THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

# PUBLIC ASSESSMENT REPORT FOR MyHEP DVIR (DACLATASVIR DIHYDROCHLORIDE EQUIVALENT TO DACLATASVIR 60 MG/ SOFOSBUVIR 400 MG) FILM-COATED TABLETS

**Version number 1.0**
**21 August, 2023**

**TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Hombolo Road, P. O. Box 1253, Dodoma – Tanzania, Telephone: +255 (26) 2961989/2061990/+255 (22) 2450512/2450751/2452108, Email: info@tmda.og.tz,** Website: **www.tmda.go.tz**

Toll free: 0800110084

## 1. Introduction

MyHEP DVIR contains daclatasvir (as dihydrochloride) and sofosbuvir. Daclatasvir is an inhibitor of non-structural protein 5A (NS5A), a multifunctional protein that is an essential component of the HCV replication complex. Daclatasvir inhibits both viral RNA replication and virion assembly. 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. GS-461203 (the active metabolite of sofosbuvir) is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase. MyHEP DVIR is approved in Tanzania for use in adults only.

**Product details**

| | |
|---|---|
| Registration number | TAN 23 HM 0235 |
| Brand name | MyHEP DVIR |
| Generic name, strength, and form | Daclatasvir Dihydrochloride equivalent to Daclatasvir 60 mg.<br>Sofosbuvir 400 mg |
| ATC classification | Daclatasvir J05AX14<br>Sofosbuvir J05AX15 |
| Distribution category | POM |
| Country of origin | India |
| Associated product | N/A |
| Marketing Authorization Holder | Mylan Laboratories Limited<br>Plot No. 564/A/22, Road No. 92, Jubilee Hills, Hyderabad - 500034,<br>Telangana, India. |
| Local Technical Representative | Pyramid Pharma Limited<br>P.O. Box 16215,<br>Dar es Salaam |

### 1.1 Assessment procedure

The application for registration of MyHEP DVIR was submitted on 07/02/2016. The product underwent full assessment. Assessment was completed in 5 (five) rounds of evaluation and the product was registered on 01/06/2023.

### 1.2 Information for users

| | |
|---|---|
| Visual description of the finished product | A Peach coloured, modified capsule shaped, biconvex bevelled edge film-coated tablet debossed with “M” on one side and “DTS” on the other side |
| Primary packing material | high density polyethylene (HDPE) bottles with desiccant |

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|---|---|
| Secondary packing materials | Printed carton box |
| Shelf-life and storage condition | 24 months, Do not store above 30°C, store in the original container. |
| Route of administration | Oral |
| Therapeutic indications | Indicated in treatment of chronic hepatitis C (CHC) in adults. For hepatitis C virus (HCV) genotype specific activity. |

## 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 DVIR

Composition: Daclatasvir Dihydrochloride equivalent to Daclatasvir 60 mg. Sofosbuvir 400 mg

Pack size: 28 tablets

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Do not store above 30°C, store in the original container

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Formulation contains lactose

The details of the primary pack include:

Brand name and strength: MyHEP DVIR (Daclatasvir Dihydrochloride equivalent to Daclatasvir 60 mg. Sofosbuvir 400 mg)

Manufacturing details: batch number, manufacturing date and 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 Ingredients

Information on the quality of the APIs was submitted in form of DMFs.

**<u>Daclatasvir Dihydrochloride</u>**

### General Information

Daclatasvir Dihydrochloride API is non-compendia.

Molecular formula: $C_{12}H_{22}O_{11}$

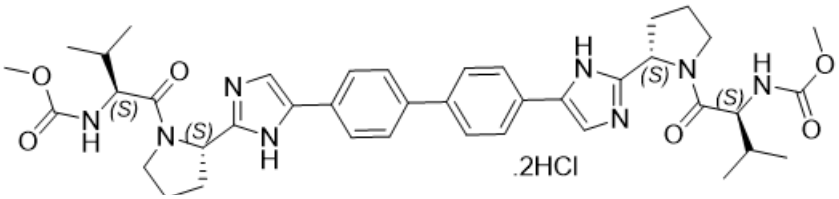
Chemical name:

Methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2 ((methoxycarbonyl)amino) -3-methylbutanoyl)-2-pyrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl) carbamate dihydrochloride.

Or

Carbamic acid, N,N'-[[ l,1'-biphenyl]-4,4'-diylbis [1H-imidazole-5,2-diyl(2S) -2,1-pyrrolidinediyl [(1S)-1-(1-methylethyl)-2-oxo-2, 1-ethanediyl]]] bis-,C,C'-dimethylester, hydrochloride (1:2)

Structure:




### General properties

Daclatasvir Dihydrochloride is a white to yellow colored powder and freely soluble in methanol and soluble in water. The API is of BCS low solubility; hence particle size distribution and polymorphism are considered critical parameters. These two parameters form part of the FPP manufacturer's API specifications, with acceptance criteria set on the information of the API lot used in the FPP biobatch.

## Manufacture

Daclatasvir Dihydrochloride API manufacturer is Mylan Laboratories Limited (Unit-8), G Chodavaram, Poosapatirega Mandal, Vizianagaram District – 535204, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the Drugs Control Administration, Andhra Pradesh, India. Daclatasvir Dihydrochloride 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

Specifications

The API specifications were set as per in-house standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, identification, water content, residue on ignition, heavy metals, enantiomeric purity, residual solvents, organic impurities, mesityl oxide content, polymorphism, and assay. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The retest period of Daclatasvir Dihydrochloride API is 60 months when packed in original container with storage condition ‘Store in a well-closed container at 25°C, excursion permitted between 15°C and 30°C’.

# Sofosbuvir

## General Information

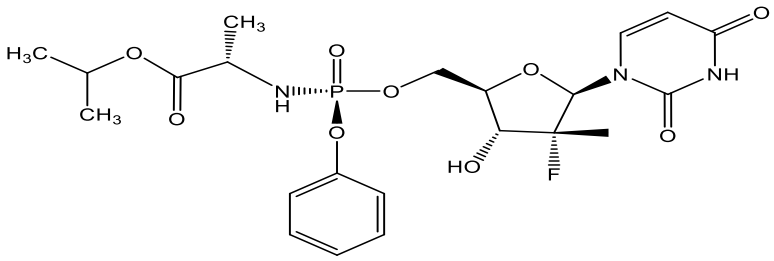
Sofosbuvir API is non-compendia.

Molecular formula: $C_{22}H_{29}FN_3O_9P$

Chemical name:

S)-Isopropyl-2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro pyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran -2-yl) methoxy)-(phenoxy)phosphorylamino) propanoate

Structure:



**General properties**

Sofosbuvir is a white to off-white powder and very slightly soluble in water. The API is of BCS low solubility; hence particle size distribution and polymorphism are considered critical parameters. These two parameters form part of the FPP manufacturer's API specifications, with acceptance criteria set on the information of the API lot used in the FPP biobatch.

**Manufacture**

Sofosbuvir API manufacturer is Mylan Laboratories Limited (Unit-8), G Chodavaram, Poosapatirega Mandal, Vizianagaram District – 535204, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the Drugs Control Administration, Andhra Pradesh, India. 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**

Specifications

The API specifications were set as per in-house standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, identification, water content, heavy metals, content of pentafluoro phenol and phosphoramidate intermediate, residual solvents, organic impurities, content of n, n-diisopropyl ethylamine, polymorphism, and assay. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The retest period of Sofosbuvir API is 24 months when packed in original container with storage condition 'Store in a well-closed container at 25°C, excursion permitted between 15°C and 30°C'.

## Quality of the Finished Pharmaceutical Product

### Formulation

MyHEP DVIR is a peach colored, modified capsule shaped biconvex beveled edge film coated tablet debossed with "M" on one side and "DTS" on the other side.

MyHEP DVIR contains the Daclatasvir Dihydrochloride and Sofosbuvir and other ingredients listed here after: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, purified water Opadry® II orange 85f530025 (polyvinyl alcohol - part. hydrolyzed, titanium dioxide, macrogol/peg, talc, iron oxide yellow, iron oxide red, ferroso ferric oxide/black iron oxide). The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8$^{th}$ Edition in terms of function and quantities. Lactose is of safety concern therefore appropriate warnings were included in the product label.

### Manufacture

The finished product manufacturer is Mylan Laboratories Limited (FDF Unit – 1), F- 4 & F-12, MIDC, Malegaon, Sinnar, Nashik - 422 113, Maharashtra, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY

### Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: appearance, identification of APIs, uniformity of dosage units (content uniformity), dissolution, organic impurities, water, assay, and microbial quality. Compliance to the standard was established using batch analysis data and stability data.

### Stability and container closure system

Stability studies were conducted on 3(three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 24 months and 40± 2°C & RH: 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 with storage condition ‘Do not store above 30°C, store in the original container.’

### Safety and efficacy information

Safety and efficacy of MyHEP DVIR was established through a bioequivalence trial.

BE trial report number C17437 was submitted.

| | |
|---|---|
| Study title | A randomized, balanced, two treatment, four period, two-sequence, single dose, full replicate, cross over oral bioequivalence study of My Hep DVIR (Daclatasvir/Sofosbuvir) 60 mg /400 mg comprimes pellicules (Tablets) of Mylan Laboratories Limited, India with DAKLINZA™ (Daclatasvir) tablets 60 mg (Bristol-Myers Squibb Company, Princeton, NJ08543, USA) and Sovaldi® (Sofosbuvir) |

<table>
<tr><td></td><td>400 mg Film-coated Tablets (Gilead sciences International Ltd. Cambridge CB 216GT United Kingdom) in normal, healthy, adult, human subjects under fasting conditions</td></tr>
<tr><td>Study design</td><td>Comparative_randomized, balanced, two treatments, four period, two-sequence, single dose, full replicate, cross over under fasting condition</td></tr>
<tr><td>Study sites</td><td>Clinical center and Pharmacokinetic and<br>Statistical center:<br>Clinical Development Division<br>Aizant Drug Research Solutions Pvt. Ltd<br>Survey No.: 172&173, Apparel Park Road,<br>Duapally Village, Qutubullapur Mandal, Hyderbad, India-500100<br><br>Bioanalytical Site<br>Mylan Laboratories Limited<br>Clinical Research Centre, Saradhi Chambers, Plot No. 4A<br>Beside Poulomi Hospital, Rukminipuri<br>Dr. A. S. Rao Nagar, Hyderbad 500062</td></tr>
<tr><td>Study dates</td><td>
<table>
<tr><th>Activities</th><th>Dates</th></tr>
<tr><td>Period I</td><td>Check in date: 07th May 2018<br>Date of first dosing: 08th May 2018<br>Discharge date: 09th May 2018<br>Date of last collected sample: 10th May 2018</td></tr>
<tr><td>Period II</td><td>Check in date: 22nd May 2018<br>Date of first dosing: 23rd May 2018<br>Discharge date: 24th May 2018<br>Date of last collected sample: 25th May 2018</td></tr>
<tr><td>Period III</td><td>Check in date: 09th June 2018<br>Date of first dosing: 10th June 2018<br>Discharge date: 11th June 2018<br>Date of last collected sample: 12th June 2018</td></tr>
<tr><td>Period IV</td><td>Check in date: 25th June 2018<br>Date of first dosing: 26th June 2018</td></tr>
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| | | |
|---|---|---|
| | | Discharge date: 27th June 2018<br>Date of last collected sample: 28th June 2018 |
| | Analysis (start date) | 02nd July 2018 |
| | Analysis (completion date) | 17th July 2018 |
| Primary objective | To investigate the bioequivalence of test product relative to reference product to healthy adults under fasting conditions | |
| Secondary objective | To monitor the safety and tolerability of a single dose of each product | |
| Number of participants | Planned-48 + 02 (additional)) subjects<br>Enrolled-48 + 02 (additional)) subjects<br>Dosing was as follows<br>Period-1: 48 subjects<br>Period-2: 42 subjects<br>Period-3: 46 subjects<br>Period-4: 45 subjects<br>Withdrawn - 11 subject<br>Bio-sample analyzed -48 subjects<br>Pharmacokinetic and statistical data analyzed – 37 subjects | |
| Monitored parameters | Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2 | |
| Investigational medicinal products | Test Product | Reference product |
| | Strength: Daclatasvir/Sofosbuvir) 60 mg /400 mg<br>Batch number: 3062517<br>Expiry date: 12/2018 | Strength: Sofosbuvir 400 mg<br>Batch number: WPZPD<br>Expiry date: 06/2018<br><br>Strength: Daclatasvir 60 mg<br>Batch number: JJ0360<br>Expiry date: 012019 |
| Analytical method | High Pressure Liquid chromatography – MS/MS – detector (LC-MS/MS) method was used for the determination of plasma concentrations of analyte | |
| Statistical method | SAS software version 9.2 | |

Efficacy results are summarized as follows:

Daclatasvir

| Parameters (Units) | Ratio of Geometric Least Squares Means | | | Acceptable Lower BE Limit (%) | Acceptable Upper BE Limit (%) | 90% Confidence Limits |
|---|---|---|---|---|---|---|
| | Test product (T) | Reference product (R) | (T/R)% | | | (T vs. R) |
| $C_{max}$ (ng/mL) | 1476.4399 | 1505.6365 | 98.06 | 75.81 | 131.91 | 91.86-104.68 |
| $AUC_{0-t}$ (ng.hr/mL) | 15978.9751 | 16084.7272 | 99.34 | 80.00 | 125.00 | 93.99-105.00 |
| $AUC_{0-inf}$ (ng.hr/mL) | 17172.9780 | 17330.7229 | 99.09 | 80.00 | 125.00 | 93.68-104.81 |

Sofosbuvir

| Parameters (Units) | Ratio of Geometric Least Squares Means | | | Acceptable Lower BE Limit (%) | Acceptable Upper BE Limit (%) | 90% Confidence Limits |
|---|---|---|---|---|---|---|
| | Test product (T) | Reference product (R) | (T/R)% | | | (T vs. R) |
| $C_{max}$ (ng/mL) | 1625.4665 | 1458.9713 | 111.41 | 69.83 | 143.21 | 100.60 -123.38 |
| $AUC_{0-t}$ (ng.hr/mL) | 1847.5201 | 1740.6457 | 106.14 | 80.00 | 125.00 | 99.53-113.19 |
| $AUC_{0-inf}$ (ng.hr/mL) | 1860.2153 | 1752.7127 | 106.13 | 80.00 | 125.00 | 99.59-113.11 |

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, My Hep DVIR (Daclatasvir/Sofosbuvir) 60 mg /400 mg Tablets of Mylan Laboratories Limited, India is equivalent and interchangeable with DAKLINZA™ (Daclatasvir) tablets 60 mg (Bristol-Myers Squibb Company, Princeton, NJ08543, USA) and Sovaldi® (Sofosbuvir) 400 mg Film-coated Tablets (Gilead sciences International Ltd. Cambridge CB 216GT United Kingdom) 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 DVIR is recommended for registration.

## 5. Post-approval updates

### Variation applications

| Reference number | Date submitted | Change requested | Recommendation | Granting date |
|---|---|---|---|---|
| | | | | |
| | | | | |

### Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

| Type of feedback | Impact | Response |
|---|---|---|
| | | |

**Re-registration applications**

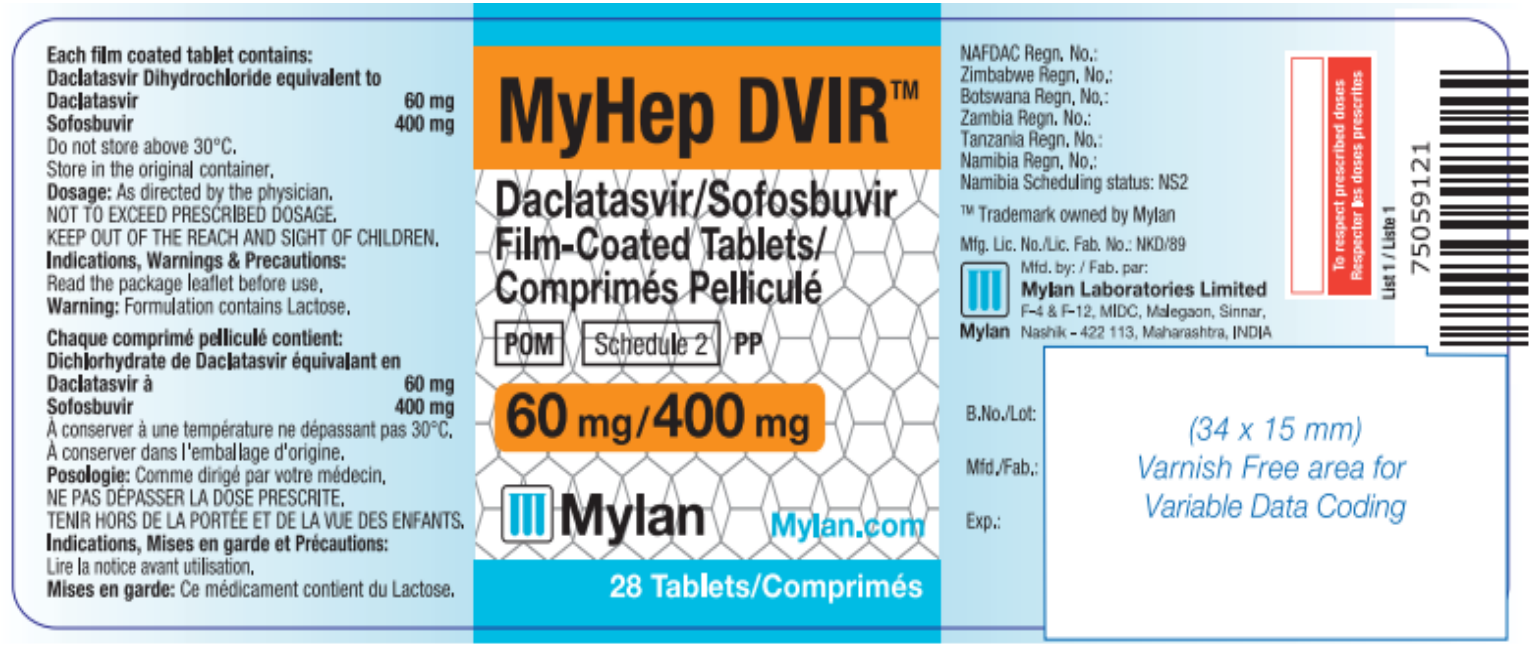
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

## PART 5: CHANGE HISTORY

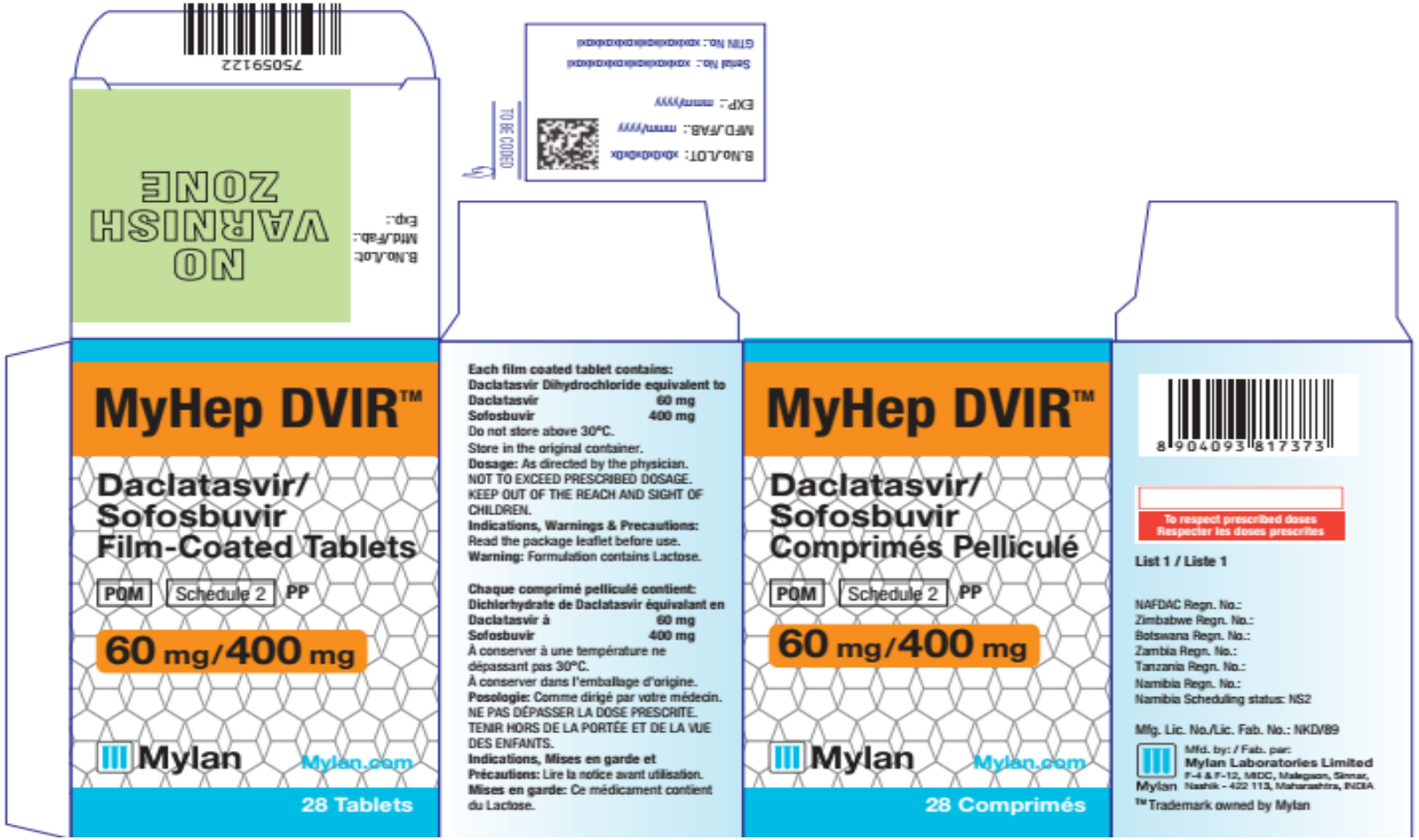
| Version number | Date | Description of update | Section(s) Modified | Approval date |
|---|---|---|---|---|
| | | | | |

**Annex I: Mock up labels;**

Primary pack label;



Secondary pack label:




Effective date: 03/10/2022