



Public Assessment Report

UKPAR

Sildenafil Crescent 25mg film-coated tablets
Sildenafil Crescent 50mg film-coated tablets
Sildenafil Crescent 100mg film-coated tablets

(Sildenafil citrate)

UK Licence No: PL 20416/0500-0502

Crescent Pharma Limited

LAY SUMMARY

Sildenafil Crescent 25mg film-coated tablets
Sildenafil Crescent 50mg film-coated tablets
Sildenafil Crescent 100mg film-coated tablets

(sildenafil citrate, film-coated tablet, 25 mg, 50 mg or 100 mg)

This is a summary of the Public Assessment Report (PAR) for Sildenafil Crescent 25mg film-coated tablets (PL 20416/0500), Sildenafil Crescent 50mg film-coated tablets (PL 20416/0501) and Sildenafil Crescent 100mg film-coated tablets (PL 20416/0502). It explains how Sildenafil Crescent 25mg, 50mg and 100mg film-coated tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Sildenafil Crescent 25mg, 50mg and 100mg film-coated tablets.

For ease of reading, the products will be collectively referred to as 'Sildenafil' throughout the remainder of this lay summary.

For practical information about using Sildenafil patients should read the package leaflet or contact their doctor or pharmacist.

What is Sildenafil and what is it used for?

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

These applications are the same as Lepak 25mg, 50 mg and 100 mg film-coated tablets (PL 19156/0105–0107; Jubilant Pharmaceuticals NV, Belgium), which are already authorised in the EU. The licence holder (Jubilant Pharmaceuticals NV, Belgium) for Lepak 25 mg, 50 mg and 100 mg film-coated tablets; PL 19156/0105-0107) has agreed that its scientific data can be used as a basis for the grant of identical licences for Sildenafil (PL 20416/0500-0502).

How does Sildenafil work?

This medicine contains the active ingredient called sildenafil which belongs to a group of medicines called phosphodiesterase type 5 (PDE 5) inhibitors. It works by helping to relax the blood vessels in the penis, allowing blood to flow into the penis when the male patient gets sexually excited. Sildenafil will only help the patient to get an erection if they are sexually stimulated.

How is Sildenafil used?

The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

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

The usual starting dose is 50 mg. The patient should not take Sildenafil more than once a day.

The patient should take a Sildenafil tablet about one hour before they plan to have sex.

The patient should swallow the tablet whole with a glass of water.

If the patient feels that the effect of Sildenafil is too strong or too weak, they should talk to their doctor or pharmacist.

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

If Sildenafil does not help the patient to get an erection, or if their erection does not last long enough for them to complete sexual intercourse they should tell their doctor.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

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

What benefits of Sildenafil have been shown in studies?

Sildenafil is considered identical to previously authorised Lekap 25 mg, 50 mg and 100 mg film-coated tablets (Jubilant Pharmaceuticals NV), with the same benefits and risks. So no new studies have been provided for Sildenafil but reference is made to the studies for Lekap 25 mg, 50 mg and 100 mg film-coated tablets (Jubilant Pharmaceuticals NV).

What are the possible side effects from Sildenafil?

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Sildenafil is considered to be identical to the previously authorised applications for Lekap 25 mg, 50 mg and 100 mg film-coated tablets (Jubilant Pharmaceuticals NV) with the same benefits and risks.

For a full list of all the side effects reported with Sildenafil see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

Why is Sildenafil approved?

The MHRA decided that the benefits of Sildenafil are greater than the risks and recommended that it is approved for use.

What measures are being taken to ensure the safe and effective use of Sildenafil?

A Risk Management Plan has been developed to ensure that Sildenafil is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Sildenafil including the appropriate precautions to be followed by healthcare professionals and patients.

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

Other information about Sildenafil

Marketing Authorisations were granted in the UK on 29 June 2018.

The full PAR for Sildenafil follows this summary.

For more information about treatment with Sildenafil read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2018.

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Crescent Pharma Limited Marketing Authorisations for the medicinal products Sildenafil Crescent 25mg film-coated tablets (PL 20416/0500), Sildenafil Crescent 50mg film-coated tablets (PL 20416/0501) and Sildenafil Crescent 100mg film-coated tablets (PL 20416/0502) on 29 June 2018. For ease of reading, the products may be collectively referred to as ‘Sildenafil’ in this scientific discussion.

The products are indicated for 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 to be effective, sexual stimulation is required.

These applications were submitted as simple abridged (informed consent) applications according to Article 10c of Directive 2001/83/EC, as amended.

The applications cross-refer to the reference products for Lepak 25 mg, 50 mg and 100 mg film-coated tablets (PL 19156/0105-0107; Jubilant Pharmaceuticals NV) which were first authorised in the UK on 04 July 2011.

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.

No new data were submitted nor were necessary to be submitted for the applications, as the data are identical to the data for the previously granted cross-referenced products.

II QUALITY ASPECTS

II.1 Introduction

These are abridged applications for Sildenafil (PL 20416/0500-0502) submitted under Article 10c of Directive 2001/83/EC, as amended.

The applications cross-refer to the reference products Lepak 25 mg, 50 mg and 100 mg film-coated tablets (PL 19156/0105-0107; Jubilant Pharmaceuticals NV), which were first authorised 04 July 2011. The applications are considered valid.

II.2. Drug Substance

Drug substance specifications

The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

II.3. Medicinal Product

Name

The proposed product names for these applications are Sildenafil Crescent 25mg, 50mg and 100mg film-coated tablets. The product has been named in line with current requirements.

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

Each film-coated tablet contains 25 mg, 50 mg or 100 mg of the active substance sildenafil (as citrate). All strengths of the finished product are packed in polyvinyl chloride (PVC)/aluminium foil blisters in cartons of 4 or 8 film-coated tablets. Not all pack sizes may be marketed.

The proposed shelf life of the unopened product is 5 years with no special storage conditions.

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

Legal status

Prescription Only Medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company

Crescent Pharma Limited, Units 3 & 4, Quidhampton Business Units, Polhampton Lane, Overton, Hampshire RG25 3ED, United Kingdom.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory CV has been provided.

Manufacturers

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

Qualitative and quantitative compositions

The proposed compositions are consistent with the details registered for the cross-reference products.

Manufacturing process

The proposed manufacturing processes are consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

Finished product/shelf-life specifications

The proposed finished product specifications are in line with the details registered for the cross-reference products.

TSE Compliance

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during production of lactose monohydrate.

This is consistent with the cross-reference products.

Bioequivalence

No bioequivalence data are required to support these simple abridged applications because the proposed products are manufactured to the same formulae utilising the same processes as the cross-reference products, Lepak 25mg, 50 mg and 100 mg film-coated tablets (Jubilant Pharmaceuticals NV).

Product Name and Appearance

See Section II.3 'Medicinal Product; Name' for details of the proposed product names. The appearance of each product is identical to the respective cross-reference product.

Summaries of Product Characteristics (SmPCs)

The proposed Summaries of Product Characteristics are consistent with the details registered for the cross-reference products.

Patient Information Leaflet (PIL) and LabellingPIL

The PIL has been prepared in line with the details registered for the cross-reference products.

Carton and label

The proposed artwork is consistent with the artwork registered for the cross-reference products and complies with statutory requirements. In line with current legislation, the applicant has also included the names of the products in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The data submitted with the applications is acceptable. The grant of Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS**Introduction**

As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Ecotoxicity/environmental risk assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are identical versions of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

Discussion on the non-clinical aspects

The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS**Introduction**

As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Sildenafil.

A summary of safety concerns is listed in the table below:

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Hypersensitivity (e.g. severe skin reaction as Steven-Johnson syndrome and toxic epidermal necrolysis) • Hypotension/ increased hypotensive effect • Serious cardiovascular events • Priapism • Sudden decrease or loss of hearing • Visual defects or Non-arteritic anterior ischaemic optic neuropathy (NAION)
Important potential risks	<ul style="list-style-type: none"> • Increased risk of incident melanoma
Missing information	<ul style="list-style-type: none"> • Use in patients with severe hepatic impairment • Effect of use in patients with bleeding disorders or active peptic ulceration • Use in patients with hypotension (blood pressure <90/50mmHg), recent stroke, myocardial infarction or <i>retinitis pigmentosa</i>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended.

V User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the PIL for Lepak 25 mg, 50 mg and 100 mg film-coated tablets (Jubilant Pharmaceuticals NV). The bridging report submitted by the applicant is acceptable.

VI Overall conclusion, benefit/risk assessment 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. Extensive clinical experience with sildenafil citrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for these medicines is presented below:

BRAILLE

Sildenafil
Film-coated tablets

25mg

Each film-coated tablet contains 25mg of sildenafil (as citrate).
Also contains lactose.

4 Film-coated tablets

Crescent
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BRAILLE

Sildenafil
Film-coated tablets

Each film-coated tablet contains
25mg of sildenafil (as citrate).

Also contains lactose.

8 Film-coated tablets

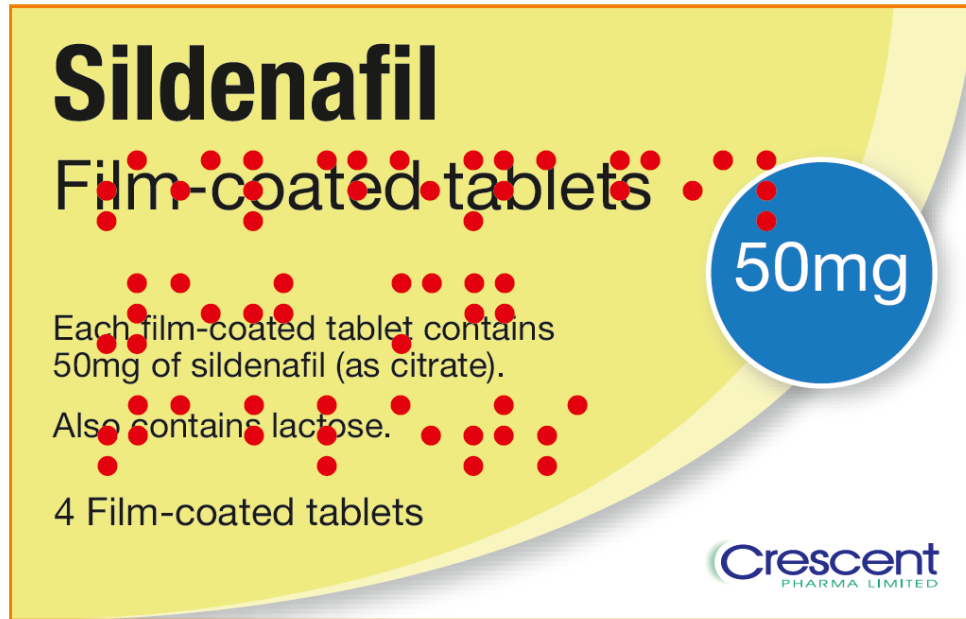
25mg

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Sildenafil
Film-coated tablets

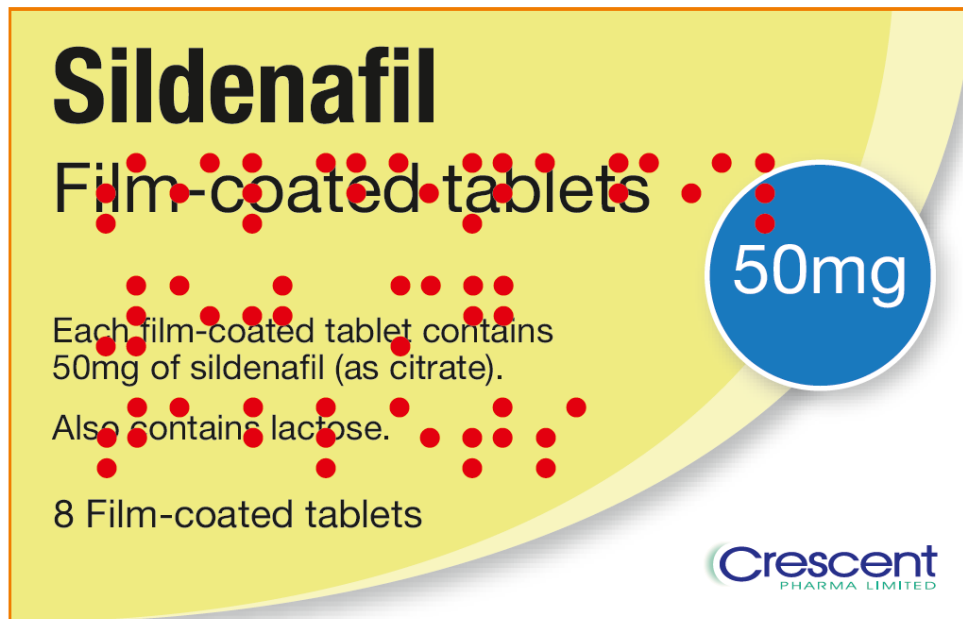
Each film-coated tablet contains 50mg of sildenafil (as citrate).
Also contains lactose.

4 Film-coated tablets

50mg

Crescent
PHARMA LIMITED

The graphic features a yellow background with a white curved bottom edge. Red dots are scattered across the text. A blue circle with a white border contains the text '50mg'. The Crescent Pharma Limited logo is in the bottom right corner.



Sildenafil
Film-coated tablets

Each film-coated tablet contains
50mg of sildenafil (as citrate).

Also contains lactose.

8 Film-coated tablets

50mg

Crescent
PHARMA LIMITED

The graphic features a yellow background with a white curved bottom edge. Red dots are scattered across the text. A blue circle with a white border contains the text '50mg'. The Crescent Pharma Limited logo is in the bottom right corner.

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BRAILLE

Sildenafil
Film-coated tablets

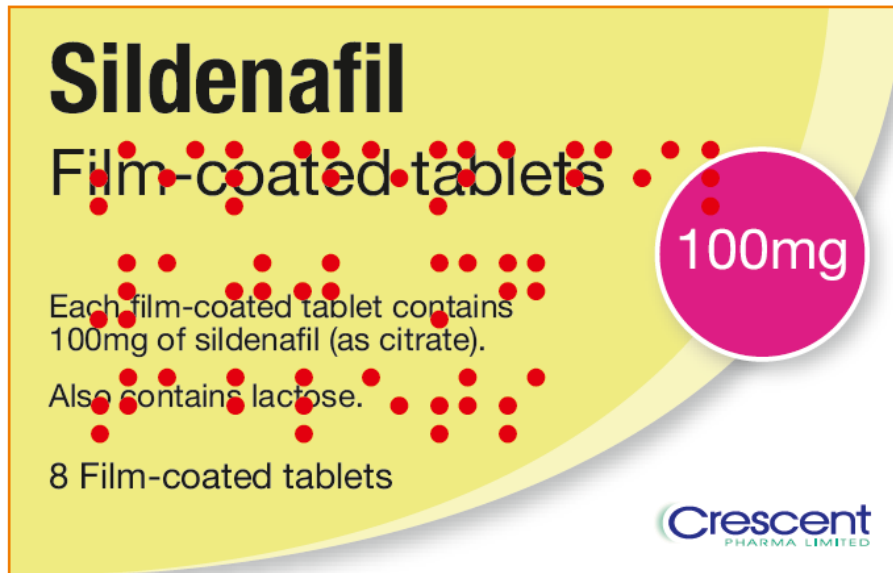
Each film-coated tablet contains
100mg of sildenafil (as citrate).
Also contains lactose.

4 Film-coated tablets

100mg

Crescent
PHARMACEUTICALS

BRAILLE



Sildenafil
Film-coated tablets

Each film-coated tablet contains 100mg of sildenafil (as citrate).
Also contains lactose.

8 Film-coated tablets

100mg

Crescent
PHARMA LIMITED

The image shows a yellow and white graphic for Sildenafil 100mg film-coated tablets. It features the product name 'Sildenafil' in large black font, followed by 'Film-coated tablets' in a smaller black font. Below this, there are three lines of text: 'Each film-coated tablet contains 100mg of sildenafil (as citrate).', 'Also contains lactose.', and '8 Film-coated tablets'. To the right of the text is a pink circular badge with '100mg' written in white. At the bottom right is the Crescent Pharma Limited logo, which consists of the word 'Crescent' in a blue sans-serif font above 'PHARMA LIMITED' in a smaller blue sans-serif font. The background of the graphic is yellow with a white curved shape on the right side.

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Sildenafil Crescent 25mg film-coated tablets
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Sildenafil Crescent 100mg film-coated tablets

(Sildenafil citrate)

UK Licence No: PL 20416/0500-0502

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome