THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR DARUNAVIR ETHANOLATE 400 MG AND RITONAVIR 50 MG FILM COATED TABLETS

Version number 01, 03/01/2023

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1. Introduction

Darunavir/Ritonavir tablets is an antiretroviral fixed dose bilayer formulation of the individual components that make up of Darunavir ethanolate and Ritonavir that has activity against HIV-1 that can be considered as generic combination of Prezista® (darunavir) tablet 400 mg of Janssen Ortho LLC, Gurabo, PR 00778 and Norvir® (ritonavir) tablet 50 mg of Abbvie Inc. North Chicago, IL 60064 USA.

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. Pharmacokinetic enhancement by ritonavir is based on its potent inhibition of CYP3A- mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co administered protease inhibitor and the impact of the co-administered protease inhibitor on the metabolism of ritonavir. Darunavir/Ritonavir tablets is approved in Tanzania for use in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing at least 40 kg.

1.1 Product details

Registration number	TAN 21 HM 0403
Brand name	Darunavir/Ritonavir
Generic name, strength and form	Darunavir (as ethanolate) / Ritonavir 400mg /50mg tablets
ATC classification	Antivirals for systemic use, protease inhibitors (darunavir: J05AR14, ritonavir: J05AE03)
Distribution category	POM
Country of origin	India
Associated product	Darunavir and Ritonavir Tablets 800mg/100mg
Marketing Authorization Holder	Hetero Labs Limited, 7-2-A2, Hetero Corporate, Industrial Estates, Sanath Nagar, Hyderabad-500 018. Telangana state, India.
Local Technical Representative	Kas Medics Limited, Umoja Complex Plot No.11, Vingunguti Industrial Area Along Nyerere Road, Dar-Es-Salaam, Tanzania.

1.2 Assessment procedure

The application for registration of Darunavir/Ritonavir tablets was submitted on 23/07/2021. The product underwent full assessment. Assessment was completed in 2(two) rounds of evaluation. Darunavir/Ritonavir tablets was registered on 09/10/2021.

1.3 Information for users

Visual description of the finished product	Yellow, capsule shaped, bevel edged, biconvex film coated tablets debossed with 'H' on one side and 'D24' on the other side
Primary packing material	30’s, 60’s, and 120’s count HDPE bottles
Secondary packing materials	N/A
Shelf-life and storage condition	24 months, Do not store above 30°C. Keep container tightly closed, dispense in original container
Route of administration	Oral
Therapeutic indications	Indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing at least 40 kg

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 that is intended for long term use, the package insert contains both full prescribing information as per SmPC and simplified information for patients.

Container labels

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

Brand name: Darunavir/Ritonavir

Composition: Each Film coated tablets contains 433.640 mg of Darunavir Ethanolate equivalent to 400 mg of Darunavir and Ritonavir USP 50 mg

Pack size: 30’s, 60’s, and 120’s tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Do not store above 30°C. Keep container tightly closed, dispense in original container

Manufacturer address: Hetero Labs Limited, Unit III, 22-110, IDA, Jeedimetla, Hyderabad, Telangana, India.

Unique identifier: N/A

Special warnings/precautions or instructions for use: Find out about medicines that should NOT be taken with Darunavir and Ritonavir. Note to pharmacist: Do not cover ALERT box with pharmacy label

The details of the primary pack include:
Brand name and strength: Darunavir/Ritonavir
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Hetero Labs 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 quality of the APIs was submitted in form of Full details.

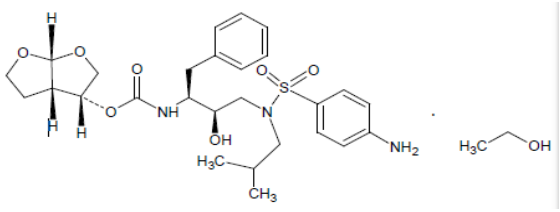
Darunavir ethanolate

General properties
Darunavir ethanolate API is non-compendia.

Molecular formula: $C_{27}H_{37}N_3O_7S.C_2H_5OH$

Chemical names: [(1S,2R-3-[[(4-Amino-phenyl) sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]-furan-3-yl ester monoethanolate

Structure:



Critical physico-chemical properties are:

Darunavir ethanolate is an off-white to cream colour hygroscopic powder. The structure and absolute configuration have been confirmed with single crystal X-ray crystallography. The manufacturer consistently produces crystalline polymorphic form A, which is routinely controlled by XRD in the specifications of the API.

Darunavir is poorly soluble substance according to the BCS is a class II substance, therefore control of polymorphism and particle size is considered critical. The control of particle size

distribution was demonstrated in the API specifications. The PSD limits are based on the results obtained for the API batch used in the manufacture of the FPP biobatch.

Manufacture

The API manufacturing site, Hetero Labs Limited, Unit-IX, Plot No.2, Hetero Infrastructure SEZ Ltd., N. Narasapuram (Village), Nakkapalli (Mandal), Visakhapatnam District - 531 081, Andhra Pradesh, INDIA. was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration of Andhra Padesh, India. Darunavir ethanolate 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: description, solubility, identification (IR, HPLC and XRPD), water content (KF), residue on ignition, related substances (HPLC), ethanol content (GC), assay (HPLC), residual solvents (GC), specific optical rotation and particle size distribution (PSD). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Darunavir ethanolate API is 30 months when packed in stored in the original packing material and stored at in a refrigerator (2 °C to 8 °C), protect from light, protect from moisture.

Ritonavir

General properties

Ritonavir API is described in the Ph. Int, Ph. Eur, and USP.

Molecular formula: $C_{37}H_{48}N_6O_5S_2$

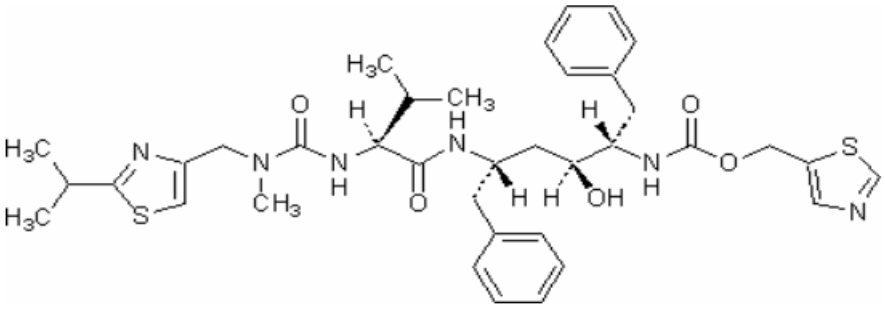
Chemical names:

i) 2, 4, 7, 12-Tetraazatridecan-13-oic acid, 10-hydroxy- 2- methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4- thiazolyl]-3,6- dioxo-8,11-bis (phenyl methyl)-5- thiazolymethyl ester [5S- (5R*,8R*,10R*,11R*)]

ii) 5-Thiazolylmethyl [(αS)- α-[(1S,3S)-1-hydroxy-3- [(2S)-2-[3- [(2-isopropyl-4-thiazolyl)methyl]-3- methylureido]-3- methyl butyramido] -4 phenyl butyl] phenethyl] carbamate

iii) Thiazol-5-ylmethyl[(1S,2S,4S)-1-benzyl-2-hydroxy-4- [[(2S)-3- methyl-2-[[methyl[[2-(1-methylethyl) thiazol- 4-yl] methyl] carbamoyl] amino] butanoyl] amino]-5 phenylpentyl] carbamate

Structure:



Critical physico-chemical properties are:

The API has four chiral centres, is practically insoluble in water and is known to exhibit polymorphism, with various crystal forms. The manufacture of ritonavir entails several steps and stereo selectively produces the desired stereoisomer. Polymorphic form II, characterised by the XRPD pattern, is consistently produced.

Ritonavir is a BCS class IV compound (low solubility and low permeability), nevertheless the polymorphic form and particle size distribution of the active substance are not considered critical quality attributes for the tablet formulation since the active substance undergoes a hot melt extrusion process and is rendered amorphous during the finished product manufacturing process.

Manufacture

The API manufacturing site, Hetero Labs Limited, Unit-IX, Plot No.2, Hetero Infrastructure SEZ Ltd., N. Narasapuram (Village), Nakkapalli (Mandal), Visakhapatnam District - 531 081, Andhra Pradesh, INDIA. was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration of Andhra Padesh, India. Ritonavir 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 USP, in-house standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, identification (IR, HPLC), polymorphic form (XRPD), water content (KF), residue on ignition, related substances (HPLC), assay (HPLC), specific optical rotation, residual solvents (GC), microbial limit. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Darunavir ethanolate API is 12 months when packed in stored in the original packing material and stored at 25ºC, excursions permitted between 15ºC and 30ºC.

Quality of the Finished Pharmaceutical Product

Formulation

Darunavir/Ritonavir tablets is a yellow, capsule shaped, bevel edged, biconvex film coated tablets debossed with 'H' on one side and 'D46' on the other side.

Darunavir/Ritonavir tablets contains Darunavir ethanolate and Ritonavir and other ingredients listed here after: crospovidone, hypromellose 5 cps, silicified microcrystalline cellulose, copovidone, colloidal silicon dioxide, magnesium stearate, sorbitan monolaurate, dibasic calcium phosphate anhydrous, dibasic calcium phosphate dihydrate, microcrystalline cellulose, corn starch, mannitol, sodium stearyl fumarate, purified water, HPMC 2910/ hypromellose 6 cP, titanium dioxide, macrogol/peg 400, HPMC 2910/Hypromellose 15 cP, hydroxypropyl cellulose, iron oxide yellow, talc, macrogol/peg 3350, colloidal anhydrous silica, polysorbate 80. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8^{th} in terms of function and quantities.

Manufacture

The finished product was manufactured at Hetero Labs Limited, Unit III,22-110, IDA,Jeedimetla, Hyderabad, Telangana, INDIA.The compliance of the site to TMDA GMP standards was confirmed through site inspection on 02/07/2020.

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 of APIs (TLC and HPLC), average weight, water content (KF), dissolution (HPLC detection), uniformity of dosage units (content uniformity), related substances (HPLC), assay (HPLC), and microbial limits. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three (3) batches of the finished product stored at 30^0 ± 2°C & 75% ± 5% RH for 24 months and 40^0 ± 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 bottles at Do not store above 30°C. Keep container tightly closed, dispense in original container.

Safety and efficacy information

The biowaiver was approved based on additional strength.

Darunavir/Ritonavir tablets fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of Darunavir (as ethanolate) / Ritonavir 400mg /50mg tablets was compared to Darunavir (as ethanolate) / Ritonavir 800mg /100mg tablets. Less than 85% of the labelled amount of Darunavir and Ritonavir had dissolved in all three media. Therefore, necessitating calculation of similarity factor f2, which was noted to be above 50.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe 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. Darunavir/Ritonavir tablets 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

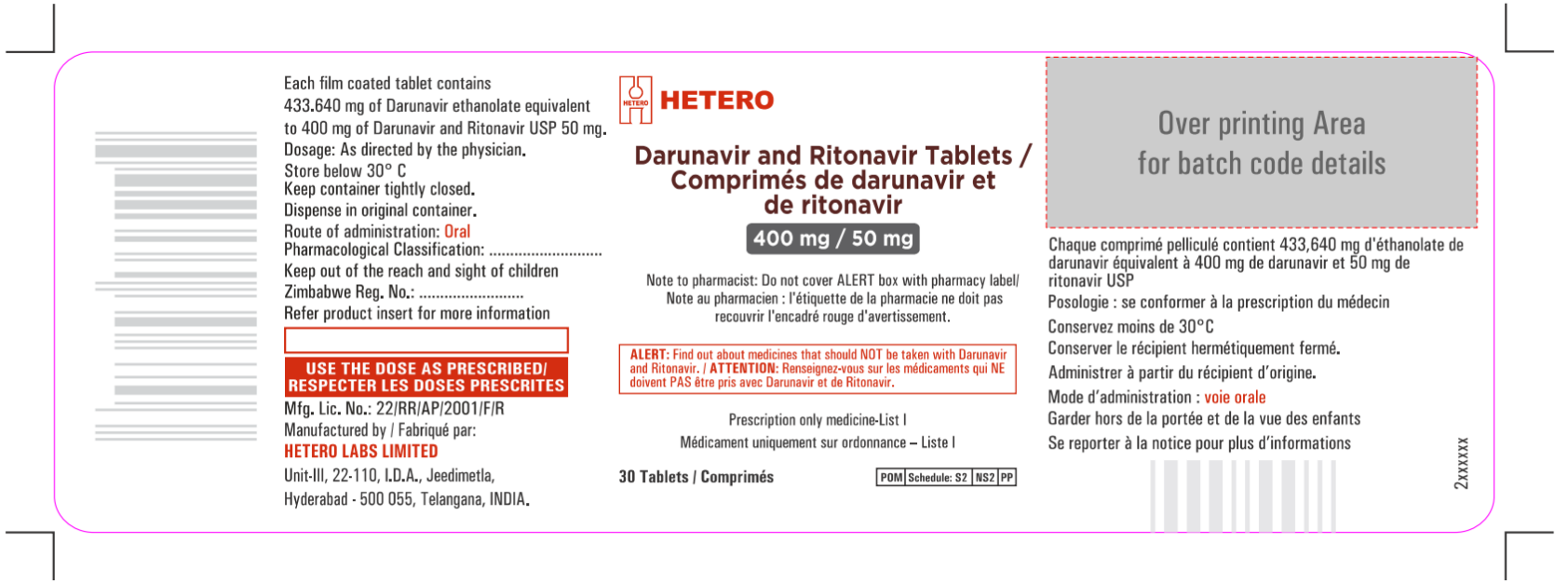
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

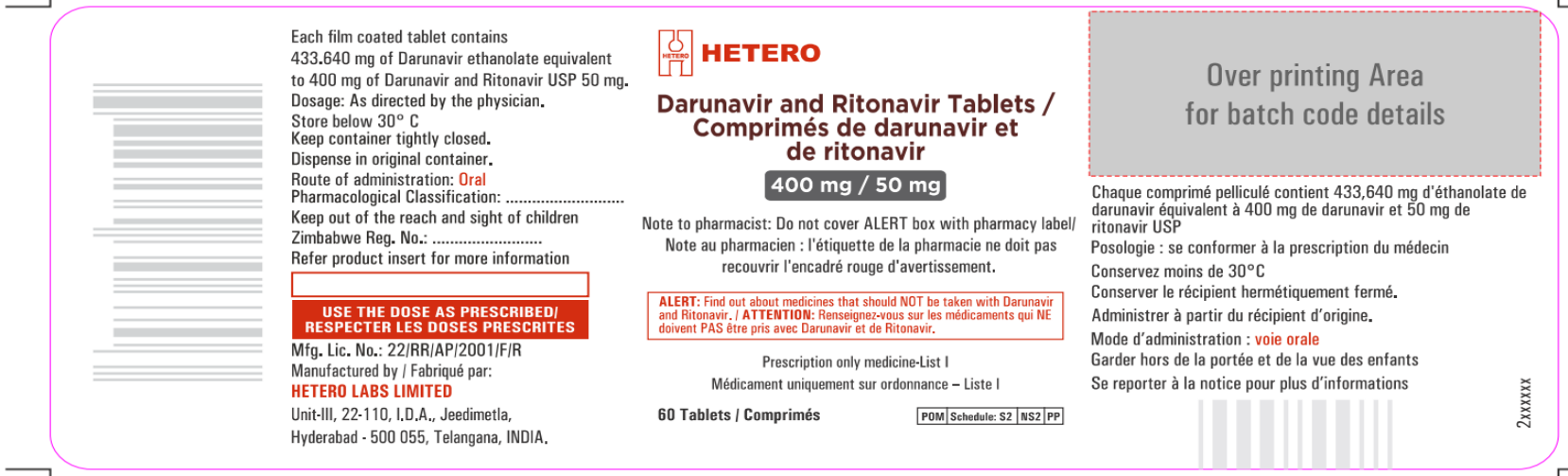
Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up label

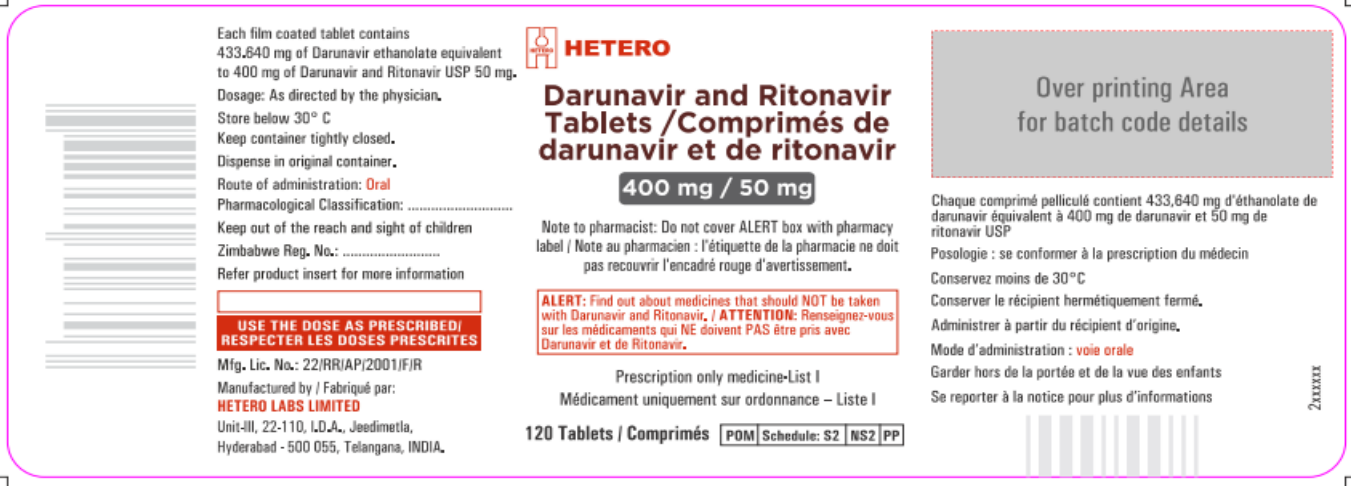
Primary labels:



Size: 120 x 40 mm



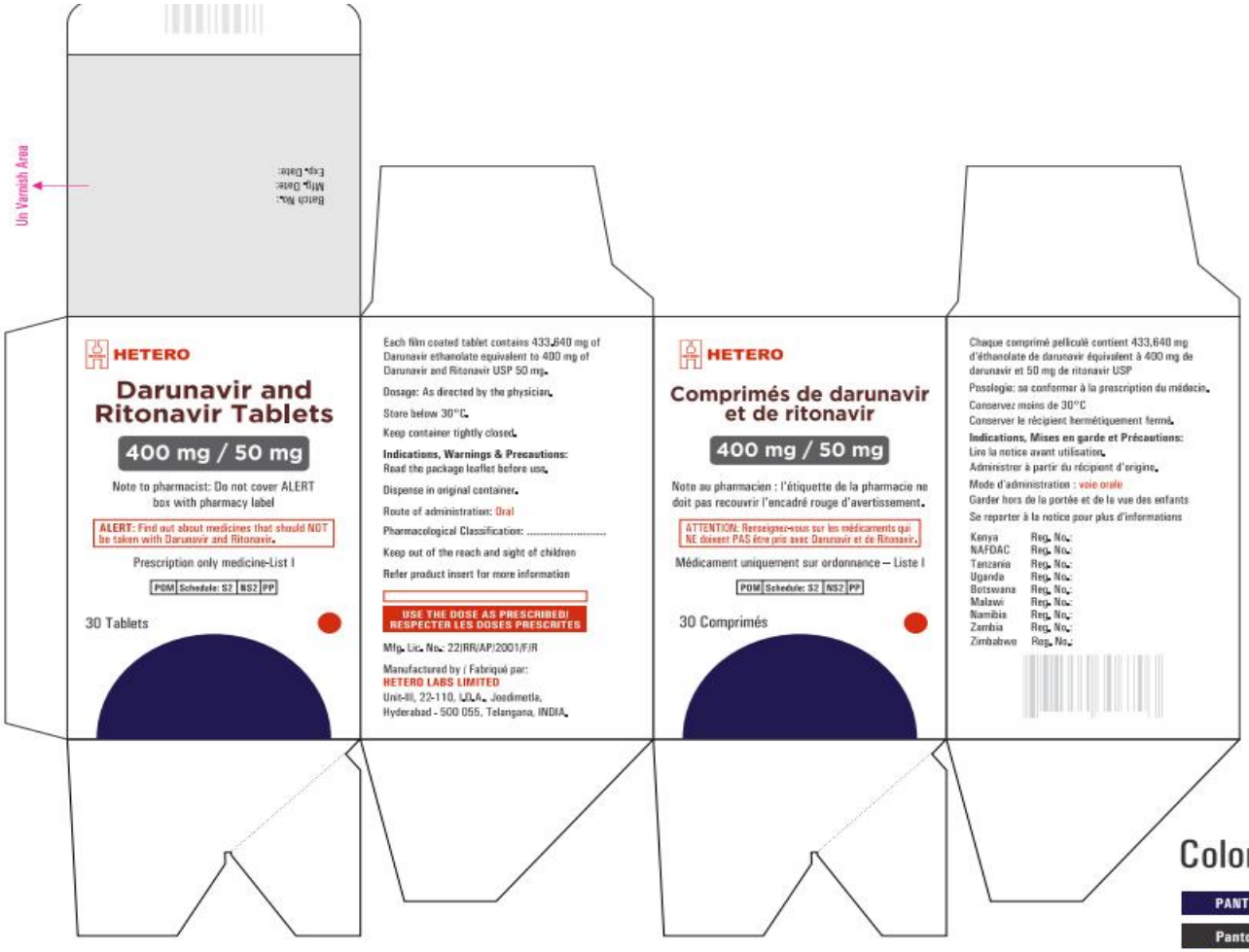
Size: 135 x 45 mm

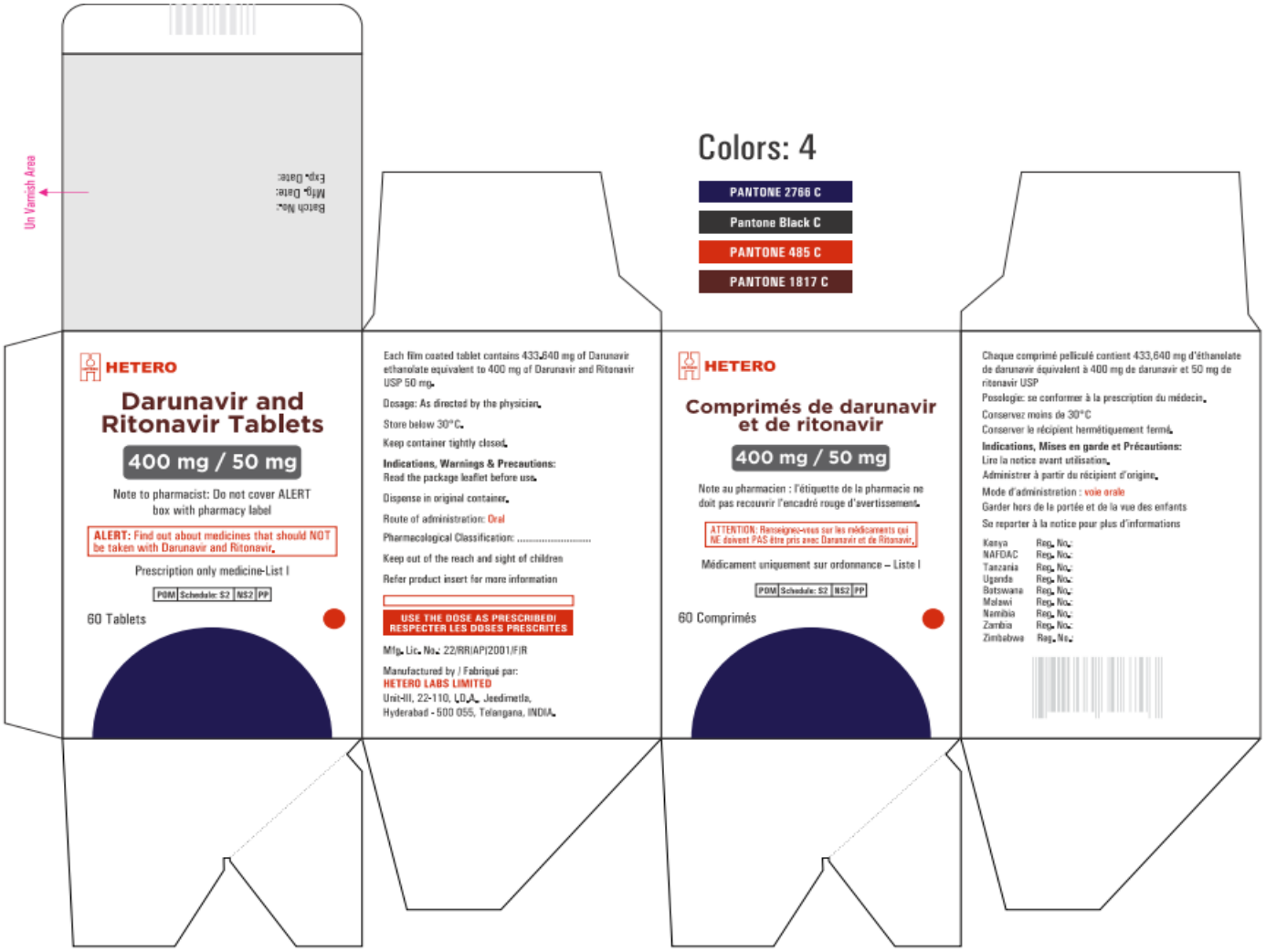


Size: 170 x 65 mm
Colours: 3

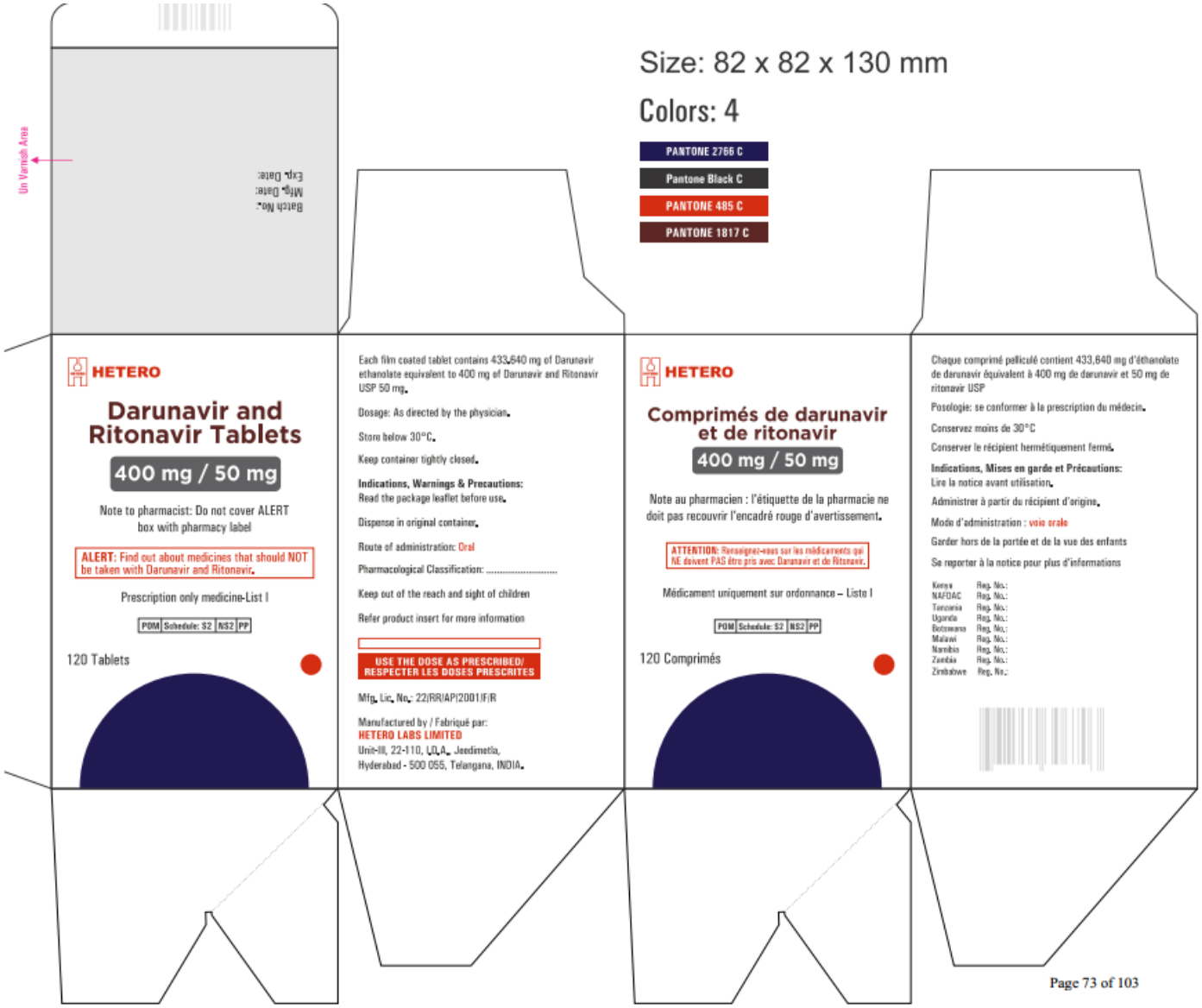
Effective date: 03/10/2022

Secondary label





Size: 72 x 72 x 106 mm


Size: 82 x 82 x 130 mm
Colors: 4
PANTONE 2766 C
Pantone Black C
PANTONE 485 C
PANTONE 1817 C
Uv Varnish Area
Batch No.:
Mfg. Date:
Exp. Date:
HETERO
Darunavir and Ritonavir Tablets
400 mg / 50 mg
Note to pharmacist: Do not cover ALERT box with pharmacy label
ALERT: Find out about medicines that should NOT be taken with Darunavir and Ritonavir.
Prescription only medicine-List I
POM Schedule: S2 NS2 PP
120 Tablets
Each film coated tablet contains 433.640 mg of Darunavir ethanolate equivalent to 400 mg of Darunavir and Ritonavir USP 50 mg.
Dosage: As directed by the physician.
Store below 30°C.
Keep container tightly closed.
Indications, Warnings & Precautions: Read the package leaflet before use.
Dispense in original container.
Route of administration: Oral
Pharmacological Classification: .....
Keep out of the reach and sight of children
Refer product insert for more information
USE THE DOSE AS PRESCRIBED/ RESPECTER LES DOSES PRESCRITES
Mfg. Lic. No.: 22|RR|AP|2001|F|R
Manufactured by / Fabriqué par:
HETERO LABS LIMITED
Unit-III, 22-110, I.D.A., Jeedimetla,
Hyderabad - 500 055, Telangana, INDIA.
HETERO
Comprimés de darunavir et de ritonavir
400 mg / 50 mg
Note au pharmacien : l'étiquette de la pharmacie ne doit pas recouvrir l'encadré rouge d'avertissement.
ATTENTION: Renseignez-vous sur les médicaments qui NE doivent PAS être pris avec Darunavir et de Ritonavir.
Médicament uniquement sur ordonnance – Liste I
POM Schedule: S2 NS2 PP
120 Comprimés
Chaque comprimé pelliculé contient 433,640 mg d'éthanolate de darunavir équivalent à 400 mg de darunavir et 50 mg de ritonavir USP
Posologie: se conformer à la prescription du médecin.
Conservez moins de 30°C
Conserver le récipient hermétiquement fermé.
Indications, Mises en garde et Précautions: Lire la notice avant utilisation.
Administrer à partir du récipient d'origine.
Mode d'administration : voie orale
Garder hors de la portée et de la vue des enfants
Se reporter à la notice pour plus d'informations
Kenya Reg. No.:
NAFDAC Reg. No.:
Tanzania Reg. No.:
Uganda Reg. No.:
Botswana Reg. No.:
Malawi Reg. No.:
Namibia Reg. No.:
Zambia Reg. No.:
Zimbabwe Reg. No.: