10 November 2016
EMA/803097/2016
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Tadalafil Generics

International non-proprietary name: tadalafil

Procedure No. EMEA/H/C/004297/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# Table of contents

# List of abbreviations

| | |
|---|---|
| 6MWT | 6-minute walk test |
| ADR | Adverse Drug Reaction |
| AE | Adverse event |
| AESI | AEs of special interest |
| ALK1 | Activin receptor-like kinase type 1 |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANSM | National Agency for the Safety of Medicine and Health Products |
| AP | Applicant's Part of ASMF |
| API | Active Pharmaceutical Ingredient |
| APPM | Association of Paediatric Palliative Medicine Master Formulary |
| AR | Assessment Report |
| ASM | Active Substance Manufacturer |
| ASMF | Active Substance Master File = Drug Master File |
| AST | Aspartate aminotransferase |
| AUC | Area Under the plasma Concentration |
| AUC0-inf | Area Under the plasma Concentration-time curve from time zero to infinity |
| AUC0-t | Area Under the plasma Concentration-time curve from time zero to t hours |
| BA | BioAvailability |
| BCT | Blinded combination therapy |
| BE | Bioequivalence |
| BID | Bis in die (twice daily) |
| BMI | Body Mass Index |
| BMPR2 | Bone morphogenetic protein receptor type 2 |
| BNFc | British National Formulary for Children |
| BNP | Brain natriuretic peptide |
| BP | Blood pressure |
| BPH | Benign prostatic hyperplasia |
| BPI | Brief Pain Inventory |
| BUN | Blood urea nitrogen |
| cGMP | Cyclic guanosine monophosphate |
| CI | Confidence interval |
| CI | Cardiac index |
| CIOMS | Suspect Adverse Reaction Report Form |
| Cl | Clearance |
| CLcr or CrCl | Creatinine clearance |
| Cmax | maximum plasma concentration |
| CMH test | Haenszel test |
| CO | Cardiac output. |
| CoA | Certificate of Analysis |
| CP | Cerebral palsy |
| CPPs | Critical process parameters |
| CQAs | Control quality attributes |
| CRO | Certified Research Organisation |
| CSF | Cerebrospinal fluid |
| CTEPH | Chronic thromboembolic pulmonary hypertension |
| CV | Coefficient of Variation |
| CW | Clinical worsening |
| CYP450 | cytochrome P450 |
| DAP | Drug Analysis Print |
| DDI | Drug-drug interactions |
| DHCP | Direct Healthcare Professional Communication |
| DMF | Drug Master File = Active Substance Master File |
| DoE | Design of experiments |

| | |
|---|---|
| DP | Decentralised (Application) Procedure |
| DP | Drug product |
| DS | Drug substance |
| DSC | Differential Scanning Calorimetry |
| EC | Europena Commission |
| ECG | Electrocardiogram |
| ED | Erectile dysfunction |
| EEG | electroencephalogram |
| eGFR | estimated glomerular filtration rate |
| eGFRCKD-EPI | estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation |
| eGFRMDRD | estimated glomerular filtration rate based on the Modification of Diet in Renal Disease equation |
| ECHO | echocardiography |
| EMA | European Madicines Agency |
| EoS | End os Study |
| ERA | endothelin receptor antagonist |
| ERA | Enviromental Risk Assessment |
| ERT | enzyme replacement therapy |
| ESI | Electro Spray Ionisation |
| ETA | endothelin receptor antagosinsts |
| EU | European Union |
| FAV | Final Assessment Visit |
| FEV1 | Forced expiratory volume in one second |
| FMEA | Failure mode and effects analysis |
| FPM | Finish Product Manufacturer |
| GABA | Gamma-aminobutyric acid |
| GAD | Generalised Anxiety Disorder |
| GCP | Good Clinical Practice |
| GFR | glomerular filtration rate |
| GGT | gamma-glutamyl transpeptidase |
| GL-3 | globotriaosylceramide |
| GLA | gene encoding α-Gal A |
| GLP | Good Laboratory Practice |
| GMP | Good manufacturing practice |
| GP | Glycopyrronium |
| GSRS | Gastrointestinal Symptoms Rating Scale |
| GTP | Guanosine triphosphate |
| Hb | Haemoglobin |
| HCl | hydrochloride |
| HCP | Health Care Professional |
| HCT | hematocrit |
| HDPE | High Density Polyethylene |
| HEK | human embryonic kidney |
| HPLC | High pressure liquid chromatography |
| HR | Hazard Ratio |
| HRD | human recommended dose |
| CHMP | Committee for Human Medicine Products |
| IAR | infusion-associated reaction |
| IC | interstitial capillary |
| IC GL-3 | interstitial capillary GL-3 |
| ICD | Informed Consent Document |
| ICMR | Indian council of medical research |
| ICSR | Individual Case Safety Report |
| IEC | Independent Ethics Committee |
| IgG | immunoglobulin G |

| | |
|---|---|
| ICH | International Conference on Harmonisation |
| IIEF | International Index of Erectile Function |
| IMP | Investigated Medicinal product |
| IMS | International Marketing Sales |
| INN | International Non-proprietary Name |
| IP | investigational product |
| IPC | In-process control |
| IR | Incidence Rate |
| IR | Immediate-release or Infra-red |
| IRB | Institutional Review Board |
| IS-normalized MF | Internal Standard-normalised Matrix Factor |
| ISR | Incurred Sample Reanalysis |
| ITT | Intention To Treat |
| IV | Intravenous |
| JP | Japanese Pharmacopeia |
| JPE | Japanese Pharmaceutical Excipients |
| K2EDTA | dipotassium ethylenediaminetetraacetic acid |
| $K_i$ | dissociation constant for binding of inhibitor to enzyme |
| L | Litres |
| LC-MS/MS | liquid chromatography coupled with tandem mass spectrometry |
| LFT | Liver Function tests |
| LLOQ | Lower Limit of Quantification |
| LOA | Letter of Access |
| LOD | Limit of Detection |
| LOQ | (1) Limit of Quantification, (2) List of Questions |
| LV | left ventricular |
| LVEDP | Left ventricular end diastolic pressure |
| LVH | Left ventricular hypertrophy |
| LVMi | Left ventricular mass index |
| lyso-Gb3 | globotriaosylsphingosine |
| M.D. | Medical Doctor |
| MA | Marketing Authorisation |
| MAA | Marketing Authorization Application |
| MAH | Marketing Authorisation holder |
| mBMRS | modified Behavioural and Medical Rating Scale |
| MC | Multicenter |
| MDRD | Modification of Diet in Renal Disease equation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligrams |
| mGFR | measured glomerular filtration rate |
| $mGFR_{iohexol}$ | glomerular filtration rate as measured by plasma clearance of iohexol |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| mITT | Modified Intended To Treat |
| mITT-amenable | patients with amenable mutations in the AT1001-011 mITT population |
| mL | milliliters |

| | |
|---|---|
| mL/min | Milliliter per minute |
| mPAP | Mean Pulmonary Artery Pressure |
| MR | Medical Representative |
| MRI | Magnetic resonance imaging |
| MS | Mass Spectrometry |
| mTDS | modified 9-point Teacher's Drooling Scale |
| MWD | minute walk distance |
| NAION | Non-Arteritic Anterior Ischemic Optic Neuropathy |
| NCA | National Competent Authority |
| ND | Not detected |
| NHS | National Health Service |
| NMR | Nuclear Magnetic Resonance |
| NMT | Not more than |
| NO | Nitric oxide |
| NP | Natriuretic peptides |
| NR | Not reported |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| NYHA | New York Heart Association |
| OECD | Organisation for Economic Co-operation and Development |
| OLE | open-label extension |
| OOS | Out of Specifications |
| OTC | Over-the-counter |
| PAH | Pulmonary Arterial Hypertension |
| PASP | Pulmonary artery systolic pressure |
| PBMC | Peripheral blood mononuclear cell |
| PBO | Placebo-controlled trial |
| PCA | Prescription cost analysis data |
| PCD | Photo-Contact Dermatitis |
| PCTFE | Polychlorotrifluoroethene |
| PCWP | Pulmonary capillary wedge pressure |
| PD | Pharmacodynamics |
| PDE | Permitted Daily Exposure |
| PDE-5 | Phosphodiesterase type-5 inhibitors |
| PE | Polyethylene |
| PEC | Predicted Enviromental Concentration |
| P-gp | P-glycoprotein |
| Ph.Eur. | European Pharmacopoeia |
| PhV | Pharmacovigilance |
| PCH | Pulmonary capillary hemangiomatosis |
| PIL | Patient Information Leaflet |
| PIP | Paediatric Investigational Plan |
| PK | Pharmacokinetic |
| PMS | Post Marketing Surveillance |
| PP | Polypropylene |
| PRO | Patient-Reported Outcome |

| | |
|---|---|
| PS | Photo-Sensitivity |
| PSMF | Pharmacovigilance Systém Master File |
| PSUR | Periodic Safety Update Report |
| PT | Preferred Term |
| PTH | Pituitary thyroid hormone |
| PUMA | Paediatric Use Marketing Authorisation |
| PVC | Poly vinyl chloride |
| PVDC | Polyvinylidene chloride |
| PVOD | Pulmonary Veno-Occlusive Disease |
| PVR | Pulmonary vascular resistance |
| QA | Quality Assurance |
| QbD | Quality by design |
| QC | Quality Control (samples) |
| QD | quaque die (once daily) |
| QOD | every other day |
| QOD | quaque otra die (once every other day) |
| QoL | Quality of life |
| QOS | Quality Overall Summary |
| QP | Qualified Person |
| QTc | QT interval corrected for heart rate |
| QTPP | Quality target product profile |
| Rf | Retention factor |
| RH | Relative Humidity |
| rhα-Gal A | recombinant human α-Gal A |
| RMM | Risk Minimization Measure |
| RMS | Reference Member State |
| RR | Reporting Rate |
| RRT | Relative retention time |
| RSD | Relative standard deviation |
| Rt | Retention time |
| RT | Reference/Test (prodcut) |
| RVSP | Right ventricle systolic pressure |
| SAE | serious adverse event |
| SAO2 | oxygen saturation |
| SEM | standard error of the mean |
| SF-36v2 | Short Form Health Survey with 36 questions, version 2 |
| sGC | soluble Guanylate Cyclase |
| SGLT1 | sodium glucose cotransporter 1 |
| SGOT | Serum glutamic oxaloacetic trnasaminase |
| SGPT | Serum glutamic pyruvic trnasmainase |
| Shire HGT | Shire human genetic therapies |
| SME | small, or medium-sized enterprise |
| SmPC | Summary of Product Characteristics |
| SMQ | Standardised MedDRA Querie |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SPC | Summary of Product Characteristics |
| STD | Standard Deviation |
| SVR | Systemic vascular resistance |
| T/R | Test/Reference (product) |
| $t_{1/2}$ | terminal elimination half-life |
| TEAE | treatment-emergent adverse event |
| TID | tris in die (three times a day) |
| TLC | Total lung capacity |
| $t_{max}$ | time to maximum plasma concentration |
| TSE | Transmissible spongiform encephalopathy |
| TSQM | Treatment satisfaction questionnaire for medication |
| TTC | Threshold of toxicological concern |
| ULN | upper limit of normal |
| USP | United States pharmacopoeial |

| | |
|---|---|
| UV | Ultraviolet |
| VAS | visual analogue scale |
| Vss | volume of distribution |
| WBC | white blood cell |
| WCI | Worst Case Imputation |
| WEU | Well Established Use |
| WHO | World Health Organization |
| WRI | worst rank imputation |
| WT | wild type |
| XRD | X-Ray Diffraction |
| XRPD | X-ray powder diffraction |
| α-Gal A | alpha-galactosidase A |
| µCi | Microcurie |
| µM | Micromolar |

Not all abbreviations might be used.

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Mylan S.A.S. submitted on 21 December 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Tadalafil Generics, through the centralised procedure under Article 3(3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 September 2015.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

*Tadalafil Generics is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity.*

*Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.*

**The legal basis for this application refers to:**

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Adcirca instead of non-clinical and clinical studies unless justified otherwise.

***Information on paediatric requirements***

Not applicable

***Information relating to orphan market exclusivity***

***Similarity***

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Cialis, 20 mg, film-coated tablet
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 12/11/2002
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/02/237/002-005, 009

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Adcirca, 20 mg, film-coated tablet

- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 01/10/2008
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/08/476/005-006

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Adcirca, 20 mg, film-coated tablet
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 01/10/2008
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/08/476/006
- Bioavailability study number(s): 080-15, 081-15

***Scientific advice***

The applicant did not seek scientific advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur appointed by the CHMP was:

Rapporteur: Radka Montoniová

- The application was received by the EMA on 21 December 2015.
- The procedure started on 28 January 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 April 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 28 April 2016.
- During the meeting on 26 May 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 31 May 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 July 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 August 2016.
- During the PRAC meeting on 2 September 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP. The PRAC assessment Overview and Advice was sent to the applicant on 25 August 2016.
- The CHMP adopted an Assessment Report on similarity for Tadalafil Generics with Volibris, Opsumit and Adempas on 15 September 2016.
- During the CHMP meeting on 15 September 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 11 October 2016.
- During the meeting on 10 November 2016, the CHMP, in the light of the overall data submitted and

the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Tadalafil Generics.

# 2. Scientific discussion

## *2.1. Introduction*

The proposed product is an immediate release film-coated 20 mg tablets containing tadalafil as active substance. Tadalafil is a chemical substance and the dosage form has been developed as generic product to the centrally authorised product Adcirca 20 mg Filmtabletten by the company Eli Lilly Nederland B.V., Netherlands containing the same active substance in the same pharmaceutical form.

Tadalafil is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

Tadalafil is approved in the EU for the treatment:

Adults

Treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic pulmonary hypertension and in pulmonary hypertension related to collagen vascular disease.

**About the disease**

Pulmonary arterial hypertension (PAH) is a rare disorder with reports estimating its prevalence at between 15 and 52 cases per one million patients (Falk JA et al., 2010). PAH is a chronic disease of the pulmonary vasculature defined as the presence of a mean pulmonary artery pressure >25 mmHg at rest (or >30 mmHg during exercise) in the presence of mean pulmonary capillary wedge pressure <15 mmHg (Katz SD et al., 2008).

The pathogenesis of this disorder is complex and incompletely characterized. Increased pulmonary artery blood pressures are associated with structural changes in the pulmonary circulation characterized by pulmonary arteriopathy (intimal thickening, medial hypertrophy, adventitial thickening, and plexiform lesions), in-situ thrombosis, and rarefaction of the microcirculation (Katz SD et al., 2008).

Clinical manifestations of PAH are related to the hemodynamic effects of increased afterload on the right ventricle and systemic manifestations of the comorbid conditions associated with elevated pulmonary vascular resistance. Progressive exercise intolerance, lower extremity edema, ascites, and syncope are common clinical presentations. Although duplex echocardiography is considered an excellent screening tool in suspected cases, cardiac catheterization with direct measurement of pulmonary artery pressures is required for definitive diagnosis. PAH is associated with progressive right ventricular failure and high mortality risk (Katz SD et al., 2008).

Traditional classification of pulmonary hypertension largely differentiated patients with idiopathic or primary cases from patients with PH from secondary causes. This classification scheme had many limitations as it did not adequately describe underlying mechanisms of the disease and their implications

for potential treatment options, based on the pathophysiology of the underlying conditions (Falk JA et al., 2010).

**Proposed indication, posology and use in special populations**

Tadalafil is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

Posology

The recommended dose is 40 mg (2 x 20 mg) taken once daily with or without food.

Special populations

*Elderly patients*

Dose adjustments are not required in elderly patients.

*Renal impairment*

In patients with mild to moderate renal impairment a starting dose of 20 mg once per day is recommended. The dose may be increased to 40 mg once per day, based on individual efficacy and tolerability. In patients with severe renal impairment the use of tadalafil is not recommended (see sections 4.4 and 5.2).

*Hepatic impairment*

Due to limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B), following single doses of 10 mg, a starting dose of 20 mg once per day may be considered. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied and therefore dosing of tadalafil is not recommended (see sections 4.4 and 5.2).

*Paediatric population*

The safety and efficacy of tadalafil in individuals below 18 years of age has not yet been established. No data are available.

**Method of administration**

Tadalafil Generics is for oral use.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The proposed product is presented as immediate release film-coated tablets containing 20 mg of tadalafil as active substance. The product has been developed as generic product to the centrally authorised product Adcirca 20 mg film-coated tablets containing the same active substance in the same pharmaceutical form.

Other ingredients are:

Tablet core: lactose anhydrous, poloxamer 188, cellulose microcrystalline (pH101), povidone (K-25), croscarmellose sodium, magnesium stearate, sodium lauril sulfate, and silica colloidal anhydrous.

Film-coat: lactose monohydrate, hypromellose (E464), titanium dioxide (E171), and triacetin.

The product is available in PVC/PE/PVdC-Alu blisters in carton.

## 2.2.2. Active substance

### *General information*

The chemical name of tadalafil is (6*R*-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12*a*-hexahydro-2-methyl-pyrazino [1', 2':1,6] pyrido[3,4-*b*]indole-1,4-dione.

The active substance is a white or almost white powder which is practically insoluble in water, freely soluble in dimethyl sulfoxide and slightly soluble in methylene chloride.

As there is a monograph of tadalafil in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for tadalafil which has been provided within the current Marketing Authorisation Application.

### *Manufacture, characterisation and process controls*

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

### *Specification*

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph.

Additional specifications have been set for impurities, residual solvents and particle size. The analytical method for particle size has been adequately validated and it was demonstrated that it is not a critical factor for either the finished product performance or the manufacturing process.

Batch analysis data on three consecutive batches of the active substance were provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

### *Stability*

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

## 2.2.3. Finished medicinal product

### *Description of the product and pharmaceutical development*

The finished product Tadalafil Generics film-coated tablets was developed as a generic bioequivalent to Adcirca by Eli Lilly Nederland B.V. from the European market. The formulation contains the active substance tadalafil, officially listed in the Ph. Eur. Tadalafil is a white or almost white powder, practically insoluble in water, freely soluble in DMSO and slightly soluble in methylene chloride. The excipients selected for the formulation development are based on literature survey, excipient compatibility studies and their functionality for development of a tablet dosage form. The choice and function of the excipients has been adequately described. The excipients in tested product are similar to those found in the originator Adcirca, with the addition of Povidone (binder), Poloxamer (solubilizer), and silica colloidal anhydrous (glidant). All of the excipients are conventional pharmaceutical ingredients that comply with

the respective requirements of the Ph. Eur., with the exception of the film coating agent Opadry II white. However, the individual components of the coating material comply with Ph.Eur. or EU regulation 231/2012 for the colorants.

The manufacturing process development strategy was to design and develop stable and bioequivalent generic product of Tadalafil film coated tablets using commonly used excipients and similar to reference product. The active substance characterization has revealed that the active substance had very poor flow properties. Therefore a wet granulation process was chosen. During development the manufacturing process was optimized with regard to the following parameters: solvent system for granulation, drying temperature, milling process, blending time, tableting speed and hardness.

The applicant evaluated the dissolution of the reference product in different dissolution media covering different pHs. Different surfactants were also evaluated. Based on the obtained results, the final conditions were selected.

The discriminatory power of the dissolution method has been studied by varying the quantitative composition of the formulation (level of disintegrant) and changing the manufacturing process (lubrication time). The results from this study demonstrated the discriminatory nature of the method proposed.

The dissolution characteristics of the finished product were compared to the reference medicinal product Adcirca from the European market. Comparative dissolution profiles were generated in relevant dissolution media.

In one medium the dissolution profiles were similar. For the other media faster release of drug in the test product was observed when compared to the reference product. This may be due to the difference in the composition between both products. Nevertheless, since Tadalafil is rapidly absorbed after oral administration, the difference in the *in-vitro* drug release at the initial time points will not have any significant impact on *in vivo* drug release. This was confirmed by the bioequivalence studies (see clinical section).

The formulation used in the clinical study and the formulation intended for commercial supplies is identical except for the Opadry film coating material which is non-functional in nature.

The primary packaging is PVC/PE/PVdC-Alu blisters. The material complies with Ph. Eur. and EC requirements. The choice of container closure system has been validated by stability data and is adequate for the intended use of the product.

***Manufacture of the product***

The product is manufactured using a wet granulation process. The manufacturing process consists of 10 main steps: dispensing, sifting, granulation and drying, milling, mixing of granules, blending, compression, coating, inspection and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

A process validation scheme has been provided and the applicant has committed to perform process validation studies on the first three production scale batches of Tadalafil 20 mg film coated tablets before the product is placed on the market.

***Product specification***

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (UV, IR), color identification, dissolution (HPLC), uniformity of dosage units (by content uniformity), assay (UV), related substances (HPLC), loss on drying (Ph. Eur.), residual solvents (GC), and microbiological test (Ph. Eur.).

Batch analysis results are provided for three batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Analytical methods were adequately described. Validations of analytical methods were provided for HPLC methods for assay, related substances and dissolution. Stability indicating capability of the HPLC method for assay, related substances and dissolution has been demonstrated through forced degradation studies.

***Stability of the product***

Stability data for five pilot scale batches of finished product stored under long term conditions at 25ºC / 60% RH for up to 36 months and for 6 months under accelerated conditions at 40ºC / 75% RH according to the ICH guidelines were provided. The batches of the medicinal product were packed in the primary packaging proposed for marketing.

Additional results on the product packed in a simulated bulk shipment pack were provided. This simulated pack only differs in size with the bulk shipment pack which will be use in the commercial setting.

Samples were tested for description, dissolution, assay (HPLC), related substances, loss on drying and microbiological quality. The analytical procedures used are stability indicating.

No change to the appearance of the tablets was observed under any of the conditions tested. Dissolution, assay, related substances, loss on drying and microbiological (if tested) results were within the shelf life specification limits at all time points in all the proposed packs. In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant difference in any of the parameters tested (namely, description, assay, related substances, loss on drying and dissolution) was observed. Therefore, it was concluded that Tadalafil Generics 20 mg film-coated tablets are photostable.

Based on the accelerated (24 weeks at 40ºC / 75% RH) and long-term (12 months at 25ºC / 60% RH) stability results on the product packaged in to simulated bulk shipment pack, a 12 month shelf life with no special storage conditions can be accepted for this packaging.

Based on available stability data, the proposed shelf-life of 3 years with no special storage conditions as stated in the SmPC is acceptable.

***Adventitious agents***

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

## 2.2.4. Discussion on chemical and pharmaceutical aspects

Information on development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### 2.2.6. Recommendation(s) for future quality development

Not applicable

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

### 2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Tadalafil Generics manufactured by Mylan S.A.S. is considered unlikely to result in any significant increase in the combined sales volumes for all tadalafil containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

### 2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology was considered adequate by the CHMP.

A valid justification for not submitting an ERA was provided.

### 2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Tadalafil Generics was provided and was accepted by the CHMP. This was in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

This is an application for tablets containing tadalafil. To support the marketing authorisation application the applicant conducted two bioequivalence studies with cross-over design under fasting and fed

conditions. These studies were the pivotal studies for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) and Question number 10 of the Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMEA/618604/2008 rev.13) are of particular relevance.

***GCP***

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

***Clinical studies***

To support the application, the applicant has submitted two bioequivalence studies.

According to the EMA Tadalafil product-specific guidance (CHMP/PKWP/EMA/423735/2013), the reference product is considered to have specific formulation characteristics to enhance the rate of absorption of the drug and therefore, it cannot be assumed that the impact of food will be the same regardless of formulation. The product can be taken without regard to food. Thus, both fasted and fed state comparisons of test to reference formulations are required to establish bioequivalence.

**Table 1. Tabular overview of clinical studies**

| Type of study | Study Identifier | Objective of the study | Study design and type of control | Test Products; Dosage regimen; Route of administration | Number of subjects | Healthy subjects or diagnosis of patients | Duration of treatment |
|---|---|---|---|---|---|---|---|
| BE | 080-15 | **Primary objective**<br>To compare the rate and extent of absorption of Tadalafil Film-coated Tablets 20 mg (Test) of Mylan Laboratories Limited, with that of Adcirca (Tadalafil) 20 mg Tablets (Reference)<br><br>**Secondary objective**<br>To monitor the adverse | An open-label, balanced, randomized, two-treatment, two sequence, two-period, cross-over, single dose, oral bio- equivalence study, in healthy, adult, male, human subjects under fasting conditions. | **Test product**<br>Tadalafil Film-coated Tablets 20 mg<br><br>**Reference Product**<br>Adcirca (Tadalafil) 20 mg Tablets<br>Single dose of 20 mg tablet for oral administration | Planned - 30 subjects<br>Enrolled - 30 subjects<br>Dosed : Period-1 : 30 Subjects<br>Period-2 : 26 Subjects<br>Withdrawn – 04 subjects<br>Completed – 26 Subjects<br>Pharmaco-kinetic statistical data | Healthy, adult, human subjects | Single dose |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | events and to ensure the safety of the subjects. | | | analyzed – 26 Subjects | | |
| BE | 081-15 | **Primary objective** To compare the rate and extent of absorption of Tadalafil Film-coated Tablets 20 mg (Test) of Mylan Laboratories Limited, with that of Adcirca (Tadalafil) 20 mg Tablets (Reference)<br><br>**Secondary objective** To monitor the adverse events and to ensure the safety of the subjects. | An open-label, balanced, randomized, two-treatment, two sequence, two-period, cross-over, single dose, oral bio- equivalence study, in healthy, adult, male, human subjects under fed conditions. | **Test product** Tadalafil Film-coated Tablets 20 mg<br><br>**Reference Product** Adcirca (Tadalafil) 20 mg Tablets Single dose of 20 mg tablet for oral administration | Planned - 30 Enrolled - 30 Withdrawn – 03 subjects Completed – 27 Subjects Bio-sample analyzed – 27 Subjects. Pharmaco-kinetic and statistical data analyzed – 27 Subjects. | Healthy, adult, human subjects | Single dose |

## 2.4.2. Pharmacokinetics

**Study No. 080-15**

***Methods***

***Study design***

This study was an open-label, balanced, randomised, two-treatment, two-sequence, two period, cross-over, single dose, oral bioequivalence study of two different tadalafil formulations in adult, male, human subjects under fasting conditions. A washout period of 14 days was maintained between the each treatment schedule.

***Test and reference products***

Tadalafil Generics 20 mg film-coated tablets manufactured by Mylan Laboratories Ltd, India (batch No 2001691, manufacturing date 12/2012; exp. Date 11/2014) has been compared to Adcirca 20mg film-coated tablets manufactured by Eli Lilly Nederland BV, Netherlands (Batch No: C458281, exp. Date 11/2017).

***Population studied***

Thirty (30) male, healthy subjects of Asian race, with a mean body mass index 22.83 kg/$m^2$ (range 18.81 – 26.34), and mean age 28 years (range: 21-39) were included in the study.

Four (4) patients in total withdrew from the study. One patient was absent during the check-in of the second period of the study. The other 3 patients withdrew due to an adverse event.

***Analytical methods***

Tadalafil concentrations were determined by HPLC method by tandem mass spectrometry and using tadalafil-d3 as an internal standard.

Calibration curves ranged from 2.011 to 603.915 ng/mL. Quantitation was based on peak area ratio of tadalafil versus internal standard. A least squares linear regression with weighing factor $1/x^2$ was used.

Samples were analysed in nineteen (19) accepted analytical runs including repeats and ISR each of them containing blank and zero samples in singlet, ten calibration standards and QC samples at five levels distributed throughout the batch of samples from both periods of two subjects.

Blank samples were chromatographically checked and no peaks were found at the retention time of analyte and ISTD. This demonstrated that there was no interference due to endogenous matrix constituents. Blank samples were run after the highest calibration curve standard.

Incurred Sample Reanalysis (ISR) was performed by using freshly prepared calibration standards and 79.63% of ISR samples were found to be within acceptance limits.

There were no protocol or SOP deviation occurred during the study.

Tadalafil was detected in several pre-dose samples in the quantities lower than 1/20 of $C_{max}$ in accordance with the Guideline on investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1.

***Den***

The PK parameters for tadalafil were calculated by using non-compartmental model by WinNonlin Professional Software (version 5.0).

***Statistical methods***

Descriptive statistics were computed and reported for all pharmacokinetic parameters of tadalafil. Analysis of variance (ANOVA) was carried out for Ln-transformed pharmacokinetic parameters Cmax and AUC0-72hr for tadalafil. ANOVA model included treatment received, the period at which it is given along with the sequence in which each treatment being received and the subject effect (nested within the sequence). Sequence effect was tested by using the subject nested within sequence mean square from the ANOVA as the error term. An F-test was performed to determine the statistical significance of the treatment and periods involved in the model at a significance level of 5% (alpha=0.05) and sequence effect involved in the model at a significance level of 10% (alpha=0.10). Summary statistics, ANOVA, 90% confidence intervals, ratio analysis, intra subject variability and power were calculated for tadalafil. Geometric means and ratio of means were calculated for tadalafil.

90% confidence intervals for the ratio of the test and reference product averages (geometric least squares means) were calculated for Cmax and AUC0-72hr of tadalafil.

Criteria for conclusion of bioequivalence were as follows:

| **Parameter** | **Range of Ln-transformed 90% CI of Tadalafil** |
|---|---|
| $C_{max}$ | 83.88-97.22 |
| $AUC_{0-72hr}$ | 92.91-103.25 |

The 90% confidence intervals for geometric least square means of ln-transformed data of Cmax and AUC0-72hr of tadalafil were within the bioequivalence acceptance range (80.00 -125.00%).

***Results***

**Table 2. Pharmacokinetic parameters for tadalafil under fasting condition (non-transformed values)**

| Pharmacokinetic parameter | Test | | Reference | |
|---|---|---|---|---|
| | arithmetic mean | SD | arithmetic mean | SD |
| $AUC_{(0-72h)}$ (hr.ng/mL) | 18651.86 | 5280.82 | 18886.53 | 4686.28 |
| $AUC_{(0-\infty)}$ (hr.ng/mL) | 26852.14 | 12220.99 | 26710.86 | 9980.00 |
| $C_{max}$ (ng/ml) | 530.26 | 141.07 | 582.61 | 134.34 |
| $T_{max}$* (hr) | 3.75 (0.50 – 24.00) | | 3.00 (0.50 – 4.50) | |

$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours

$AUC_{0-72h}$ area under the plasma concentration-time curve from time zero to 72 hours>

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

$C_{max}$ maximum plasma concentration

$T_{max}$ time for maximum concentration (* median, range)

**Table 3. Statistical analysis for tadalafil under fasting conditions (ln-transformed values)**

| Pharmacokinetic parameter | Geometric Mean Ratio Test/Reference | 90% Confidence Interval | CV%* |
|---|---|---|---|
| $AUC_{(0-72h)}$ | 97.95% | (92.91%, 103.25%) | 11.2 |
| $C_{max}$ | 90.31% | (83.88%, 97.22%) | 15.6 |

* estimated from the Residual Mean Squares

There were four pre-dose concentrations in period II, however these subjects were included for bioanalysis, pharmacokinetic analysis and statistical evaluations as these subjects showed pre-dose values lower than 5% of Cmax.

***Safety data***

In total six adverse events were reported in five subjects during entire duration of the study.

- Three adverse events were reported in three subjects during period-I (vomiting, pyrexia, diarrhoea)
- One adverse event was reported in one subject during period-II check-in (pyrexia)
- No adverse events were reported in Period-II.
- Two adverse events were reported in two subjects as laboratory abnormalities during post study lab investigations.

No deaths or serious adverse events were reported during the study.

**Study No. 081-15**

***Methods***

***Study design***

This study was an open-label, balanced, randomised, two-treatment, two-sequence, two period, cross-over, single dose, oral bioequivalence study of two different tadalafil formulations in adult, male, human subjects under fed conditions. A washout period of 14 days was maintained between the each treatment schedule.

***Test and reference products***

Tadalafil Generics 20 mg film-coated tablets manufactured by Mylan Laboratories Ltd, India (batch No 2001691, manufacturing date 12/2012; exp. Date 11/2014) has been compared to Adcirca 20mg film-coated tablets manufactured by Eli Lilly Nederland BV, Netherlands (Batch No: C458281, exp. Date 11/2017).

***Population studied***

Thirty (30) male, healthy subjects of Asian race, with a mean body mass index 23.24 $kg/m^2$ (range 18.80 – 28.35), and mean age 27.63 years (range: 20-43) were included in the study.

Three (3) patients withdrew from the study, as they were absent for the check-in of the second period of the study.

***Analytical methods***

Tadalafil concentrations were determined by HPLC method by tandem mass spectrometry and using tadalafil-d3 as an internal standard.

Calibration curves ranged from 2.012 to 603.587 ng/m. Quantitation was based on peak area ratio of tadalafil versus internal standard. A least squares linear regression with weighing factor $1/x^2$ was used.

Samples were analysed in nineteen (19) accepted analytical runs including repeats and ISR each of them containing blank and zero samples in singlet, ten calibration standards and QC samples at five levels distributed throughout the batch of samples from both periods of two subjects.

Blank samples were chromatographically checked and no peaks were found at the retention time of analyte and ISTD. This demonstrated that there was no interference due to endogenous matrix constituents. Blank samples were run after the highest calibration curve standard.

Incurred Sample Reanalysis (ISR) was performed by using freshly prepared calibration standards and 95.37% of ISR samples were found to be within acceptance limits.

There were no protocol or SOP deviation occurred during the study.

Tadalafil was detected in nineteen (19) of fifty four (54) pre-dose samples. There is not any subject for whom the pre-dose concentration is greater than 5 percent of the $C_{max}$ value for the subject in that period. Therefore no subject was excluded from statistical analysis.

***Pharmacokinetic variables***

These were the same as for Study No. 081-15.

***Statistical methods***

These were the same as for Study No. 081-15.

Criteria for conclusion of bioequivalence were as follows:

| **Parameter** | **Range of Ln-transformed 90% CI of Tadalafil** |
|---|---|
| $C_{max}$ | 103.24-119.22 |
| $AUC_{0-72hr}$ | 95.31-109.80 |

The 90% confidence intervals for geometric least square means of ln-transformed data of Cmax and AUC0-72hr of tadalafil were within the bioequivalence acceptance range (80.00 -125.00%).

***Results***

**Table 4. Pharmacokinetic parameters for tadalafil under fed conditions, (non-transformed values)**

| **Pharmacokinetic parameter** | **Test** | | **Reference** | |
|---|---|---|---|---|
| | **arithmetic mean** | **SD** | **arithmetic mean** | **SD** |
| $AUC_{(0-72h)}$ (hr.ng/mL) | 14376.53 | 3983.43 | 14055.04 | 3122.90 |
| $AUC_{(0-\infty)}$ (hr.ng/mL) | 21192.58 | 12469.98 | 20763.95 | 9784.04 |
| $C_{max}$ (ng/ml) | 501.12 | 135.20 | 446.58 | 64.70 |
| $T_{max}$* (hr) | 4.00 (1.00 – 4.50) | | 4.50 (1.00 – 8.00) | |
| $AUC_{0-72h}$ | area under the plasma concentration-time curve from time zero to 72 hours | | | |
| $AUC_{0-\infty}$ | area under the plasma concentration-time curve from time zero to infinity | | | |
| $C_{max}$ | maximum plasma concentration | | | |
| $T_{max}$ | time for maximum concentration (* median, range) | | | |

**Table 5. Statistical analysis for tadalafil under fed conditions (ln-transformed values)**

| **Pharmacokinetic parameter** | **Geometric Mean Ratio Test/Reference** | **90 % Confidence Interval** | **CV%*** |
|---|---|---|---|
| $AUC_{(0-72h)}$ (hr.ng/mL) | 102.30% | (95.31%, 109.80%) | 15.3 |

| Pharmacokinetic parameter | Geometric Mean Ratio Test/Reference | 90 % Confidence Interval | CV%* |
|---|---|---|---|
| $C_{max}$ (ng/ml) | 110.94% | (103.24%, 119.22%) | 15.6 |
| * estimated from the Residual Mean Squares | | | |

In fourteen (14) pre-dose samples from Period-2 tadalafil was detected in concentrations 1.4 - 34 times lower than LLOQ. However pre-dose samples of six (6) subjects from Period-2 contained tadalafil in concentrations 1.1 – 8.1 times higher than LLOQ.

***Safety data***

In total thirteen adverse events were reported in five subjects during entire duration of the study.

- Three adverse events were reported in three subjects during period-I (headache and myalgia in two subjects)
- Ten adverse events were reported in six subjects as laboratory abnormalities during post study lab investigations.
- No adverse events were reported in Period-II.

There were no serious adverse events or deaths reported in the study.

***Conclusions***

Based on the presented bioequivalence studies, Tadalafil Generics 20 mg film-coated tablets are considered bioequivalent with Adcirca20 mg film-coated tablets.

## 2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

## 2.4.4. Post marketing experience

The medicinal product has not been marketed in any country in the EU.

## 2.4.5. Discussion on clinical aspects

To support the application, the Applicant conducted two open-label, balanced, randomised, two-treatment, two-sequence, two period, cross-over, single dose, oral bioequivalence studies of Tadalafil Film-coated Tablets 20 mg (Test) of Mylan Laboratories Limited and Adcirca (Tadalafil) 20 mg Tablets (Reference) of Eli Lilly Nederland B.V. in healthy, adult, male, human subjects under fasting and fed conditions.

In both studies, the ratio of the geometric least squares mean of test product and reference product for the the $AUC_{0-\infty}$ and for the $C_{max}$ was within the pre-specified bioequivalence limits of 80.00-125.00%.

## 2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of tadalafil and two bioequivalence studies were provided to demonstrate that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product and was accepted by the CHMP.

## *2.5. Risk management plan*

***Safety concerns***

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Priapism (MedDRA PT: Priapism)<br><br>• Hypotension/Increased Hypotensive Effect (MedDRA PTs: Hypotension, Blood pressure decreased) |
| Important potential risks | • Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) (MedDRA PT: Optic ischaemic neuropathy)<br><br>• Sudden Hearing Loss (MedDRA HLT: Hearing losses)<br><br>• Increased uterine bleeding (MedDRA PTs: menorrhagia, polymenorrhagia, metrorrhagia, menometrorrhagia, uterine haemorrhage and vaginal haemorrhage) |
| Missing information | None |

***Pharmacovigilance plan***

Not applicable.

***Risk minimisation measures***

| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
|---|---|---|
| Important identified risks:<br><br>Priapism | Sections 4.4 and 4.8 of the SPC contain adequate information on this safety concern.<br>Sections 2 and 4 of PL advise patients on this safety concern. | None |
| Important identified risks:<br><br>Hypotension/Increased Hypotensive Effect | Sections 4.3, 4.4, 4.5 and 4.8 of the SPC contain adequate information on this safety concern.<br>Sections 2 and 4 of PL advise patients on this safety concern. | None |
| Important potential risks:<br><br>Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) | Sections 4.3, 4.4, 4.5 and 4.8 of the SPC contain adequate information on this safety concern.<br>Sections 2 and 4 of PL advise patients on this safety concern. | None |
| Important potential risks:<br><br>Sudden Hearing Loss | Sections 4.3, 4.4 and 4.8 of the SPC contain adequate information on this safety concern.<br>Sections 2 and 4 of PL advise patients on this safety concern. | None |
| Important potential risks:<br><br>Increased uterine bleeding | Section 4.8 of the SPC contains adequate information on this safety concern.<br>Sections 4 of PL advise patients on this safety concern. | None |

***Conclusion***

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

## *2.6. PSUR submission*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.7. Pharmacovigilance*

***Pharmacovigilance system***

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

## *2.8. Product information*

### 2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the design and layout of Duloxetine Mylan 30 mg Hard gastro-resistant capsules (EMEA/H/C/003981). Furthermore, the content of the Tadalafil Generics 20- mg film-coated tablets was prepared to be identical with the leaflet the reference product, ADCIRCA 20 mg film-coated tablets  The bridging report submitted by the applicant has been found acceptable.

# 3. Benefit-risk balance

This application concerns a generic version of tadalafil tablets. The reference product Adcirca 20 mg tablets is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. No non-clinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics or the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The applicant submitted two open-label, balanced, randomised, two-treatment, two-sequence, two period, cross-over, single dose, oral bioequivalence studies of two different tadalafil formulations in adult, male, human subjects. One study was performed under fed conditions and the other under fasting conditions. The design of the studies was considered adequate to evaluate the bioequivalence of this formulation and line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out periods were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Tadalafil Generics 20 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the Adcirca 20mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters $AUC_{0-\infty}$, and $C_{max}$ were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

# 4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tadalafil Generics is favourable in the following indication: treatment in adults of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (see section 5.1).

Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

***Other conditions and requirements of the marketing authorisation***

**Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.