TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR MYDEKLA™ 60 (DACLATASVIR 60 MG) FILM COATED TABLETS

Version number 1,
23 March, 2022

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1. Introduction

MyDekla 60 is a generic medicine of innovator product Daklinza tablets manufactured by Bristol-Myers Squibb S.r.l., Italy. MyDekla 60 contains Daclatasvir Dihydrochloride which is in a group of antivirals for systemic use belonging to ATC code J05AP07; Antivirals for treatment of HCV infections.

The applicant has applied for the following indication; MyDekla 60 is indicated in combinations with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults. The applied indication has been approved in Tanzania.

1.1 Product details

Registration number	TAN 21 HM 0062
Brand name	MyDekla 60
Generic name, strength and form	Daclatasvir Dihydrochloride 60 mg
ATC classification	J05AP07
Distribution category	POM
Country of origin	India
Associated product	MyDekla 30 and MyHep DVIR from the same MAH, they are under reveiw
Marketing Authorization Holder	Mylan Laboratories Limited, Plot No. 564/A/22, Road No. 92, Jubilee Hills, Hyderabad - 500034, Telangana, India. kulbhushan.ganotra@mylan.in
Local Technical Representative	Pyramid Pharma Limited, 1st floor, TTCL Building, Garden Road/New Bagamoyo Road, Kijitonyama, P. O. Box 16215, Dar Es Salaam. Tanzania. E-Mail: aokore@pyramidpharma.com

1.2 Assessment procedure

The application for registration of MyDekla 60 was submitted on 05 October, 2016. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 24 December, 2020.

1.3 Information for users

Visual description of the finished product	A green film-coated, PENTAGON shaped, biconvex tablet debossed with “DT” on one side and “60” on the other side
Primary packing material	Round, blue opaque 40 cc HDPE bottle with 33 mm neck and 33mm blue opaque polypropylene screw closure with wad containing aluminium induction sealing liner (Pack size: 28 tablets)
Secondary packing materials	Printed Carton Box
Shelf-life and storage condition	24 months when stored at or below 30°C in its

	origin container
Route of administration	Oral
Therapeutic indications	Daclatasvir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults

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: MyDekla 60
Composition: Each film-coated tablet contains: Daclatasvir Dihydrochloride equivalent to Daclatasvir 60 mg
Pack size: 28 tablets in Blue HDPE bottle
Manufacturing details: batch number, manufacturing date, expiry date are indicated
Storage conditions: Do not store above 30^0C. Store in the original container
Manufacturer address: physical address of release site is indicated
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: MyDekla 60 (Daclatasvir 60 mg)
Manufacturing details: batch number, manufacturing date, expiry date is indicated
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 from two manufacturers was submitted in form of DMF.

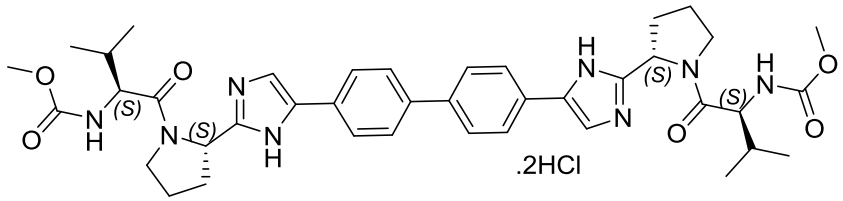
General Information

Daclatasvir Dihydrochloride API is non-compendia.

Molecular formular: $C_{40}H_{50}N_8O_6.2HCl$

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

Structure:



Daclatasvir Dihydrochloride

General properties

Daclatasvir is a white to yellow crystalline non-hygroscopic powder. It is freely soluble in water, dimethyl sulfoxide, methanol, soluble in ethanol (95%), practically insoluble in dichloromethane, tetrahydrofuran, acetonitrile, acetone and ethyl acetate. Daclatasvir is a chiral molecule with four stereocenters in the S configuration. It exhibits polymorphism. The manufacturing process consistently produces the same polymorphic form.

Manufacture

The API Daclatasvir Dihydrochloride is sourced from two different manufacturers.

The API manufacturing site, Mylan Laboratories Limited (Unit-8), G Chodavaram, Poosapatirega Mandal, Vizianagaram District – 535204 Andhra Pradesh, India was noted to comply with cGMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration, Government of Andhra Pradesh, India. Daclatasvir 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.

The API manufacturing site, Laurus Labs Private Limited located at Plot No. 21, Jawaharlal Nehru Pharma City, Parawada, Vishakhapatnam – 531 021, Andhra Pradesh, India was noted to comply with cGMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration, Government of Andhra Pradesh, India. Daclatasvir 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 Daclatasvir is non compendia, specifications were set as per in-house standards and ICH guidelines. The parameters monitored during quality control are: description, solubility, identification (by IR, HPLC and test for Chlorides), water content (by KF), residue on ignition, heavy metals, enantiomeric purity (HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), mesityl oxide content (GC) and identification of Polymorph (PXRD). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of Daclatasvir API is 48 months when packed in LDPE bag and stored at or below 25°C.

Quality of the Finished Pharmaceutical Product

Formulation
MyDekla 60 is a green film-coated, PENTAGON shaped, biconvex tablet debossed with "DT" on one side and "60" on the other side. Such 28 tablets are packed in a round, blue opaque 40 cc HDPE bottle with 33 mm neck and 33mm blue opaque polypropylene screw closure with wad containing aluminium induction sealing liner.

MyDekla 60 contains the API Daclatasvir Dihydrochloride.

The excipients are: Lactose anhydrous (Supertab 21 AN), Silicified Microcrystalline cellulose (Prosolv 90), Croscarmellose Sodium (Ac-Di-Sol), Magnesium Stearate (Hyqual), Silica, Colloidal anhydrous (Aerosil 200 pharma), Opadry green 03B510052 and Purified Water.

The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 7th Edition in terms of function and quantities. The formulation contains Lactose anhydrous which is of safety concern therefore appropriate warnings are included in the product label and summary of product characteristics (SmPC).

Manufacture
The finished product manufacturer is Mylan Laboratories Limited located at F- 4 & F-12, MIDC, Malegaon, Sinnar, Nashik -422 113, Maharashtra, India. The manufacturing site complies with TMDA cGMP standards.

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: Description, Identification (HPLC and UV), Color identifications (for Iron Oxide and Titanium dioxide), Dissolution (HPLC), Uniformity of dosage units (By content uniformity), Assay (HPLC), related substances (HPLC), Water (KF) and microbial tests. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system
Stability studies were conducted on 6 (six) batches (three batches were for the API sourced from Mylan Laboratories Ltd and the other three were for the API sourced from Laurus Labs Pvt Ltd) of the finished product stored at 30°C ± 2°C/75 ± 5 % RH for 18 months and 40°C ± 2°C/75 ± 5 % RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Blue HDPE Bottle of 28 tablets at or below 30◦C.

Safety and efficacy information

Safety and efficacy of MyDekla 60 was established through bioequivalence trial. BE trial report number C15239 was submitted.

Study title	A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral

<table>
<tr><td></td><td>bioequivalence study of Daclatasvir film-coated Tablets 60 mg of Mylan Laboratories Limited, India, with DAKLINZATM (daclatasvir) 60 mg Tablets, Manufactured for: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA, in normal healthy adult human subjects under fasting conditions</td></tr>
<tr><td>Study design</td><td>A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study</td></tr>
<tr><td>Study site</td><td>Clinical Development Division
Aizant Drug Research Solutions Pvt. Ltd.,
Survey No.: 172 & 173,
Apparel Park Road, Dulapally Village,
Quthbullapur Mandal,
Hyderabad, India-500100</td></tr>
<tr><td>Study dates</td><td>
<table>
<tr><th>Event</th><th>Period-1</th><th>Period-2</th></tr>
<tr><td>Check- in date</td><td>23 Dec 2015</td><td>06 Jan 2016</td></tr>
<tr><td>Dosing date</td><td>24 Dec 2015</td><td>07 Jan 2016</td></tr>
<tr><td>Check- out date</td><td>25 Dec 2015</td><td>08 Jan 2016</td></tr>
<tr><td>Period-2 (Last sample collected date)</td><td colspan="2">10 Jan 2016</td></tr>
<tr><td>Clinical study completion date (Last AE closed date)</td><td colspan="2">09 Feb 2016</td></tr>
</table>
</td></tr>
<tr><td>Primary objective</td><td>To evaluate the oral bioequivalence of Daclatasvir film-coated Tablets 60 mg of Mylan Laboratories Limited, India, with DAKLINZATM (daclatasvir) 60 mg Tablets, Manufactured for: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA, in normal healthy adult human subjects under fasting conditions</td></tr>
<tr><td>Secondary objective</td><td>To monitor the adverse events and to ensure the safety of the subjects</td></tr>
<tr><td>Number of participants</td><td>40 subjects</td></tr>
<tr><td>Monitored parameters</td><td>Cmax, AUC_{0-t}, AUC_{0-inf}, Tmax, t1/2, $AUC_{0-t}/AUC_{0-inf*100}$ and Kel</td></tr>
<tr><td>Investigational medicinal products</td><td>
<table>
<tr><td>Test Product</td><td>Reference product</td></tr>
<tr><td>Strength: Daclatasvir film coated Tablets 60 mg
Batch number: 2010608
Expiry date: Oct 2017</td><td>Strength: DaklinzaTM (daclatasvir) Tablets 60 mg
Batch number: 4G78431B
Expiry date: Dec 2016</td></tr>
</table>
</td></tr>
<tr><td>Analytical method</td><td>LC-MS/MS methods were used for the determination of plasma concentrations of analyte

The analyte (Daclatasvir) was extracted using a Solid Phase Extraction method

The analytical range was 10.004 – 2401.059 ng/ml in the biostudy</td></tr>
<tr><td>Statistical method</td><td>The statistical analysis was carried out according to the bioequivalence guideline</td></tr>
</table>

Efficacy results are summarized as follows:

Parameter	**Test**	**Reference**	**% Ratio of geometric**	**90 % Confidence interval**	**DF**	**CV (%)**

			means			
AUC0-t (ng. hr/mL)	*15239.983*	*15419.446*	*98.84*	*91.95 – 106.24*	*38*	*19.3*
AUC0-inf (ng. hr/mL)	*15701.376*	*15801.725*	*99.36*	*92.75 – 106.45*	*38*	*18.4*
Cmax (ng/mL)	*1500.394*	*1469.533*	*102.10*	*94.33 – 110.51*	*38*	*21.2*

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, *MyDekla 60* is equivalent and interchangeable with *DAKLINZA™ (daclatasvir) 60 mg Tablets* 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. *MyDekla 60* 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

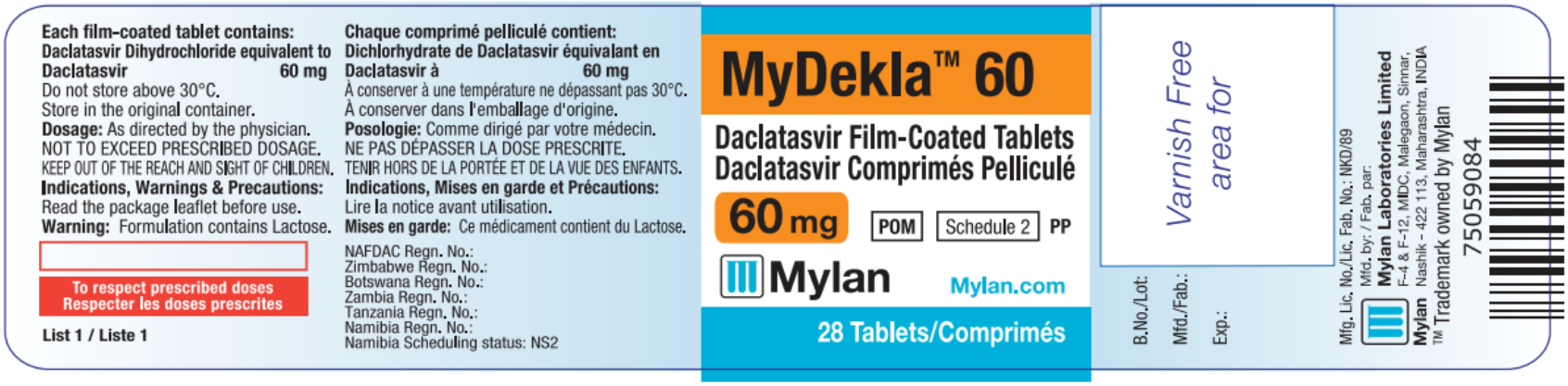
NA

PART 5: CHANGE HISTORY

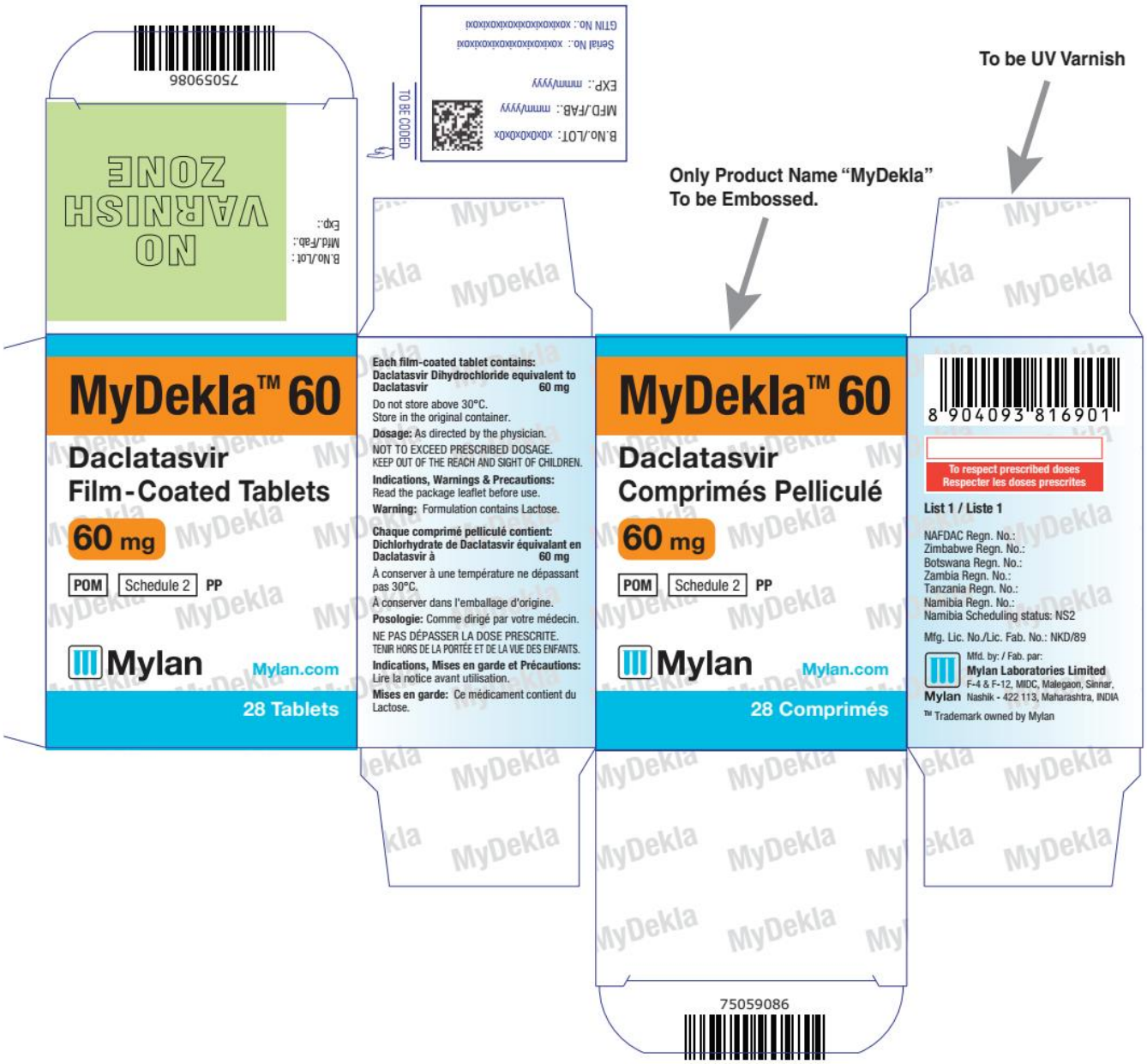
Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up label

Primary pack label;



Secondary pack label;


75059086
NO VARNISH ZONE
B.No./Lot:
Mfd./Fab.:
Exp.:
TO BE CODED
B.No./LOT: xxxxxxxx
MFD./FAB.: mmm/yyyy
EXP.: mmm/yyyy
Serial No.: xxxxxxxxxxxxxxxx
GTIN No.: xxxxxxxxxxxxxx
To be UV Varnish
Only Product Name "MyDekla"
To be Embossed.
MyDekla™ 60
Daclatasvir
Film-Coated Tablets
60 mg
POM Schedule 2 PP
Mylan
Mylan.com
28 Tablets
Each film-coated tablet contains:
Daclatasvir Dihydrochloride equivalent to Daclatasvir 60 mg
Do not store above 30°C.
Store in the original container.
Dosage: As directed by the physician.
NOT TO EXCEED PRESCRIBED DOSAGE.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Indications, Warnings & Precautions:
Read the package leaflet before use.
Warning: Formulation contains Lactose.
Chaque comprimé pelliculé contient:
Dichlorhydrate de Daclatasvir équivalant en Daclatasvir à 60 mg
À conserver à une température ne dépassant pas 30°C.
À conserver dans l'emballage d'origine.
Posologie: Comme dirigé par votre médecin.
NE PAS DÉPASSER LA DOSE PRESCRITE.
TENIR HORS DE LA PORTÉE ET DE LA VUE DES ENFANTS.
Indications, Mises en garde et Précautions:
Lire la notice avant utilisation.
Mises en garde: Ce médicament contient du Lactose.
MyDekla™ 60
Daclatasvir
Comprimés Pelliculé
60 mg
POM Schedule 2 PP
Mylan
Mylan.com
28 Comprimés
8 904093 816901
To respect prescribed doses
Respecter les doses prescrites
List 1 / Liste 1
NAFDAC Regn. No.:
Zimbabwe Regn. No.:
Botswana Regn. No.:
Zambia Regn. No.:
Tanzania Regn. No.:
Namibia Regn. No.:
Namibia Scheduling status: NS2
Mfg. Lic. No./Lic. Fab. No.: NKD/89
Mfd. by: / Fab. par:
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F-4 & F-12, MIDC, Malegaon, Sinnar,
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