TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR MYHEP 400 (SOFOSBUVIR 400MG) FILM COATED TABLETS

Version number 1.0
14th April, 2022

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1. Introduction

MYHEP 400 is a generic medicine of Sovaldi ™ tablets 400mg of Gilead Sciences, Inc. MYHEP 400 is an antiviral medicine belonging to antivirals for systemic use, direct-acting antiviral group. Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with a 50% inhibitory concentration (IC50) value ranging from 0.7 to 2.6 µM. GS-461203 (the active metabolite of sofosbuvir) is not an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase

MYHEP 400 is approved in Tanzania for use in adults, children (aged 3 years) and elderly

1.1 Product details

Registration number	TAN 21 HM 0096
Brand name	MYHEP 400
Generic name, strength and form	Sofosbuvir, 400 mg film coated tablets
ATC classification	ATC code: J05AP08 Antivirals for systemic use, direct-acting antiviral
Distribution category	POM
Country of origin	India
Associated product	LEDVIR (ledipasvir 90mg/sofosbuvir 400mg) and MyHep ALL (Sofosbuvir 400mg and Velpatasvir 100mg)
Marketing Authorization Holder	Mylan Laboratories Limited Plot No. 564/A/22, Road No. 92, Jubilee Hills, Hyderabad - 500034, Telangana, INDIA. E-Mail:Kulbhushan.Ganotra@mylan.in
Local Technical Representative	Pyramid Pharma Limited, P.O.Box 16215, Dar es salaam

1.2 Assessment procedure

The application for registration of MYHEP 400 was submitted on 28th January, 2016. The product underwent full assessment. Assessment was completed in 3 rounds of evaluation. MYHEP 400 was registered on 29th March, 2021

1.3 Information for users

Visual description of the finished product	Peach coloured, capsule shaped, biconvex, bevelled edge film-coated tablets debossed with "SF400" on one side of the tablet and "M" on the other side

Primary packing material	Blue High Density PolyEthylene (HDPE) bottle with PP cap
Secondary packing materials	Carton box
Shelf-life and storage condition	24 months, do not store above 30°C
Route of administration	Oral
Therapeutic indications	Sofosvubir 400mg film coated tablet is indicated for the treatment of chronic hepatitis C (CHC) in adults, this is in combination with other medicinal products

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM, the package insert contains full prescribing information as per SmPC

Container labels
The product label information is presented in English. Details in the secondary pack label include:

Brand name: MYHEP 400

Composition: Sofosbuvir 400 mg

Pack size: 28's per bottle

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Do not store above 30°C

Manufacturer address: Mylan Laboratories Limited, F- 4 & F-12, MIDC, Malegaon, Sinnar, Nashik-422 113, Maharashtra, India

Unique identifier: NA

Special warnings/precautions or instructions for use: NA

The details of the primary pack include:
Brand name and strength: MYHEP 400 (Sofosbuvir 400 mg)

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: Mylan Laboratories Limited

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I

3. Scientific discussion

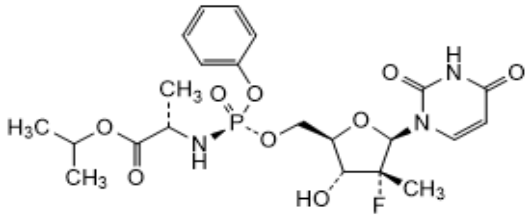
Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of Full details

General information

Sofosbuvir API is compendia in International Pharmacopeia
Molecular formula: $C_{22}H_{29}FN_3O_9P$
Chemical name: Propan-2-yl N-[(S)-{[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyloxolan-2-yl]methoxy}phenoxyphosphoryl]-l-alaninate

Structure:



Physico-chemical properties of the API

Sofosbuvir is a white to - off white, non-hygroscopic powder that is slightly soluble in water, soluble in ethanol methanol and practically insoluble in toluene and heptane. Sofosbuvir show polymorphism. Polymorphc form I and VI have been identified. Manufacturer confirm to consistently produce Sofosbuvir form VI which was confirmed and characterized by pXRD analysis and Diferential Scanning Calorimetry (DSC)

Manufacture

The API manufacturing site, Mylan Laboratories Limited (Unit-8), G Chodavaram, PoosapatiregaMandal, Vizianagaram District – 535204, Andhra Pradesh, India**.** was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by WHO-PQ, USFDA, EDQM, BGV Hamburg, COFEPRIS. Sofosbuvir API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per in-house standards and ICHQ3A. The parameters monitored during quality control are: appearance (visual), identification (IR, HPLC/UPLC), water content (KF), heavy metals (USP), related substances (HPLC/UPLC), assay (HPLC/UPLC),

residual solvents (GC), polymorphism (pXRD) and particle size (Malvern analysis). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of Sofosbuvir API is 24 months when packed in a white Low density polyethylene bag (LDPE and white polyethylene bag (HMLDPE) in a triple Laminated Aluminium Bag & HDPE drum and stored at 25ºC ± 2ºC, 60 ± 5% RH

Quality of the Finished Pharmaceutical Product

Formulation
MYHEP 400 is a Peach coloured, capsule shaped, biconvex bevelled edge film coated tablet debossed with 'SF400' on one side of the tablet and 'M' on other side. MYHEP 400 contains Sofosbuvir and other ingredients listed here after:

Core tablets
Mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, purified water

Film coating (Opadry II orange 85F530025)
Polyvinyl alcohol, Titanium dioxide, Macrogol/PEG, Talc, Iron oxide red, Iron oxide yellow and Ferroseferic oxide/black iron oxide

The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th in terms of function and quantities.

Manufacture
The finished product was manufactured at Mylan Laboratories Limited, F- 4 & F-12, MIDC, Malegaon, Sinnar, Nashik -422 113, Maharashtra, India.The compliance of the site to TMDA GMP standards was confirmed through site inspection on 15th April 2017.

Specifications
The FPP is International Ph. The manufacturer controls the quality of the finished product as per in-house and ICHQ3B requirements. The parameters monitored during quality control are:

<appearance, identification (HPLC,UV-PDA), dissolution (UV), uniformity of dosage units (mass variation), assay (HPLC), related substances (HPLC), water content (KF) and microbiological test (Ph. Uer.). Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system
Stability studies were conducted on 3 batches of the finished product stored at 30 ± 2°C/75 ± 5% RH for 24 months and 40 ± 2°C/75 ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in HDPE Bottle with desiccant at "Do not store above 30°C"

Safety and efficacy information

Safety and efficacy of MYHEP 400 was established through bioequivalence trial. BE trial report number BA15101179-01 was submitted.

Study title	Single dose oral bioequivalence study of Sofosbuvir Film coated tablets 400mg manufactured by Mylan Laboratories Ltd, India and Sovaldi™ (Sofosbuvir) film coated tablets 400mg manufactured by Patheon Inc. Mississauga, ON L5N 7K9, Canada, in healthy adult human subjects under fed conditions	
Study design	An open label, randomized, single dose, two-treatment, two-period, two-sequence, cross-over balanced oral bioequivalence study.	
Study site	<u>Clinical, pharmacokinetic and statistical site</u> Cliantha Research Limited Opposite Pushparaj Towers Nr. Judges Bungalows, Bodakdev, Ahmedabad-380 054, Gujarat, India <u>Bioanalytical facility</u> Mylan Laboratories limited Clinical research Centre, Saradhi Chambers, plot No. 4-A, Beside Poulomi Hospital, Rukminipuri, Dr. A.S. Rao Nagar, Hyderabad-50062, India	
Study dates	13th May 2015 – 11th June 2015	
Primary objective	To compare and evaluate the oral bioavailability of Sofosbuvir Film coated tablets 400mg manufactured by Mylan Laboratories Ltd, India and Sovaldi™ (Sofosbuvir) film coated tablets 400mg manufactured by Patheon Inc. Mississauga, ON L5N 7K9, Canada, in healthy adult human subjects under fed conditions	
Secondary objective	To monitor the safety of the subjects	
Number of participants	Planned for Completion: 80 Screened: 89 Enrolled and Randomized: 80 Dropouts/ Withdrawals: 2 Completed study: 78	
Monitored parameters		
Investigational medicinal products	Test Product	Reference product
	Strength: 400 mg Batch number: 2008668 Expiry date: Feb 2017	Strength: 400 mg Batch number: PKYBD Expiry date: June 2016
Analytical method	High Performance Liquid chromatograph with tandem mass spectrometry (LC-MS/MS)	
Statistical method	SAS®, Version 9.1 and WinNonlin® professional software Version 5.3	

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	N	CV (%)
AUC0-t (ng.hr/mL)	1446.365	1448.398	99.86	95.96 – 103.92	78	15.032
AUC0-inf (ng.hr/mL)	1461.593	1472.744	99.24	95.43 – 103.21	77	14.675
Cmax (ng/mL)	1173.179	1136.521	103.23	94.97 – 112.20	78	32.055

The acceptance limits of 80 – 125% are met by the AUC and Cmax values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, MYHEP 400 is equivalent and interchangeable with Sovaldi™ under acceptable in vivo experimental conditions.

4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. MYHEP 400 is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date
TFDA0016/HM/0050/A1	14th July 2017	1. Change in the manufacturing process of Sofosbuvir API. 2. Addition of batch size i.e. 465.000 kg equivalent to 387,500 Tablets, 840.000 kg equivalent to 700,000 Tablets and 1680.000 kg equivalent to 1,400,000 Tablets for MYHEP 400 mg (Sofosbuvir Tablets 400 mg)	Approved	22nd November 2021

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

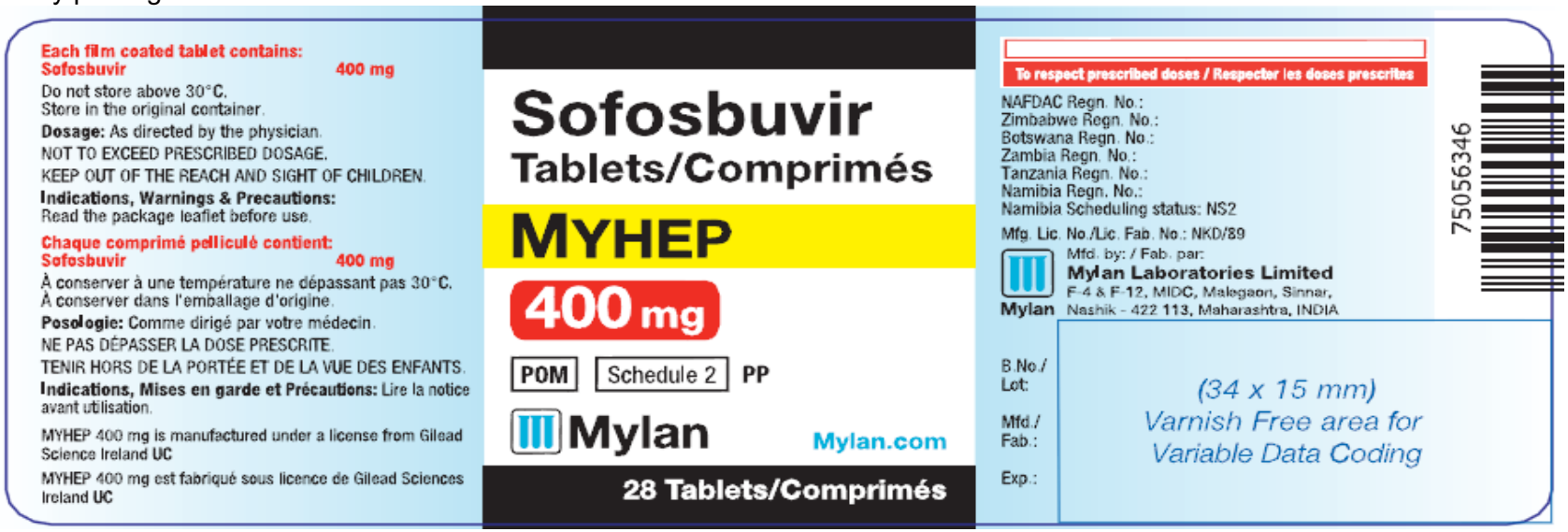
Re-registration applications
NA

PART 5: CHANGE HISTORY

Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up label

Primary package label



Secondary package label