, it may take a couple of attempts before they are able to achieve an erection. If the patient feels the effect of Sildenafil Film-coated Tablets is too strong or too weak, they should talk to their pharmacist or doctor.

For further information on how Sildenafil Film-coated Tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can be obtained without a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Sildenafil Film-Coated Tablets have been shown in studies?
Sildenafil Film-coated Tablets are considered identical to the previously authorised product with the same benefits and risks. No new studies have been provided for Sildenafil Film-coated Tablets, however, reference is made to the studies for Sildenafil Accord 50mg Film coated Tablets.

What are the possible side effects of Sildenafil Film-coated Tablets?
Sildenafil Film-coated Tablets are considered to be identical to the previously authorised product with the same benefits and risks.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why were Sildenafil Film-coated Tablets approved?
The MHRA decided that the benefits of Sildenafil Film-coated Tablets are greater than the risks and recommended that this medicine is approved for use.

What measures are being taken to ensure the safe and effective use of Sildenafil Film-coated Tablets?
During the national assessment procedure, Sildenafil Film-coated Tablets were re-classified from a Prescription Only Medicine (legal status POM) to a Pharmacy (P) medicine; an annex following this report describes the reclassification in more detail.

A Risk Management Plan (RMP) has been developed to ensure that Sildenafil Film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

In addition to the safety information provided in the Sildenafil Film-coated Tablets product information, the RMP includes provision of pharmacists training material and a pharmacist checklist to ensure the safe and effective use of Sildenafil Film-Coated Tablets.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Sildenafil Film-coated Tablets
A Marketing Authorisation was granted in the UK on 19 September 2019

The full PAR for Sildenafil Film-coated Tablets follows this summary.

This summary was last updated in November 2019.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Sildenafil 50mg Film-coated Tablets (PL 16028/0165) could be approved.

The product is approved for the following indication:

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

In order for Sildenafil 50mg Film-coated Tablet to be effective, sexual stimulation is required.

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 for sildenafil to produce its intended beneficial pharmacological effects.

This combined application consists of a national abridged application and a reclassification application, which were submitted in parallel.

The national abridged application was submitted under Article 10c of Directive 2001/83/EC, as amended (an informed consent application). The application cross-refers to the reference product Sildenafil Accord 50mg Film coated Tablets (PL 20075/0199; legal status: Prescription Only Medicine), which is held and was originally granted in the UK to the Marketing Authorisation Holder Accord Healthcare Limited on 05 April 2011.

During the national assessment procedure, Sildenafil Film-Coated Tablets were re-classified from a Prescription Only Medicine (POM) to a Pharmacy (P) medicine. Details of the assessment of the reclassification is provided in 'Reclassification Annex'' at the end of this Scientific Discussion.

No new non-clinical or clinical data have been supplied and none are required for this informed consent application.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment (ERA). As the application is for an identical version of an already authorised product, no increase in environmental exposure is anticipated and no ERA is required for this informed consent application.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this/these product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A Marketing Authorisation was granted on 19 September 2019.

II. EXPERT REPORTS

The applicant cross-refers to the data for Sildenafil Accord 50mg Film coated Tablets (PL 20075/0199; Accord Healthcare Limited), to which this application is claimed to be identical. This is acceptable.

III. ASSESSOR'S COMMENTS ON THE PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPC is in line with that for the analogous legal status (Pharmacy) product Viagra Connect 50 mg film-coated tablets (PL 00165/0392), dated August 2018. Please refer to the Reclassification Annex for details of the reclassification assessment.

PATIENT INFORMATION LEAFLET

A leaflet mock-up has been provided which has been aligned with that for the analogous legal status (Pharmacy) product, Viagra Connect 50 mg film-coated tablets (PL 00165/0392), dated August 2018. Please refer to the Reclassification Annex for details of the reclassification assessment.

The user test report submitted for PL 20075/0199 have been provided.

LABEL

Label text and/or mock-ups have been provided.

IV. QUALITY ASPECTS

IV.1 Drug Substance

Drug substance specification

The sources of the active substance are in line with the cross-reference product. The proposed drug substance specification is consistent with the details registered for the cross-reference product.

IV.2. Drug Product

Name

The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes

Sildenafil 50mg Film-coated Tablets are available in polyvinylchloride/aluminium in a pack size of 2, 4 and 8 tablets. Not all pack sizes may be marketed.

The appearance of the product is identical to that of the cross-reference product.

The proposed shelf life of the product is 30 months with no special storage conditions.

The proposed packaging, shelf life and storage conditions are consistent with the details registered for the reference product.

Legal status

Pharmacy (P) medicine

Manufacturers

The proposed manufacturing sites are consistent with the details registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative compositions

The composition of the proposed product is consistent with the details registered for the cross-reference product.

Manufacturing process & control of critical steps

The proposed manufacturing processes and process controls are consistent with the details registered for the reference product and the maximum batch size is stated.

Finished product release/shelf life specification

The proposed finished product specification is in line with the details registered for the cross-reference product.

TSE Compliance
With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final product.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

V. NON-CLINICAL ASPECTS
As this application is submitted under Article 10c of Directive 2001/83/EC, as amended, (as an informed consent application) no new non-clinical data have been supplied and none are required.

VI. CLINICAL ASPECTS
As this application is submitted under Article 10c of Directive 2001/83/EC, as amended, (as an informed consent application) no new clinical data have been supplied and none are required.

VII. RISK MANAGEMENT PLAN (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional risks and safety measures have been proposed:

Additional risk minimisation measures
Essential information for pharmacists – The training guide provides information to pharmacists on the safe use of Sildenafil
Pharmacist checklist

This is acceptable.

VIII. USER CONSULTATION
A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to Sildenafil Accord 50mg Film coated Tablets (PL 20075/0199; Accord Healthcare Limited) and Viagra Connect 50 mg film-coated tablets (PL 00165/0392; Pfizer Consumer Healthcare Limited).The bridging report submitted by the applicant is acceptable.

IX. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. The benefit/risk balance is, therefore, considered to be the same as for the cross-reference product and positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the cross-reference product.

In accordance with Directive 2012/84/EU, the current approved UK version of the SmPC and PIL for this product is available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.



= Foil Board



= White Ink



= Foil Board



= White Ink

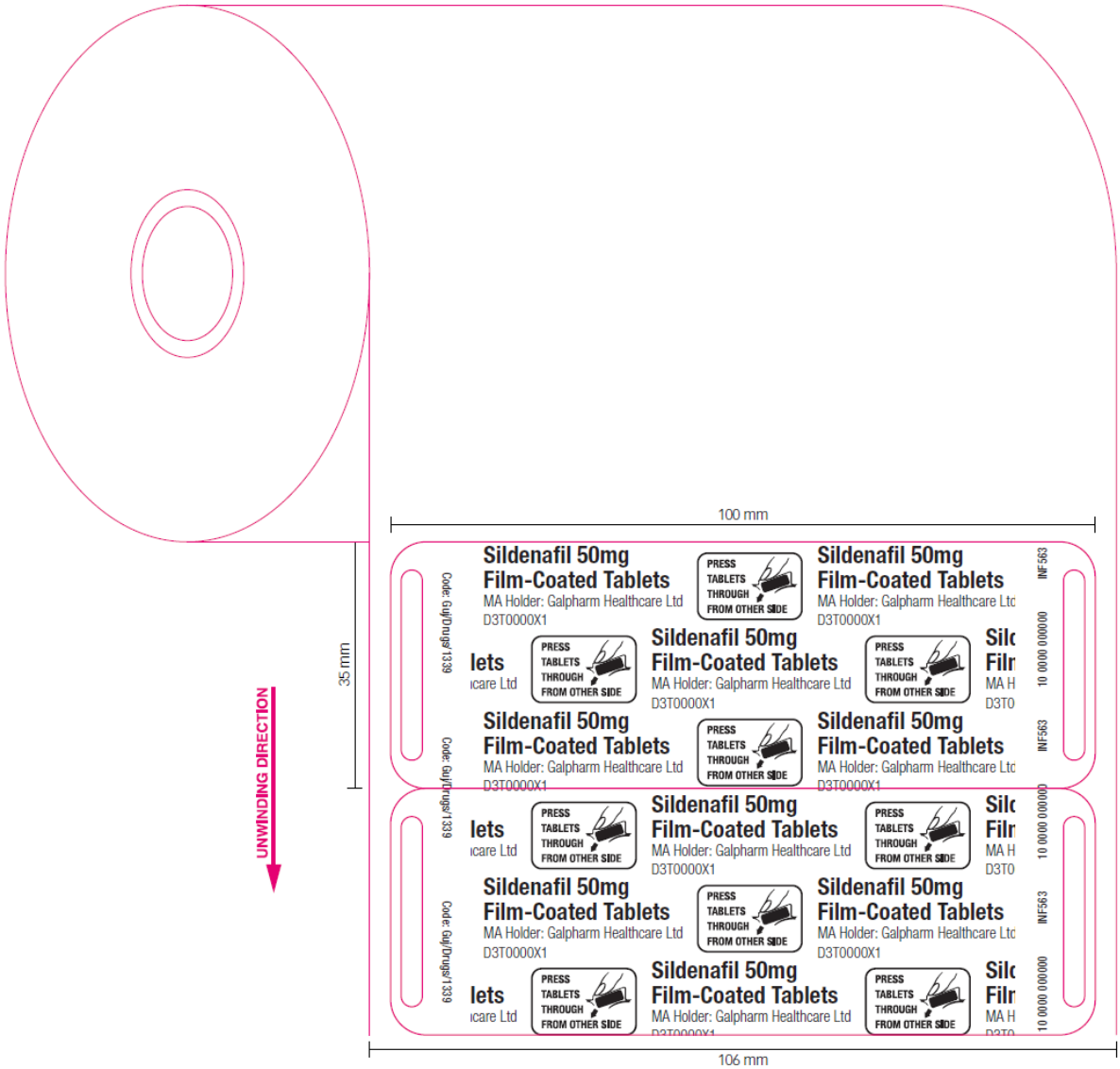

100 mm
35 mm
UNWINDING DIRECTION
Sildenafil 50mg
Film-Coated Tablets
MA Holder: Galpharm Healthcare Ltd
D3T0000X1
PRESS TABLETS THROUGH FROM OTHER SIDE
Code: Gal/Drugs/1339
INF563
10 0000 000000
106 mm

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**

RECLASSIFICATION ANNEX

Public Assessment Report

Prescription Only Medicine to Pharmacy Reclassification

Sildenafil 50mg Film-coated Tablets

Sildenafil (50mg)

PL 16028/0165 – 0001

GALPHARM HEALTHCARE LIMITED

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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 (https://yellowcard.mhra.gov.uk/).

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Alternative format versions of this report are available on request from reclassification@mhra.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 're-classification'. This is sometimes referred to as 'switching'. To decide on this change, MHRA may:

- take advice from the Commission on Human Medicines and its Expert Advisory Groups[1]
- 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 (i.e. not frequently or to a wide extent used correctly)
- 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

[1] The Commission on Human Medicines (CHM) is an advisory non-departmental public body, sponsored by the Department of Health. The CHM advises ministers on the safety, efficacy and quality of medicines. The CHM is supported in its work by Expert Advisory Groups (EAGs), covering various areas of medicine. The CHM's views are sought on reclassifications when more complex or new reclassifications of medicines are being proposed.

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 50mg Film-coated Tablets

Sildenafil 50mg Film-coated Tablets is a medicine to be taken by mouth for use in adult men with erectile dysfunction.

The full name of the medicine is Sildenafil 50mg Film-coated Tablets. In this document, we will call it 'Sildenafil Tablets'.

The Medicines and Healthcare Products Regulatory Agency (MHRA) considers this product sufficiently safe to be sold without prescription only from pharmacies, by or under the supervision of a pharmacist. This report outlines the evidence that the MHRA reviewed and which led to the decision to approve the application.

What is in Sildenafil Tablets?

Each tablet of the product contains 50mg of sildenafil citrate.

What are Sildenafil Tablets used for?

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 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.

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

Who has made the proposal?
The licence holder[2], Galpharm Healthcare Limited, applied to make Sildenafil Tablets available through pharmacies.

3. Proposed Terms of Reclassification

What are the details of this change?

Sildenafil Tablets will be made available through pharmacy outlets under the following conditions:

a) For oral use in the form of tablets

b) For use in adult men with erectile dysfunction
c) Maximum strength: 50mg
d) Maximum dose: 50 mg
e) Maximum daily dose: 50mg
f) Maximum pack size: 8 tablets

[2] A licence holder or marketing authorisation holder is the company with legal authorisation to make the medicine available to patients

4. How the application was assessed

A medicine will be non-prescription unless it fulfils 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)[3].

Assessment of suitability for Pharmacy availability

Viagra Connect, a sildenafil-containing product to treat erectile dysfunction was approved as a P medicine in 2017 with identical conditions of supply to those proposed for Sildenafil Tablets. There have been no additional safety concerns since the launch of this product in March 2018.

5. Further details on the application

Risk Management Plan

The application contained a risk management plan (RMP). RMPs contain information on a medicine's safety profile and one or more of the following:

- How any risks identified in the safety profile will be prevented or minimised in patients
- Plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine
- Risk factors for side effects
- Measuring the effectiveness of measures taken to prevent or minimise risks

Viagra Connect was reclassified as a P product under the following conditions for risk minimisation measure:

- The main risks associated with the product and proposed additional warnings on the labelling and patient information leaflet
- A pharmacist training guide
- A checklist that can be used for the supply of the product
- A survey-based study to assess the utility and effectiveness of the above proposed pharmacy risk minimisation material in conveying the key messages to pharmacists and how these impact on self-reported pharmacy practice

Since the data collection period of the study was completed during the processing of this application a separate study was not required to be undertaken as part of this reclassification. However, any findings from the results of the Viagra Connect study that require changes to the terms of the Marketing Authorisation for Viagra Connect will also apply to this product. The remaining risk minimisation measures are aligned with those of Viagra Connect.

[3] The Human Medicines Regulations 2012. http://www.legislation.gov.uk/uksi/2012/1916/contents/made

6. Reasons for not seeking advice from the Commission on Human Medicines

No major issues have been identified in the assessment of this application for Sildenafil Tablets as a P medicine based on the following reasons:

- Viagra Connect, a sildenafil-containing product to treat erectile dysfunction was approved as a P product in 2017
- The proposed indication, dose, route of administration, strength, duration of treatment and maximum pack size are as per Viagra Connect
- CHM were consulted on the reclassification of Viagra Connect to a P product. No additional changes have been made to the product information of Sildenafil Tablets which would require additional advice from CHM
- Since the reclassification of Viagra Connect, no additional safety concern has been raised as a result of its availability as a P product

7. Conclusion

The MHRA has taken the decision to approve Pharmacy legal status for Sildenafil Tablets under the following conditions:

a) For oral use in the form of tablets

b) For use in adult men with erectile dysfunction
c) Maximum strength: 50mg
d) Maximum dose: 50 mg tablet
e) Maximum daily dose: 50mg
f) Maximum pack size: 8 tablets

Medicines and Healthcare products Regulatory Agency
September 2019