



Servizio  
Sanitario  
della  
Toscana

**UOC FARMACEUTICA – POLITICHE DEL FARMACO**

Direttrice Drssa Ielizza Desideri

AZIENDA OSPEDALIERO UNIVERSITARIA PISANA

**LABORATORIO DI GALENICA CLINICA**

## **OPERATING INSTRUCTION**

**LOPINAVIR 400 mg / RITONAVIR 100 mg**

**POWDER FOR ORAL SUSPENSION**

### **1. PURPOSE, SCOPE AND APPLICABILITY**

Antiretroviral drugs were among the first medicines used in COVID-19 disease, both in the early and in the advanced intensive care, for which clinical trials are ongoing.

The lopinavir / ritonavir association, indicated for treatment of HIV, is marketed in Italy only in tablets. The oral liquid formulation is not promptly available on Italian market but it is subject to import authorization and delivery time.

In absence of availability of formulations for the administration of Lopinavir /Ritonavir<sup>1</sup> based drugs in uncooperative patients, such as those in ICU or with dysphagia, a galenic formulation has been developed starting from the tablets, which can be administered in liquid form by nasogastric tube.

Galenic formulation have to be safe, of quality and effective<sup>2</sup>, and should be obtained by simple and fast operating methods.

Studying the formulation method, we focused to critical aspects concerning both preparation and administration phases.

Simplicity of preparation in pharmacy lab and simplicity of reconstitution and administration in hospital ward, are the main purposes of this operating instruction, in addition to the stability of the formulation, that has to be long enough to guarantee therapy during pharmacy closing time, when it can not prepare the drug.

To overcome low bioavailability of the active ingredients obtained from crushing and water dispersion of the tablets<sup>3-5</sup>, we studied different dispersing phases by nuclear magnetic resonance spectroscopy (NMR)<sup>6</sup>, to identify the formulation with the best availability of drugs profile and simplicity in preparation, comparing to the commercial formulation, Kaletra<sup>®</sup> oral solution.

This operating instructions have been drawn up on the basis of the obtained results and allows to realize an oral dispersion with availability of the drugs of about 90% of the commercial formulation.

As the last step specific primary containers have been chosen able to avoid administration accidents<sup>7-8</sup>, especially in IC departments, where mainly intravenous formulations are used for and operators work overload are critical about clinical risk management.

Operating instructions for the galenic products preparations and packaging methods have been studied to define the proper use of excipients for not warm methods formulations and to rule out administration mistakes.

### **2. TITLE OF THE GALENIC PREPARATION**

LOPINAVIR 400 mg / RITONAVIR 50 mg

POWDER FOR ORAL SUSPENSION

### **3. PHARMACEUTICAL FORM**

Powder for oral Suspension, single dose preparation



Servizio  
Sanitario  
della  
Toscana

## UOC FARMACEUTICA – POLITICHE DEL FARMACO

Direttrice Drssa Ielizza Desideri

AZIENDA OSPEDALIERO UNIVERSITARIA PISANA

LABORATORIO DI GALENICA CLINICA

#### 4 .QUALITATIVE AND QUANTITATIVE COMPOSITION

Lopinavir 200 mg / Ritonavir 50 mg, 2 tablets

Ethanol 96% Ph.Eur, 2 ml

Glycerol Ph.Eur, 3 ml

Water highly purified, 23 ml

#### 5. PACKAGING

a. Container 1: Lopinavir 400 mg / Ritonavir 100 mg, powder for oral suspension

b. Container 2: Solution containing Ethanol 96% 2 ml and Glycerol 3 ml

c. Enteral Feeding Syringe: Water highly purified, 23 ml

#### 6. OPERATING INSTRUCTIONS

Prepare working area to prevent microbial contaminations and operate reducing contamination risks. Wear appropriate DPI.

Preparation is arranged for single pharmaceutical dose to reduce redundant actions and powder dispersion. Packaging and labelling will be for single dose unit, such as two tablets at a time.

##### Preparation Container 1

(Lopinavir 400 mg /Ritonavir 100 mg, Powder for Oral Suspension)

Two Lopinavir 200 mg / Lopinavir 50 mg tablets have to be used for each dose.

Crush both tablets in a mortar to fine amorphous powder. Collect the powder in the center of the mortar by a metallic spatula and pour into the screw cap container. Shut the container and place the label.

##### Preparation Container 2

(Solution of Ethanol 96% Ph.Eur / Glycerol Ph.Eur)

Prepare the alcoholic solution of glycerol in a sterile screw cap container.

To ease the transfer of glycerol, which is a viscous liquid, and speed up preparation of the galenic formulation, we recommend to prepare the dispersant solution in multiple dose, e.g. for 5 doses (10 ml Ethanol 96% and 15 ml Glycerol) and pick the amount of a single dose up (5 ml). Pour the dose into the screw cap container and place the label.

##### Preparation of Enteral Feeding Syringe

(Water highly purified)

Get 23 ml of water highly purified, shut with the cap and put the label.

We recommend to use enteral feeding syringes, which have a connection incompatible with intravenous devices and have identification colour code.



Servizio  
Sanitario  
della  
Toscana

## UOC FARMACEUTICA – POLITICHE DEL FARMACO

Direttrice Drssa Ielizza Desideri

AZIENDA OSPEDALIERO UNIVERSITARIA PISANA

LABORATORIO DI GALENICA CLINICA

### Packaging

Container 1: Lopinavir 400 mg / Ritonavir 100 mg, powder for oral suspension; store at room temperature

Container 2: Solution containing Ethanol 96% 2 ml and Glycerol 3 ml; store at 2°C to 8°C.

Enteral Feeding Syringe: Water highly purified, 23 ml; store at 2°C to 8°C.

Due to the different temperature storage, pack separately Container 1 (powder for oral suspension) and Container 2 and the Syringe for enteral administration (liquid dispersant phase).

Attach to the galenic preparation a document "Instructions for Use *in Ward*" that summarize reconstitution and administration methods.

### 7. PREPARATION CHECK

Operations performed

Homogeneous appearance of the fine powder

Homogeneous and clear appearance of Ethanol/Glycerol solution

Containers and sealing cap

### 8. GALENIC PREPARATION VALIDITY

Galenic preparation validity was defined by the pharmacist according to Italian Pharmacopoeia, "*Norme di Buona Preparazione*"<sup>2</sup> and "*Stability of preparations*" (Chapter 10), taking into consideration powder hygroscopicity and microbiological stability of dispersant phase.

Chemical and physical in-use stability of the reconstituted suspension has been demonstrated by NMR Spettroscopy for six days at 2°C to 8°C.

### 9. SPECIAL PRECAUTION FOR STORAGE

CONTAINER 1 - Lopinavir 400 mg / Ritonavir 100 mg, powder for oral suspension – store at room temperature protected from light for max 7 days.

CONTAINER 2 - Solution containing Ethanol 96% and Glycerol , 5 ml- Store in a refrigerator (2°C-8°C) for max 7 days.

ENTRERAL FEEDING SYRINGE - Water highly purified, 23 ml - Store in a refrigerator for max 7 days (2°C-8°C).

### 10. METHOD OF RECONSTITUTION OF THE ORAL SUSPENSION

a. Add to the Container 2 solution to the Container 1 powder and shake by dynamic horizontal movements for 10 seconds to wet completely the powder, then let it rest for 10 minutes.

b. Add the water of the enteral feeding syringe to the Container 1, containing the powder wet by Ethanol – Glycerol solution and shake vigorously to obtain an homogeneous suspension.

c. Get the oral suspension by the enteral syringe and administer by nasogastric tube.

### 11. SPECIAL PRECAUTIONS

Reconstitute suspension before use

Only for oral or nasogastric tube administration



## UOC FARMACEUTICA – POLITICHE DEL FARMACO

Direttrice Drssa Ielizza Desideri

AZIENDA OSPEDALIERO UNIVERSITARIA PISANA

LABORATORIO DI GALENICA CLINICA

## 12. REFERENCES

<sup>1</sup> Up-date available COVID-19 off -label drugs, AIFA, 24.03.2020 (<https://www.aifa.gov.it/web/guest/-/aggiornamento-sui-farmaci-resi-disponibili-per-covid-19-al-di-fuori-delle-indicazioni-terapeutiche>)

<sup>2</sup> Farmacopea Ufficiale Italiana, XII Ed, Norme di Buona Preparazione

<sup>3</sup> J Acquir Immune Defic Syndr. 2011 Dec 1; 58(4): 385–391. Pharmacokinetics of Lopinavir/Ritonavir Crushed versus Whole Tablets in Children. Brookie M. Best, Pharm.D., M.A.S.,<sup>1,2</sup> Edmund V. Capparelli, Pharm.D.,<sup>1,2</sup> Huy Diep, B.S.,<sup>1</sup> Steven S. Rossi, Ph.D.,<sup>2</sup> Michael J. Farrell, R.N.,<sup>2</sup> Elaine Williams, R.N., M.S.N.,<sup>3,4</sup> Grace Lee, B.S.,<sup>3</sup> John N. van den Anker, M.D., Ph.D.,<sup>3,4</sup> and Natella Rakhmanina, M.D., Ph.D.

<sup>4</sup> Pharmacotherapy. 2016 Nov;36(11):1145-1165. A HAART-Breaking Review of Alternative Antiretroviral Administration: Practical Considerations with Crushing and Enteral Tube Scenarios. Huesgen E, DeSear KE, Egelund EF, Smith R, Max B, Janelle J.

<sup>5</sup> Acta Pharm Sin B. 2015 Sep;5(5):442-53. Insoluble drug delivery strategies: review of recent advances and business prospects. Kalepu S, Nekkanti V

<sup>6</sup> Optimization of galenic liquid formulations from commercial solid forms: NMR study of the availability of the active ingredients lopinavir / ritonavir (Next submission for publication. Collaboration UO Farmaceutica – Politiche del Farmaco, Azienda Ospedaliero Universitaria Pisana e Dipartimento di Chimica e Chimica Industriale Università di Pisa.)

<sup>7</sup> Raccomandazione Ministero della Salute n. 7, Prevenzione della morte, coma o grave danno derivati da errori in terapia farmacologica, 2008 e successivi aggiornamenti

<sup>8</sup> Raccomandazione Ministero della Salute n. 14, Raccomandazione per la manipolazione delle forme farmaceutiche orali solide, 2019