

P. Drug Product (Sildenafil Citrate Comparator for PF-00446687-01, Tablets)

Sildenafil citrate film-coated tablets 100 mg will be used as a comparator. These tablets have the same qualitative and quantitative composition as those commercially available as Viagra® 100 mg (Marketing Authorisation EU/1/98/077/9-12).

The comparator sildenafil citrate film-coated tablets 100 mg will be manufactured using the same manufacturing process detailed in the Viagra marketing authorisation dossier (EU/1/98/077/9-12). The comparator sildenafil citrate film-coated tablets 100 mg differ from the commercial Viagra tablets 100 mg only in their appearance. The comparator sildenafil citrate film-coated tablets 100 mg are not debossed with VGR100 and only contain the Pfizer debossing on one face of the tablets, with the opposing face plain.

P.1. Description and Composition of the Drug Product (Sildenafil Citrate Comparator for PF-00446687-01 , Tablets)

The quantitative composition of the comparator, sildenafil citrate film-coated tablets 100 mg is given in Table CP.1-1.

Table CP.1-1. Composition of the Comparator - Sildenafil Citrate Film-Coated Tablet 10

Tablet Core		
Names of Ingredients	Unit Quantity (mg/tablet)	Reference to Quality Standards
Sildenafil Citrate		Pfizer
Microcrystalline Cellulose		Ph.Eur.
Calcium Hydrogen Phosphate (Anhydrous)		Ph.Eur.
Croscarmellose Sodium		Ph.Eur.
Magnesium Stearate		Ph.Eur.
Tablet Core Weight		N/A
Film-Coated Tablet		
Names of Ingredients	Unit Quantity (mg/tablet)	Reference to Quality Standards
Sildenafil Citrate 100 mg Tablet Core		N/A
Opadry® Blue (OY-LS-20921)		Pfizer ^(b)
Purified Water		USP
Opadry® Clear (YS-2-19114-A)		Pfizer ^(b)
Purified Water		USP.
Tablet Weight		N/A
Tablet Size/Shape	Blue, round diamond-shaped tablets (14.1 mm x 10.2 mm) debossed with “Pfizer” on one side and plain on the reverse	

^(a)Equivalent to 100 mg sildenafil based on a theoretical activity of 71.2%.

^(b)Specification provided in. Section P.4.1 Specifications (Non-Compndial Excipients)

^(c)Lost during processing and does not appear in the final product.

N/A = not applicable

P.2. Pharmaceutical Development

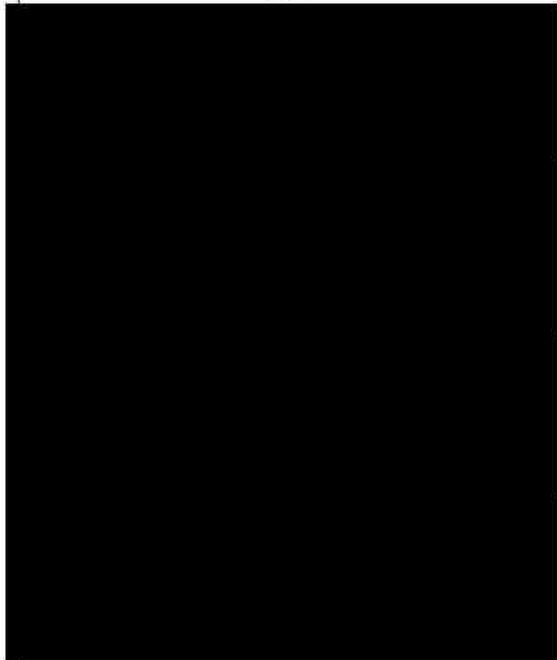
Pharmaceutical development for the formulation of the comparator sildenafil citrate film-coated tablet 100 mg is contained in the Marketing Authorisation (EU/1/98/077/9-12). The minor difference in the appearance (not debossing with VGR100) does not impact the dissolution profile, consequently dissolution data are not provided.

P.3. Manufacture

P.3.1. Manufacturer(s)

The addresses of the manufacturing or release sites for sildenafil citrate film-coated tablets 100 mg are provided in Table CP.3.1-2.

Table CP.3.1-2. Manufacturing Sites and Responsibilities for Release of the Comparator, Sildenafil Citrate Film-Coated Tablets 100 mg

Site	Site Responsibilities
	Manufacture and release testing
	Packaging and final release
	Packaging and final release
	Packaging and final release

P.3.2. Batch Formula

The batch size may vary depending on clinical demands. Current batch sizes are within the range of [REDACTED] of common blend. [REDACTED]

Table CP.3.2-3. Formula for a 140 Kg Batch of Sildenafil Citrate Film-Coated Tablets 100 mg

Name of Ingredient	Reference to Quality Standard	Quantity Required (g)
Sildenafil Citrate	Pfizer	[REDACTED]
Microcrystalline Cellulose	Ph. Eur.	
Calcium Hydrogen Phosphate (anhydrous)	Ph. Eur.	
Crosscarmellose Sodium	Ph. Eur.	
Magnesium Stearate	Ph. Eur.	
Opadry Blue	Pfizer ³	
Opadry Clear	Pfizer ³	

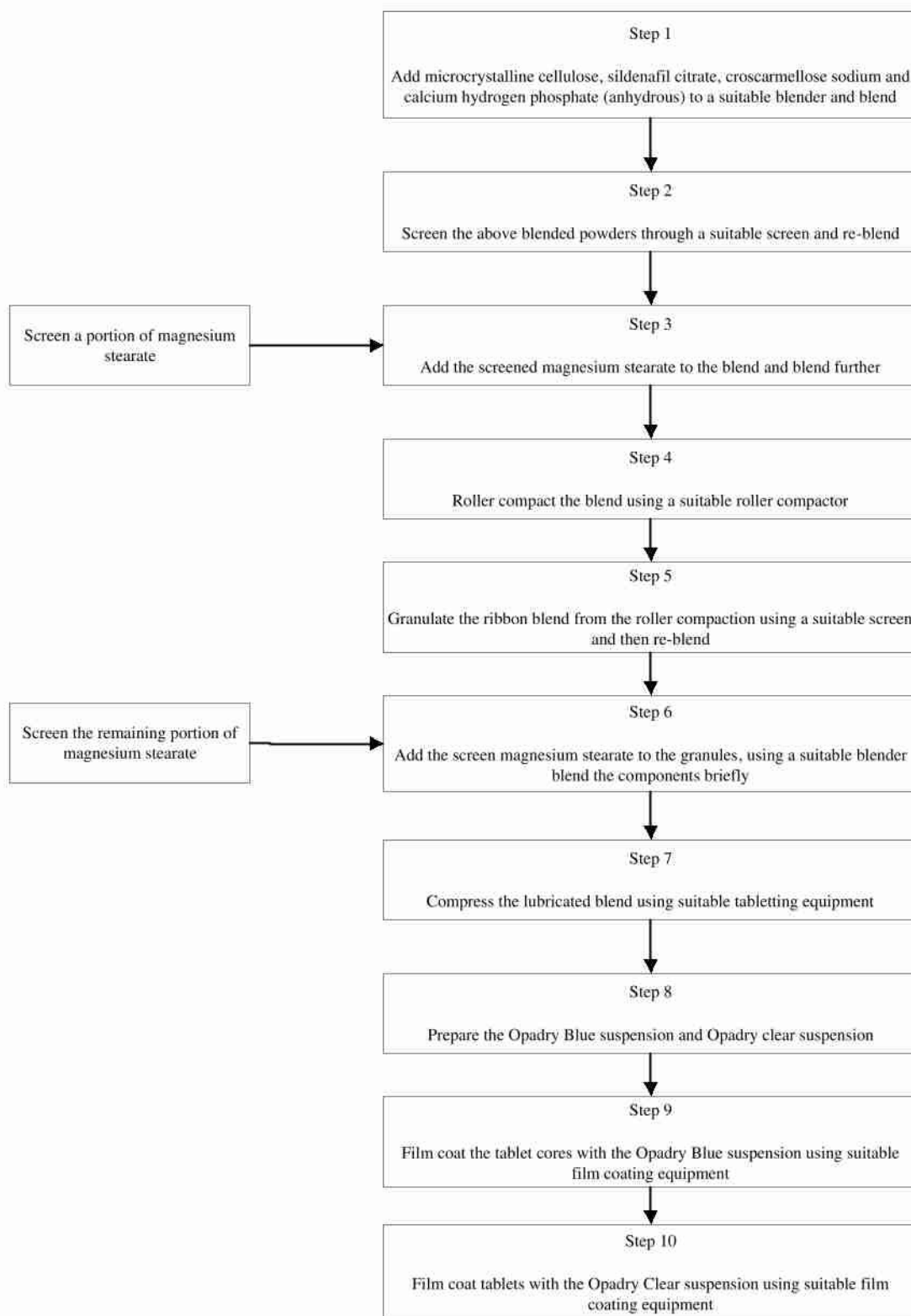
¹ 25% Used pre-roller compaction and 75% used post roller compaction

² Specifications provided in Section P.4.1 Specifications (Non-compendial Excipients)

³ An excess of both blue and clear coating suspensions are prepared and coating continues until a 2.5 %w/w blue coat and a 0.75 %w/w clear coat have been added sequentially

P.3.3. Method of Manufacture

Flow diagram for the manufacturing process for comparator tablet is outlined below:



P.4. Control of Excipients**P.4.1. Specification****Compendial Excipients**

Microcrystalline cellulose, croscarmellose sodium and calcium hydrogen phosphate (anhydrous) and magnesium stearate, all meet the requirements of the Ph. Eur. Purified Water meets the requirements of the USP.

Non-Compendial Excipients**Table CP.4.1-4. Composition of Opadry® Blue (OY-LS-20921)**

Name of Ingredient	Reference to Quality Standard	% w/w
Lactose Monohydrate	Ph. Eur.	
Hydroxypropyl methylcellulose 2910 (15 cP)	Ph. Eur.	
Titanium Dioxide (E 171)	Ph. Eur.	
Glycerol Triacetate	Ph. Eur.	
Indigo Carmine Aluminium Lake (FD&C Blue No. 2)	E132	

Table CP.4.1-5. Test and Acceptance Criterion for Opadry® Blue (OY-LS-20921)

Test	Procedure	Acceptance criterion
Appearance		
Identity		
Residue on ignition		
Heavy metal		

Table CP.4.1-6. Composition of Opadry® Clear (YS-2-19114-A)

Name of Ingredient	Reference to Quality Standard	Name of Ingredient
Hydroxypropyl methyl cellulose 2910 (15cP)	Ph. Eur.	
Glycerol Triacetate	Ph. Eur.	

Table CP.4.1-7. Test and Acceptance Criterion for Opadry® Clear (YS-2-19114-A)

Test	Procedure	Acceptance criterion
Appearance		
Identity		
Residue on Ignition		
Heavy Metals		

P.4.2. Analytical Procedures

This information can be found in the Marketing Authorisation EU/1/98/077/9-12.

P.4.3. Validation of Analytical Procedures

This information can be found in the Marketing Authorisation EU/1/98/077/9-12.

P.4.4. Justification of Specifications

This information can be found in the Marketing Authorisation EU/1/98/077/9-12.

P.4.5. Excipients of Human or Animal Origin

The magnesium stearate used in the comparator sildenafil citrate film-coated 100 mg tablets is of vegetable origin.

The lactose monohydrate used in the comparator sildenafil citrate film-coated 100 mg tablet formulation is a milk derivative and is classified as a Category I (no detectable infectivity) excipient in the CPMP Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products EMEA/410/01.

P.4.6. Novel Excipients

There are no novel excipients used to manufacture the comparator.

P.5. Control of Drug Product (Sildenafil Citrate Comparator for PF-00446687-01, Tablets)**P.5.1. Specifications**

The specification and acceptance criteria for the comparator sildenafil citrate film-coated tablets 100 mg are given in Table CP.5-1-8.

Table CP.5.1-8. Specification for Sildenafil Citrate Film-Coated Tablets 100 mg

Test	Method	Acceptance Criteria
Visual Identity		
Sildenafil Identity (IR)		
Citrate Identity (HPTLC)		
Assay (HPLC)		
Dissolution (15 minutes)		
Content Uniformity	USP <905>	
Water Content		
Total Degredation products		

P.5.2. Analytical Procedures

This information can be found in the Marketing Authorisation EU/1/98/077/9-12.

P.5.3. Validation of Analytical Procedures

This information can be found in the Marketing Authorisation EU/1/98/077/9-12.

P.5.4. Batch Analyses

Certificates of Analysis for representative batches are appended to the appendix.

P.6. Reference Standards or Materials

This information can be found in the Marketing Authorisation EU/1/98/077/9-12.

P.7. Container Closure System

The sildenafil citrate film-coated tablets 100 mg will be packaged in HDPE bottles with child resistant caps.

P.8. Stability

Details of the sildenafil citrate film-coated tablets 100 mg (Viagra 100) are contained in the Marketing Authorisation Application approved by the European Agency for the Evaluation of Medicinal Products (ref EU/1/98/077/9-12). These tablets have been assigned a shelf-life of five years when packed in HDPE containers and stored at or below 25°C.

The tablets proposed for the clinical trial differ only from Viagra® tablets with respect to tablet debossing. A shelf life of five years has therefore been assigned to the product based on the extensive historical data available on the Viagra® product.