

Public Assessment Report
Decentralised Procedure

**Sildenafil Ajanta Pharma 50 mg and 100 mg
Film-coated Tablets**

Sildenafil citrate

UK/H/4912/001-2/DC

UK licence no: PL 39315/0001-2

Ajanta pharma UK Limited

LAY SUMMARY

On 10th December 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) to Ajanta Pharma UK Limited for the medicinal products Sildenafil Ajanta Pharma 50 mg and 100 mg Film-coated Tablets (PL 39315/0001-2, UK/H/4912/001-2/DC). These are prescription-only medicine (POM)

Sildenafil Tablets belongs to a group of medicines called phosphodiesterase type 5 (PDE 5) inhibitors. It works by helping to relax the blood vessels in your penis, allowing blood to flow into your penis when you get sexually excited. Sildenafil tablets will only help you to get an erection if you are sexually stimulated. This product should not be taken if you do not have erectile dysfunction or if you are a woman.

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

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Sildenafil Ajanta Pharma 50 mg and 100 mg Film-coated Tablets outweigh the risks. Hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 4
Module 2: Summary of Product Characteristics	Page 5
Module 3: Patient Information Leaflet	Page 6
Module 4: Labelling	Page 7
Module 5: Scientific Discussion	Page 11
I. Introduction	
II. About the Product	
III. Scientific Overview and Discussion	
III.1. Quality aspects	
III.2. Non-clinical aspects	
III.3. Clinical aspects	
IV. Overall conclusion and Benefit-Risk Assessment	
Module 6 Steps taken after initial procedure	Page 18

Module 1

Product Name	Sildenafil Ajanta Pharma 50 mg and 100 mg Film-coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Sildenafil citrate
Form	Film-coated Tablets
Strength	50 mg and 100 mg Film-coated Tablets
MA Holder	Ajanta Pharma UK Limited 2 Cabot House, Compass Point Business Park, St. Ives, Cambridgeshire, PE27 5JL, UK
RMS	UK
CMS	Belgium, Bulgaria, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Republic of Ireland, Spain and The Netherlands
Procedure Numbers	UK/H/4912/001-2/DC
Timetable	Day 210 – 27 th September 2012

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

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



















Module 3

PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4

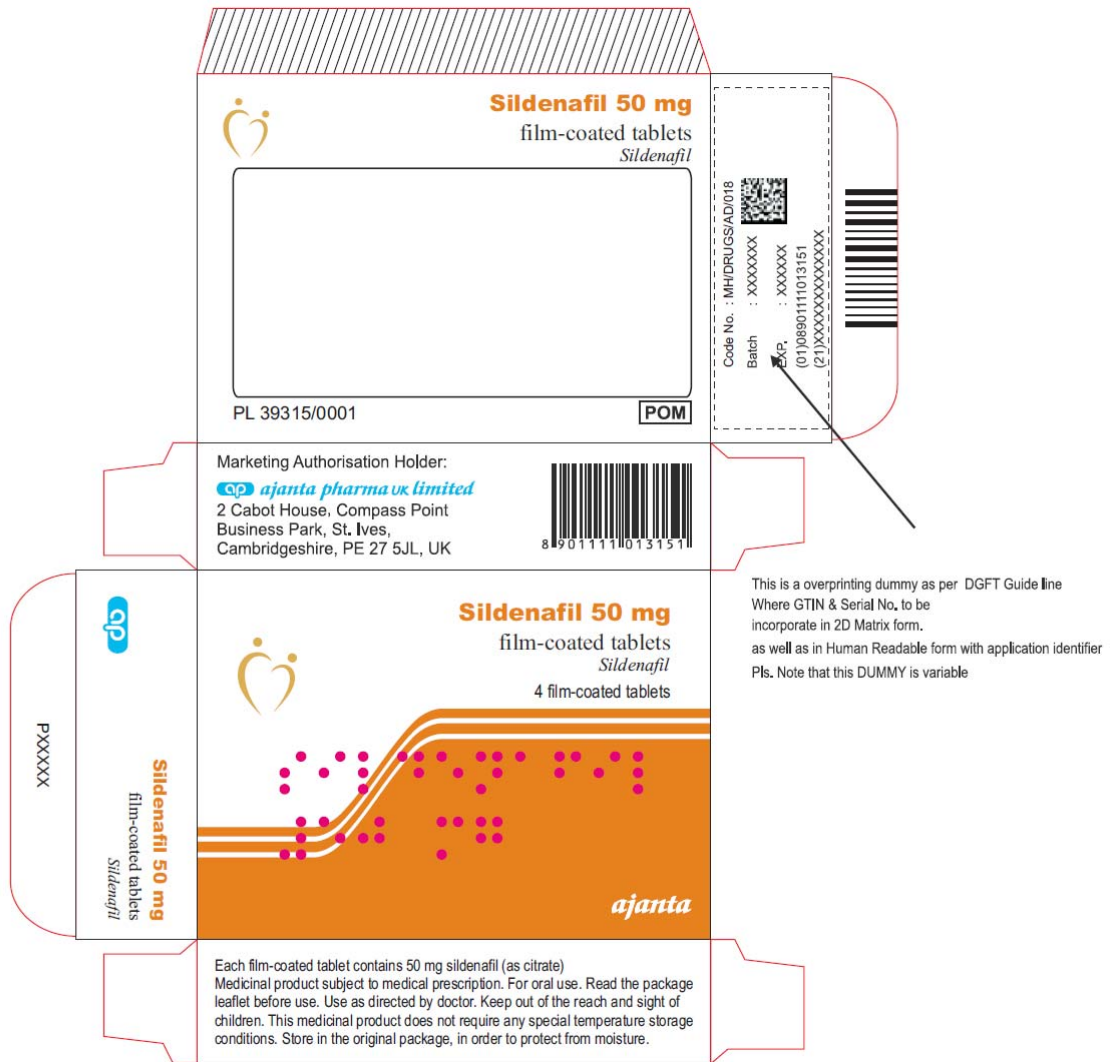
Labelling

<p> Sildenafil 50 mg film-coated tablets Sildenafil</p>	<p> Sildenafil 50 mg film-coated tablets Sildenafil</p>	<p>Code No. MH/DRUGS/AD/018  Ajanta Pharma UK Limited PXXXXX</p> <p>Code No. MH/DRUGS/AD/018  Ajanta Pharma UK Limited PXXXXX</p> <p>Code No. MH/DRUGS/AD/018  Ajanta Pharma UK Limited PXXXXX</p> <p>Code No. MH/DRUGS/AD/018  Ajanta Pharma UK Limited PXXXXX</p> <p>Code No. MH/DRUGS/AD/018  Ajanta Pharma UK Limited PXXXXX</p> <p>Code No. MH/DRUGS/AD/018  Ajanta Pharma UK Limited PXXXXX</p>
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EXP.

Batch



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Sildenafil Ajanta Pharma 50 mg and 100 mg Film-coated Tablets in the treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance, could be approved.

These applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended for Sildenafil Ajanta Pharma 50 mg and 100 mg Film-coated Tablets, claiming to be generic medicinal products of Viagra® 50 mg and 100 mg (EU/1/98/077/002-019), which were first licensed to Pfizer Limited, UK, on 14th September 1998 via a centralised procedure.

With UK as the RMS in these Decentralised Procedures (UK/H/4912/001-2/DC), Ajanta Pharma UK Limited applied for the Marketing Authorisations for Sildenafil Ajanta Pharma 50 mg and 100 mg Film-coated Tablets in Belgium, Bulgaria, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Republic of Ireland, Spain and The Netherlands.

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.

No new non-clinical or clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. A bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

For manufacturing sites inside and outside the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant respective licences for the above products at the end of procedure (Day 210 – 27th September 2012). After a subsequent national phase, the UK granted licences for these products on 10th December 2012 (PL 39315/0001-2).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Sildenafil Ajanta Pharma 50 mg and 100 mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Sildenafil citrate
Pharmacotherapeutic classification (ATC code)	Group: Drugs used in erectile dysfunction ATC Code: G04B E03
Pharmaceutical form and strength(s)	Film-coated Tablet, 50 mg, 100 mg
Reference numbers for the Decentralised Procedures	UK/H/4912/01-02/DC
Reference Member State	United Kingdom
Concerned Member States	Belgium, Bulgaria, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Republic of Ireland, Spain and The Netherlands.
Marketing Authorisation Number(s)	PL 39315/0001-2
Name and address of the authorisation holder	Ajanta Pharma UK Limited 2 Cabot House, Compass Point Business Park, St. Ives, Cambridgeshire, PE27 5JL,UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

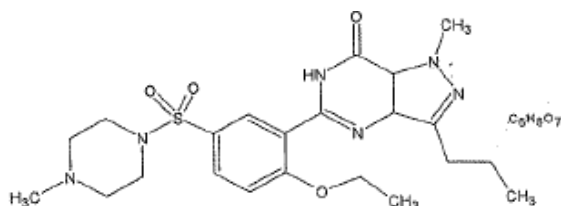
DRUG SUBSTANCE

INN: Sildenafil Citrate

Chemical Names:

- i) 1-[[3-(4,7-Dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4- methylpiperazine citrate
- ii) 5-[2-ethoxy-5-(4-methylpiperazinylsulfonyl) phenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*] pyrimidin-7-one citrate

Structure:



Molecular Formula: $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$

Molecular Weight: 666.7

General Properties: Sildenafil citrate is a white to off white crystalline powder, which is slightly soluble in water and methanol. Practically insoluble in n Hexane

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients sodium starch glycolate, povidone, microcrystalline cellulose, talc, magnesium stearate making up the tablet core; and film-coat

consisting of hypromellose, instacoat Sol IC-S-3788 Green (hypromellose, polyethylene glycol, talc, lake brilliant blue (E133), lake quinoline yellow (E104) and titanium dioxide (E171)) and titanium dioxide (E171).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Instacoat Sol IC-S-3788 Green which is covered by an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

All excipients used are of synthetic origin except sodium starch glycolate and magnesium stearate which are of vegetable origin and talc which is of natural origin. Appropriate statements of TSE / BSE risk have been provided by the suppliers.

Pharmaceutical Development

The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Viagra® 50 mg and 100 mg tablets, Pfizer Limited UK.

Comparative impurity and dissolution profiles have been presented for the test and reference products. The applicant has committed to provide comparative dissolution data of further batches upon commercialization.

Manufacture

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System

The finished product is packed in polyvinylchloride/aluminium foil blisters in cartons of 4 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years has been set. These medicinal products do not require any special temperature storage conditions. The products need to be stored in the original package, in order to protect from moisture. This is satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

The SPCs, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains

Marketing Authorisation Application (MAA) Forms

The MAA forms are pharmaceutically satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of sildenafil citrate are well known.

No new pre-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of an environmental risk assessment. This was satisfactory.

There are no objections to the approval of these products from a non-clinical point of view.

III.3 CLINICAL ASPECTS

Clinical Pharmacology

Pharmacokinetics

In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence study:

This is a single-dose, randomized, two-period, two-sequence, crossover bioequivalence study comparing the pharmacokinetics of the test product Sildenafil 100 mg film-coated tablets (Ajanta Pharma Limited, India) versus the reference product Viagra® 100 mg film-coated tablets (Pfizer Ltd., France) in healthy volunteers under fasting conditions.

Study drug was administered after an overnight fast with 240 ml water. The blood samples were collected pre-dose and at 0.167, 0.333, 0.500, 0.667, 1.000, 1.250, 1.500, 1.75., 2.000, 2.50, 3.000, 3.500, 4.000, 5.000, 6.000, 8.000, 10.000, 12.000 and 24.000 hours post dose in each period. There was a washout period of 14 days between study drug administrations.

**Geometric Means, Ratios and 90% Confidence Interval for Sildenafil (n=27)
On Log transformed Data**

Parameter (Units)	*Geometric Mean			90% Confidence Interval
	Test (A)	Reference (B)	Ratio (A/B)%	
C _{max}	675.37	634.63	106.4209	95.43-118.68 %
AUC _{0-t}	1884.41	1934.48	97.4114	89.05 – 106.55 %
AUC _{0-∞}	1988.41	2048.61	97.0612	88.94 – 105.93 %

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits. Bioequivalence has been shown for the test formulation (Sildenafil 100 mg Film-coated Tablets) and the reference formulation (Viagra 100 mg Film-coated Tablets). According to the Committee for Proprietary Medicinal Products Notes for Guideline on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), the results of the study for 100 mg formulation can be extrapolated to the other strength i.e 50 mg Film-coated Tablets.

Pharmacodynamics

No new data have been submitted and none are required for applications of this type.

Clinical Efficacy

No new data have been submitted and none are required.

Clinical Safety

No new data have been submitted and none are required.

Expert Report

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

The SmPCs, PIL and labelling are medically satisfactory and consistent with those for the reference products.

Marketing Authorisation Application (MAA) Forms

The MAA forms are medically satisfactory.

Conclusion

There are no objections to the approval of these products from a clinical point of view.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Sildenafil Ajanta Pharma 50 mg and 100 mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL

No new pre-clinical data were submitted and none are required for applications of these type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Sildenafil 100 mg Film-coated Tablets and the reference product, Viagra[®] 100mg Film-coated Tablets.

According to the Committee for Proprietary Medicinal Products Notes for Guideline on "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), the results of the study for 100 mg formulation can be extrapolated to the other strength i.e 50 mg Film-coated Tablets.

No new or unexpected safety concerns arose from these applications.

The SPCs and PIL are satisfactory and consistent with those of the reference products. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with sildenafil citrate is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome