

THE INDONESIAN FOOD AND DRUG AUTHORITY

# **INFORMATORIUM OF COVID-19 DRUGS IN INDONESIA**

THE INDONESIAN FOOD AND DRUG AUTHORITY

MARCH 2020

# **INFORMATORIUM OF COVID-19 DRUGS IN INDONESIA**

THE INDONESIAN FOOD AND DRUG AUTHORITY

ISBN 978-602-415-009-9

First Edition

March 2020

## **COPYRIGHT PROTECTED BY LAW**

Reproduction of this book in part or whole, in any form and by any means, mechanically or electronically, including photocopies, records, and others without written permission from the publisher.

This informatorium is based on information up to the time of publication and is subject to change if there is the latest data/information



## FOREWORD

Our praise and gratitude for the presence of God Almighty for His blessings and gifts, "The Informatorium of COVID-19 Drugs in Indonesia" has been compiled and can be published amidst the COVID-19 outbreak in Indonesia.

As we know, the infections due to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) began to plague in December 2019 in Wuhan City, Hubei Province, People's Republic of China. The disease was caused by SARS-CoV-2 infection which was later known as Coronavirus Disease 2019 (COVID-19) which in early 2020 began to spread to several countries and eventually spread to almost all countries in the world. On March 11, 2020, WHO announced COVID-19 as a global pandemic.

In Indonesia, the first case was officially announced on March 2, 2020. Considering that the spread of COVID-19 has been widespread and has an impact on social, economic, defense, and public welfare aspects in Indonesia, the President of the Republic of Indonesia established the Task Force for the Acceleration of COVID-19 Handling aiming to increase readiness and ability to prevent, detect and respond to COVID-19.

As part of the COVID-19 countermeasure effort, the Chairperson of the Indonesian Food and Drug Authority established a Task Force for the Prevention and Control of the Spread of COVID-19 for the Indonesian FDA. One of the tasks is to compile and publish information to the community, including health workers as an effort to overcome COVID-19. Therefore, NADFC thinks that it is important to provide

Informatorium of COVID-19 Drugs in Indonesia which aims to provide information on the main drugs for COVID-19 treatment intended for health workers in all referral hospitals and other health facilities in Indonesia. In addition, of course, it may also be functional to other parties involved.

This Informatorium was prepared by the Indonesian Food and Drug Authority (Indonesian FDA) and was supported by a team of experts from various scientific backgrounds in the health sector. The Informatorium contains 16 drugs that are selected based on therapeutic procedures/management in Indonesia and several other countries, such as China, Japan, US, Singapore, and scientific publications/journals related to the development of COVID-19 drugs and therapy. The information in this Informatorium is prepared by with current treatment developments and can be updated by with the advancement of COVID-19 drug development and management.

To all parties, especially the Expert Team from universities, health facilities and professionals as well as the Indonesian Food and Drug Authority who have made great contributions to this Informatorium of COVID-19 drugs, I would like to express my humble gratitude for the good cooperation. I hope this Informatorium shall be useful in supporting the treatment and management of COVID-19 in Indonesia.

Jakarta, March 31, 2020

The Chairperson of the Indonesian Food and Drug Authority

Dr. Penny K. Lukito, MCP

## **DRAFTING TEAM**

Director : Dr. Ir. Penny Kusumastuti Lukito, MCP

Person in Charge : Dra. Rita Endang, Apt., M.Kes

Chairman : Dra. Togi J. Hutadjulu, Apt., MHA

Team of Experts :

1. Prof. Dr. dr. Rianto Setiabudy, SpFK.
2. Prof. Dra. Arini Setiawati, Ph.D.
3. Prof. dr. Faisal Yunus, Ph.D., Sp.P(K).
4. Dra. Lucky S. Slamet, M.Sc., Apt.
5. dr. Erlina Burhan, Sp.P(K), M.Sc., Ph.D.
6. Dr. dr. Cleopas Martin Rumende, SpPD,KP,FINASIM, FCCP.
7. Prof. Dr. Elin Yulinah, Apt
8. Prof. Dr. Arry Yanuar, M.Si, Apt
9. Dra. Antonia Retno Tyas Utami, Apt., M.Epid.
10. Dra. Endang Woro T., Apt.,M.Sc.
11. Dr. dr. Dewi Selvina Rosdiana, M.Kes.
12. Dr. dr. Anggi Gayatri, SpFK.
13. Dra. Retnosari Andrajati, Apt., PhD.

Members :

1. Dr. Lucia Rizka Andalusia, Apt, M.Pharm, MARS
2. Dra. Ratna Irawati, Apt.,M.Kes
3. Dra. Tri Asti Isnariani, Apt.,M.Pharm
4. Dra. Nurma Hidayati, Apt., M.Epid
5. Daryani, S.Si, M.Sc
6. Dian Putri Anggraweni, S.Si, Apt, M.Farm
7. Nova Emelda, S.Si.,Apt.,MS
8. Juliati,S.Si.,Apt.,M.Biomed

9. Dra. Rumondang Simanjuntak, Apt
10. Hanny Musytika, S.Si, Apt, MPH
11. Anggi Tiarani, S.Si., AptAnggrida Saragih, S.Si, Apt
12. Ayu Candra Dewi, S.Farm, Apt
13. Annisa Kamil, S.Farm, AptShinta Ayu Nurfaradilla, S.Farm, Apt
14. Fauziah Ridho, S.Farm, M.Si
15. Yuly Proboningrum, S.Farm, Apt
16. Lina Sulistia Nurrachmani, S.Farm, Apt
17. Anis Khilyatul Auliya, S. Farm, Apt

## TABLE OF CONTENTS

FOREWORD	4
DRAFTING TEAM	6
TABLE OF CONTENTS	7
TABLE OF FIGURES	10
CHAPTER I INTRODUCTION	11
A. BACKGROUND	11
B. OBJECTIVES	13
C. SCOPE	13
CHAPTER II DEVELOPMENT OF GLOBAL COVID-19 THERAPY	15
A. GENERAL	15
B. DEVELOPMENT OF GLOBAL COVID-19 THERAPY	19
CHAPTER III PROCEDURES FOR COVID-19 PATIENT TREATMENT IN INDONESIA	33
A. GENERAL	33
B. SPECIAL ATTENTION TO DRUG ADMINISTRATION FOR COVID-19 IN INDONESIA	34
CHAPTER IV INFORMATORIUM OF COVID-19 DRUGS	42
A. ANTIVIRAL DRUGS	42
1. LOPINAVIR + RITONAVIR	42
2. FAVIPIRAVIR	47
3. REMDESIVIR	52
4. OSELTAMIVIR	54
B. ANTIVIRAL DRUGS IN EMERGENCY	58
1. CHLOROQUINE PHOSPHATE	58
2. HYDROXYCHLOROQUINE SULPHATE	64
C. ANTIBIOTICS	72
1. AZITHROMYCIN	72
2. LEVOFLOXACIN	74

3. MEROPENEM	82
4. CEFOTAXIME	88
D. NON-OPIOID ANALGESICS	93
1. PARACETAMOL (ACETAMINOPHEN)	93
E. SELECTIVE BETA-2 ADRENORECEPTOR AGONIST	95
1. SALBUTAMOL SULPHATE	96
F. CENTRAL NERVE SYSTEM DRUGS – BENZODIAZEPINE CLASS	99
1. MIDAZOLAM	99
G. EXPECTORANT	103
1. ACETYLCYSTEINE	103
H. VITAMIN	105
1. ASCORBIC ACID (VITAMIN C)	105
2. ALPHA TOCOPHEROL ACETATE	108
REFERENCES	109
APPENDIX	118
A. LIST OF DRUGS	118
B. DRUG INTERACTION	132

## TABLE OF FIGURES

Figure 1. Cutting Scheme of Gag and Gag-Pol by HIV-1 protease

Figure 2. Mechanism of action of favipiravir

Figure 3. Mechanism of action of oseltamivir

# CHAPTER I

## INTRODUCTION

### A. BACKGROUND

Coronavirus Diseases 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1</sup> The virus is a new type of virus from the Coronavirus family that can cause various diseases of the respiratory system starting from mild to severe symptoms. SARS-CoV-2 is transmitted through direct contact with patients, droplets released by patients when coughing/sneezing, as well as hands that touch the mouth, nose, and eyes after touching objects contaminated with the virus.<sup>2</sup> WHO has also provided a warning of possible transmission of SARS-CoV-2 virus through the air for health workers (airborne precaution for medical staff) based on studies that coronaviruses can survive in the air in certain environments, such as health facilities that carry out aerosol procedures.<sup>3</sup>

Based on epidemiological studies, the incubation period for COVID-19 varies, ranging from 1 to 14 days, and generally within 3 to 7 days. The main clinical manifestations are fever, cough, and shortness of breath. While other symptoms such as nasal congestion, runny nose, pharyngalgia, myalgia, and diarrhea are relatively rare. Symptoms and signs in severe cases are shortness of breath and/or hypoxemia (usually occurs after one-week onset), and in the worst cases can quickly develop into acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis that is difficult to be corrected, abnormalities in coagulation

and bleeding, multiple organ failure, and others. Most patients have a good prognosis, based on recent cases. As for the elderly and people with chronic diseases, generally have a poor prognosis. While cases in children generally have relatively mild symptoms.<sup>4</sup>

The COVID-19 case in Wuhan City, Hubei Province, China (People's Republic of China) was first reported on December 31, 2019 by the WHO China representative office. An increase in the number of COVID-19 cases has taken place significantly to other countries, and currently, there have been 197 countries infected with COVID-19. China established COVID-19 as a Class B communicable disease, and was later treated as a Class A4 Infectious Disease. Since 11 March 2020, WHO has designated the COVID-19 outbreak as a global pandemic.

The number of positive cases of COVID-19 in Indonesia continues to increase. The President of the Republic of Indonesia has established the Task Force for the Acceleration of COVID-19 Handling through a Presidential Decree Number 9/2020 on Amendment to Presidential Decree Number 7/2020 on Task Force for the Acceleration of COVID-19 Handling, with the Head of National Disaster Management Agency (BNPB) as the Chairperson. Based on data from the Task Force for the Acceleration of COVID-19 Handling, the number of positive cases of COVID-19 in Indonesia as of March 31, 2020, was 1,528 people, with 136 deaths and 81 recovered.<sup>5</sup>

At present, there is no specific therapy or treatment for COVID-19<sup>7</sup>. However, several potential drugs have been used for people with COVID-19, although they are still in a test drug status and the results show significant

efficacy. WHO has initiated to organize a solidarity clinical trial involving countries that are interested in participating in clinical studies for potential drug candidates in the treatment of COVID-19<sup>8</sup>.

Considering the variety of drugs used as test drugs against COVID-19, it is necessary to establish Informatorium of COVID-19 Drugs in Indonesia which can be used as a reference for health workers in all COVID-19 Referral Hospitals in Indonesia in the procedures/management of therapy of COVID-19 treatment as well as other related parties. The information contained in this Informatorium is based on procedures/management of therapy published by the Indonesian Pulmonary Association (Perhimpunan Dokter Paru Indonesia-PDPI) and several other countries, such as China, Japan, US, and Singapore, several global guidelines, as recommended by WHO, and scientific publications.

## **B. OBJECTIVE**

This Informatorium is intended to provide information on COVID-19 drugs and as a reference for health workers in the procedures/management of therapy for COVID-19 treatment in health care facilities, including the COVID-19 Referral Hospitals in Indonesia.

## **C. SCOPE**

This Informatorium of COVID-19 Drugs in Indonesia contains a list of drugs, product information, and therapeutic regimens based on the results of quality, efficacy, and safety evaluations conducted by the Indonesian Food and Drug

Authority, national guidelines/protocols for COVID-19 treatment regimens and scientific publications related to testing results in several countries in COVID-19 treatment efforts.

## CHAPTER II

### DEVELOPMENT OF GLOBAL COVID-19 THERAPY

#### A. GENERAL

Based on several references related to the management or clinical management of COVID-19, including those from WHO<sup>10</sup> and the US Centers for Disease Control and Prevention (CDC)<sup>11</sup>, there is currently no specific therapy or treatment for COVID-19. However, based on an analysis of case reports of handling infectious diseases due to other coronaviruses, such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Ebola virus infections, as well as experience of therapy or treatment of mild to severe conditions of COVID-19, especially in China<sup>12</sup>, several drugs have been used within the framework of clinical trials (Investigational agents) for the treatment or medication of COVID-19.

By with WHO reference<sup>10</sup>, the use of anti-COVID-19 Investigational agents needs to consider the following requirements:

1. ethical aspects; and the drugs shall have the latest therapeutic priorities<sup>13</sup>;
2. the implementation refers to the WHO Core Clinical Randomized Controlled Trial (RCT) Protocol for evaluating the efficacy and safety of drugs in line with inpatient care standards for COVID-19 patients<sup>14</sup>; and
3. If the implementation of RCT is not possible, then the use of Investigational agents must be carried out by with the WHO Monitored Emergency Use of Unregistered Interventions Framework (MEURI), until the RCT can be carried

out<sup>15</sup>.

Besides, according to various references such as WHO<sup>9,16</sup> and the US CDC<sup>7</sup>, the clinical evolution and epidemiological information of COVID-19 are not well distributed, causing the absence of population-related guidance for therapy or treatment, including the endpoint of the efficacy of a drug candidate. Therefore, it is necessary to identify the COVID-19 drug candidates that can improve the clinical outcome of treatment and can reduce the severity of illness and death. The identification is related to the role of host target therapies (host-targeted therapies), including: in-vitro/in-vivo data on COVID-19, PK / PD analysis, consideration of dosage, method and time of use, and most importantly data efficacy and safety in humans. Several types of drugs have been used in COVID-19 therapy with results depending on the status/condition of COVID-19 patients.

For fever/fever therapy which is an early symptomatic symptom of COVID-19, antipyretic/analgesia is used according to the applicable treatment guidelines. All drugs that have been approved by the Indonesian FDA for indications of fever can be used, although the use of paracetamol is preferable. Information relating the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, with the occurrence of COVID-19 severity is still uncertain with clinical data in humans and being discussed by other State Authorities such as European Medicines Agency (EMA)<sup>17</sup>, US FDA<sup>18</sup> and WHO<sup>19</sup>.

For the acute condition of COVID-19 and when the rapid test of antibodies for patients with COVID-19 who were treated at the hospital showed

positive results, empirical antibiotics are given according to the severity of the condition, including bacterial pneumonia (secondary bacterial pneumonia). Since the use of antibiotics is not directly indicated for COVID-19, a broad-spectrum antibiotic is forced to be administered given the progress of the disease<sup>7</sup>.

Based on various sources, the types of test drugs used globally<sup>7,20,21</sup> for therapy or COVID-19 treatment can be seen in the list as follows:

Table 1. Types of Test Drugs for COVID-19 Therapy

No	Types of Test Drugs	Status	Notes
1	Chloroquine phosphate	Test Drugs Off Label Use*	The main indications are malaria and anti-amoebiasis drugs
2	Hydroxychloroquine	Test Drugs Off Label Use*	The main indications for systemic lupus erythematosus
3	Fixed combination of lopinavir/ritonavir	Test Drugs Off Label Use*	The main indications are second-line HIV/AIDs therapy in combination with other antivirals
4	Oseltamivir	Used because many cases of COVID-19 resemble influenza; has never been tested for COVID-19	Main indications for the treatment and prevention of influenza A
5	Favipiravir	Test Drugs Off Label Use*	Registered in Japan as a special drug only for the treatment of new or re-emerging influenza viruses with caution.

No	Types of Test Drugs	Status	Notes
			Approved in the People's Republic of China for COVID-19 drugs
6	Remdesivir	Compassionate use**	<p>Drugs that are being used in phase II/III clinical trials in America, China, and Europe.</p> <p>EMA<sup>22,23</sup> approved the use of remdesivir as a compassionate use for adult patients and children aged <math>\geq 12</math> years with bodyweight <math>\geq 40</math> kg requiring invasive mechanical ventilation at a dose of:</p> <p>Adult: Day 1: 200 mg</p> <p>Day 2 - to day 9: 100 mg IV for 30 - 120 minutes.</p> <p>Pediatric &gt; 12 years with bodyweight <math>\geq 40</math> kg: Same as adult dose.</p>
7	Other drugs, such as ribavirin (in combination with interferon or lopinavir / ritonavir), interferon beta, tosilizumab, injection of high doses of vitamin C	Test Drugs Off Label Use*	Used as a test drug for the treatment of COVID-19 with various precautionary measures.

Notes:

\* Off Label Use is using outside the indicated drug indicated in the drug label registered.

\*\* Compassionate use is providing treatment that is still in the development stage and has not yet obtained a marketing authorization for patients with life-threatening, severe or chronic diseases for which no alternative treatment is available.

## B. DEVELOPMENTS OF GLOBAL COVID-19 THERAPY

Types of drugs used in the therapy or treatment of COVID-19, based on WHO<sup>9</sup>, International Pulmonologist's Consensus on COVID-19<sup>24</sup> and in several other countries such as China<sup>12</sup>, United States, Japan, and Singapore, among others, are as follows:

### 1. World Health Organization (WHO)

The types of drugs used by WHO<sup>25</sup> for therapy or COVID-19 treatment can be seen in Table 2.

Table 2. Types of drugs used by WHO for the treatment of COVID-19

Product Type and Candidate	Licensed for	Licensed dose	Dosage submitted for COVID-19
Off label			
Chloroquine	NA	NA	Hydroxychloroquine 400 mg per day for 5 days
Ritonavir + lopinavir (Kaletra®)	HIV infection	Adult 5 mL oral solution (400 mg / 100 mg)  twice a day	500 mg twice a day for 2 weeks
Ribavirin + Ritonavir + Lopinavir	Ribavirin <sup>24</sup> : chronic hepatitis C infection combined with interferon $\alpha$ -227  Ritonavir +  Lopinavir:  HIV infection	Ribavirin <sup>26</sup> : a. For bodyweight $\leq$ 75 kg: 2 x 200 mg capsules before noon, 3 x 200 mg capsules after noon b. For bodyweight > 75 kg: 3 x 200 mg	Clinical trials: lopinavir 400 mg / ritonavir 100 mg orally twice a day, plus ribavirin 2.4 g orally as a loading dose followed by 1.2 g orally every 12 hours.  The duration of

Product Type and Candidate	Licensed for	Licensed dose	Dosage submitted for COVID-19
		<p>capsules before noon, 3 x 200 mg capsules after noon</p> <p>Ritonavir + lopinavir: Adult 5 ml oral solution (400mg / 100mg) twice a day</p>	<p>therapy is up to 10 days.</p> <p>Case study: ribavirin 600 mg twice daily and lopinavir + ritonavir 1000 mg once daily</p>
Darunavir (with cobicistat) (Prezista® / Prezcobix® and generic	HIV Infection	Treatment of naive patients and patients who do not experience substitution-related resistance: 800 mg is used with ritonavir 100 mg once daily	Darunavir 800 mg/ cobicistat 150 mg 4 times daily
Approved in the country of origin for other diseases			
Favipiravir (or T-705 or Avigan®)	Influenza (registered in Japan)	<p>Day 1: 1600 mg twice a day</p> <p>Days 2 to day 5: 600 mg twice a day</p>	An initial dose of 1600 mg, followed by 3 x 600 mg 1 day for a maximum of 14 days
Umifenovir (Arbidol®)	Influenza and other viral infections. Since 2004, Arbidol is patented by Masterlek™ as an antiviral agent for atypical pneumonia	<p>For internal use, to be taken on an empty stomach.</p> <p>Single-dose amount:</p> <p>a. Pediatric 2-7 years: 50 mg</p>	<p>CT ChiCTR200002959: not mentioned</p> <p>CT ChiCTR200002957:</p>

Product Type and Candidate	Licensed for	Licensed dose	Dosage submitted for COVID-19
	<p>induced by SARS-CoV.</p> <p>Did not get approval from EMA/FDA.</p>	<p>b. Pediatric 7 - 12 years: 100 mg</p> <p>c. Pediatric 12 years - adults: 200 mg<sup>27</sup></p> <p>Influenza therapy:</p> <p>a. Pediatric 2-7 years: 50 mg 4 times daily for 5 days</p> <p>b. Pediatric 7 - 12 years: 100 mg 4 times daily for 5 days</p> <p>c. Pediatric 12 years-adult: 200 mg 4 times daily for 5 days<sup>27</sup></p>	<p>Umifenovir 200 mg tablets orally 3 times daily.</p> <p>CT NCT04252885: regular therapy is added to the umifenovir regimen (100 mg) (orally, 3 times daily, 200 mg, given for 7-14 days).</p>
Novaferon, Nova	Approved in China for hepatitis B	As a test drug	20 g, inhalation of atomization (in one trial, in combination with umifenovir tablets 200 mg 3 times daily).
Phase 2/Phase 3/Observational			
GS-5734 / remdesivir	As a test drug	<p>Adult:</p> <p>a. Day 1, initially given 200 mg IV once daily (for &gt; 30 minutes)</p> <p>b. Day 2 to day 10 are given 100 mg IV</p>	<p>CT NCT04252664: 200 mg as loading dose on day 1, followed by 100 mg IV once daily as a maintenance dose for 9 days.</p>

Product Type and Candidate	Licensed for	Licensed dose	Dosage submitted for COVID-19
		<p>once daily (for &gt; 30 minutes)</p> <p>Pediatrics:</p> <p>For pediatrics with bodyweight &lt;40 kg: 5 mg / kg IV on day 1 (for &gt; 30 minutes), then given 2.5 mg / kg IV once daily (for &gt; 30 minutes).</p>	<p>CT NCT04257656: 200 mg as loading dose on day 1, followed by 100 mg IV once daily as maintenance dose for 9 days.</p>

## 2. International Pulmonologist’s Consensus on COVID-19

Pulmonologists from various countries are working together to draw up a consensus for the prevention and treatment of COVID-19. The pulmonologists involved in preparing this consensus came from India, Iran, the United States, China, Italy, United Kingdom, United Arab Emirates, Colombia, Egypt, Singapore, Romania, Ireland, Malaysia, Bolivia, Saudi Arabia, Sudan, and Greece. The types of drugs used by the International Pulmonologist’s Consensus on COVID-19<sup>24</sup> for therapy or treatment of COVID-19 can be seen in Table 3 as follows:

Table 3. Types of drugs used by the International Pulmonologist's Consensus on COVID-19 for the treatment of COVID-19

Drugs	Dose	Notes
<b>ANTI-VIRAL MOLECULES UNDER TRIAL (Experimental options) for COVID-19</b>		
Remdesevir	1. Adult Day 1: 200 mg IV  Day 2 to day 9: 100 mg IV once daily  2. Pediatric: <40 kg: 5mg/kg IV on day 1, then 2.5 mg/kg IV every 24 hours	<ul style="list-style-type: none"> <li>- Compassionate use only</li> <li>- Investigational antiviral drug with reported in vitro activity against SARS-CoV-2</li> <li>- No published phase 3 trials</li> <li>- Tried in Ebola virus too</li> <li>- Side effects - Hepatotoxicity</li> </ul>
Lopinavir/Ritonavir	1. Adult:  Oral tablets 400 mg/100 mg peroral every 12 hours  2. Pediatric:  a. Oral Solution <ul style="list-style-type: none"> <li>- &lt;15 kg: 12 mg/kg/dose every 12 hours</li> <li>- 15-40 kg: 10mg/kg/dose every 12 hours</li> <li>- &gt; 40 kg: 400mg dose every 12 hours</li> </ul> b. Oral tablet <ul style="list-style-type: none"> <li>- ≥15-25kg: 200 mg every 12 hours</li> <li>- ≥25-35 kg: 300 mg every 12 hours</li> <li>- &gt;35 kg: 400 mg every 12 hours</li> </ul>	<ul style="list-style-type: none"> <li>- In vitro reduces replication by 50% in MERS coronavirus</li> <li>- Definite efficacy not proven</li> <li>- Maybe also tried in combination with Interferon alpha or Ribavirin</li> <li>- Potent CYP3A4 inhibitor – monitor for drug interactions</li> </ul>

Drugs	Dose	Notes
Ribavirin	- 2 grams x 1 dose, then 600 mg every 8 hours	<ul style="list-style-type: none"> <li>- Inhibitor of RNA polymerization</li> <li>- The concentration required to inhibit MERS-CoV in vitro exceeds peak levels in the blood after therapeutic doses in humans.</li> <li>- High risk of toxicity</li> <li>- NO study results yet in SARS CoV2</li> </ul>
Oseltamivir	- 150mg twice daily x 5 days	<ul style="list-style-type: none"> <li>- A Neuraminidase enzyme inhibitor in influenza</li> <li>- Efficacy not proven in SARS CoV2</li> <li>- Hence better to give the drug to avoid patient worsening due to influenza</li> </ul>
Chloroquine/ Hydroxychloroquine	<p>As a test drug.</p> <p>Adult: 400 mg peroral every 12 hours x 1 day, 200 mg peroral every 12 hours x 4 days</p> <p>Pediatric: 6.5 mg/kg peroral every 12 hours x 1 day, then 3.25 mg/kg peroral every 12 hours x 1 day, then 3.25 mg/kg peroral every 12 hours x 4 days (up to adult maximum dose)</p>	<ul style="list-style-type: none"> <li>- Proposed mechanism – Hampers the low pH dependant steps of viral replication</li> <li>- Side effects: QT prolongation</li> </ul>
Tocilizumab (optional)	4-8 mg/kg (max 400mg) IV once daily	<ul style="list-style-type: none"> <li>- IL-6 inhibitor</li> <li>- Proposed to reduce the cytokine storm in COVID-19</li> <li>- Adverse effects: elevation</li> </ul>

Drugs	Dose	Notes
		of liver enzymes, increased risk of re-activation of other Respiratory infections
Ascorbic Acid	Administration of a moderate dose of IV vitamin C could be considered (e.g. 1.5 grams IV q6 ascorbic acid plus 200mg thiamine IV every 12 hours)	<ul style="list-style-type: none"> <li>- Ascorbic acid, corticosteroids, and thiamine did appear to improve mortality in the multi-center CITRIS-ALI trial.</li> <li>- Extremely limited evidence suggests that ascorbic acid could be beneficial in animal models of coronavirus</li> <li>- There is no high-quality evidence to support ascorbic acid in viral pneumonia</li> </ul>
<b>ANTIBACTERIAL THERAPY</b> <ul style="list-style-type: none"> <li>- COVID-19 itself is not an indication to start antibiotics</li> <li>- Antibiotics can be initiated to treat secondary bacterial pneumonia</li> <li>- Broad-spectrum antibiotics to be initiated according to the institution based guidelines</li> </ul>		
<b>OTHER AGENTS</b>		
Baricitinib Darunavir/Cobicistat		
Umifenovir (Arbidol) – 200 mg TDS		
Favilavir – first approved drug in China		
Galidesivir		
Leronlimab		
Brilacidin		
Combination of monoclonal antibody		

### 3. Diagnosis and Treatment Protocol of COVID-19 (Trial Version 7) – China

The types of drugs used by China<sup>28</sup> for therapy or COVID-19 treatment can be seen in Table 4.

Table 4. The types of drugs used by China for COVID-19 treatment

Types of Drugs	Dose
<b>Antiviral therapy</b>	
Alpha-interferon 5 million U	Inhalation twice daily
Lopinavir-ritonavir (200 mg.50 mg)	2 pills (500 mg/50 mg per tablet) twice daily, no longer than 10 days
Ribavirin (500mg)	twice or three times daily
Chloroquine phosphate (500 mg)	- Adults > 50 kg, 500 mg twice daily for 7 days - Adults < 50 kg: For Days 1 and 2: 500 mg twice daily For Days 3-7: 500 mg once daily
Umifenovir (200 mg)	200 mg three times daily no longer than 10 days
<b>Antibiotic drug treatment</b>	
<b>Treatment of severe and critical cases</b>	
Rescue therapy	
Circulatory therapy	
Renal failure and renal replacement therapy	
Convalescent plasma treatment	
<b>Immunotherapy</b>	
Tocilizumab	The initial dose is 4-8mg/kg with the recommended dose of 400mg diluted with 0.9% normal saline to

Types of Drugs	Dose
	<p>100ml.</p> <p>If the initial medication is not effective, one extra administration can be given after 12 hours (same dose as before). The infusion time should be more than 1 hour.</p> <p>No more than two administrations should be given with the maximum single dose no more than 800mg.</p>
Glucocorticoid	
Methylprednisolone	1-2 mg/kg/day for three to five days

#### 4. The United States

There has been no specific drug approved by the US-FDA to treat COVID-19. COVID-19 treatment is currently carried out with clinical management, namely infection prevention, and control as well as supportive care such as oxygen and mechanical ventilators if needed. The US-FDA collaborates with various stakeholders including the US CDC, government organizations, academia, and or other partners in the world to accelerate the development of drugs for COVID-19 therapy.

On March 28, 2020, the FDA issued an Emergency Use Authorization (EUA) that allowed donations of the following drugs, such as chloroquine phosphate and hydroxychloroquine sulfate to the Strategic National Stockpile (SNS) to be distributed and used for inpatients with COVID-19. EUA requires that a fact sheet be provided for health care providers and contains important information regarding the use of chloroquine phosphate and hydroxychloroquine sulfate in the treatment of COVID-19, regarding the risks identified by the use of these drugs and drug interactions.<sup>29</sup>

Some of the drugs used in the US to treat COVID-19 include hydroxychloroquine and chloroquine (approved) and remdesivir (still as a test drug or compassionate use). The list of drugs used by the United States<sup>7,30-37</sup> for therapy or COVID-19 treatment can be seen in Table 5.

Table 5. Types of drugs used by the United States for the treatment of COVID-19

No	Drugs	Dose	Notes
	Remdesivir	Day 1: 200 mg IV Day 2 to day 10: 100 mg IV	Currently, the US, sponsored by the National Institutes of Health (NIH) is conducting a phase 3 randomized clinical trial of the remdesivir test drug developed by Gilead Sciences Inc.
	Hydroxychloroquine	The optimal dosage and duration of use for COVID-19 are unknown.  The recommended dosage at EUA is to treat adults and adolescents who weigh $\geq 50$ kg and are hospitalized.  Dosage: 800 mg on day 1, and then 400 mg daily for 4-7 days in total treatment based on clinical evaluation.  The recommended dosage and duration can be updated when	Hydroxychloroquine is currently in clinical trials for pre- and post-exposure prophylaxis against SARS-CoV-2 infection, and treatment of COVID-19 patients with mild, moderate, and severe symptoms.

No	Drugs	Dose	Notes
		data from clinical trials are available. <sup>31</sup>	
	Chloroquine	<p>The optimal dosage and duration of use for COVID-19 are unknown.</p> <p>The recommended dosage at EUA is to treat adults and adolescents who weigh <math>\geq 50\text{kg}</math> and are hospitalized.</p> <p>Dosage: 1000 mg on day 1, followed by 500 mg daily for 4-7 days of total treatment based on clinical evaluation.</p> <p>Dosage and duration are it is recommended to be updated when data from clinical trials are available</p>	Based on the results of clinical trials in China, the administration of chloroquine in COVID-19 patients is clinically and virologically beneficial.
	Lopinavir and ritonavir		Clinical trial results show lopinavir and ritonavir do not show promising potential in the treatment of COVID-19 patients with pneumonia in China. Lopinavir and ritonavir are currently in a WHO investigation.

## 5. Concept of antiviral drug treatment for COVID-19, 1<sup>st</sup> edition, Ministry of Health, Labour and Welfare (MHLW), Japan

The types of drugs used by Japan<sup>38</sup> for therapy or COVID-19 treatment can be seen in Table 6.

Table 6. The types of drugs used by Japan for COVID-19 treatment

Drug	Dose
Favipiravir	Day 1: 1800 mg twice daily Day 2 to day 14: 800 mg twice daily.
Lopinavir + ritonavir	1. Lopinavir/ritonavir (combination tablets): 400 mg/100 mg Day 1 to day 10: 400 mg tablets twice daily. 2. Lopinavir/ritonavir (solution) Day 1 to day 10: 400 mg/100 mg (15 mL) twice daily.

## 6. Health Sciences Authority (HAS), Singapore

Singapore does not have specific COVID-19 treatment guidelines. The COVID-19 therapy regimen used by Singapore is the WHO Landscape analysis of therapeutics. The National University of Singapore (NUS) compiles reports on drug use in hospitals for COVID-19 patients. The types of drugs used by Singapore<sup>39</sup> for therapy or COVID-19 treatment can be seen in Table 7 as follows:

Table 7. Types of drugs used by Singapore for the treatment of COVID-19

Drug	Dose	Notes
<b>Main Therapy</b>		
Remdesivir	Broad-spectrum Investigational Agent for the Treatment of Ebola and MERS Coronavirus	In reference to WHO Landscape
Lopinavir/ritonavir with/without interferon	Antivirals for HIV / AIDS	Lopinavir/ritonavir 400 mg/100 mg (Kaletra 2 times daily 2 tablets)
Interferon (IFN)	Remitting multiple sclerosis	-
Chloroquine	Anti-malaria medicine 500 mg twice daily for 10 days	Based on Guidelines in China
Hydroxychloroquine	Treatment of systemic lupus erythematosus 400 mg per day	Based on Guidelines in South Korea
<b>Considered Therapy (based on ongoing clinical trials)</b>		
<b>Antiretroviral (HIV)</b>		
Darunavir/Cobicistat		
Emtricitabine/Tenofovir		
Saquinavir		
Azuvudine		
<b>Antiviral (Influenza)</b>		
Favipiravir		
Unifenvir		
Oseltamivir		
Baloxavir marboxil		
<b>Antiviral (Hepatitis)</b>		
Ribavarin		

Drug	Dose	Notes
Sofosbuvir		
Beclabuvir		
Galidesivir		
Simeprevir		
<b>Anti-parasite</b>		
Nitazoxanide		
Nlclosamide		
<b>Immunotherapy</b>		
Human Monoclonal Antibody (mAb)		
Tosilizumab		
REGN3048-3051		
Sarilumab (Kevzara)		
Leronlimab		
Foralumab		
Camrelizumab		
IFX-1		

## CHAPTER III

### PROCEDURES FOR COVID-19 PATIENT TREATMENT IN INDONESIA

#### A. GENERAL

The Indonesian Pulmonary Doctors Association (PDPI) has compiled the COVID-19 Patient Management<sup>40</sup>. The following is the treatment procedure for patients who are positive for COVID-19:

Table 8. Management of PDPI COVID-19 Patients

Degree of Severity	Therapy Options
No Symptom	Vitamin C, 3 x 1 tablet (for 14 days)
Mild Symptoms	<ul style="list-style-type: none"><li>- Vitamin C, 3 x 1 tablet (for 14 days)</li><li>- Chloroquine phosphate, 2 x 500 mg (for 5 days) or hydroxychloroquine, 1 x 400 mg (for 5 days)</li><li>- Azithromycin, 1 x 500 mg (for 3 days)</li><li>- Symptomatic (paracetamol and others).</li><li>- If needed, Antivirus can be given: oseltamivir, 2 x 75 mg OR favipiravir (Avigan), 2 x 600 mg (for 5 days)</li></ul>
Moderate Symptoms	<ul style="list-style-type: none"><li>- Vitamin C is given IV during treatment</li><li>- Chloroquine phosphate, 2 x 500 mg (for 5 days) OR hydroxychloroquine dose 1x 400 mg (for 5 days)</li><li>- Azithromycin, 1 x 500 mg (for 3 days)</li><li>- Antivirus: oseltamivir, 2 x 75 mg OR favipiravir (Avigan) loading dose 2 x 1600 mg day 1 and then 2 x 600 mg (days 2-5)</li><li>- Symptomatic (paracetamol and others)</li></ul>

Degree of Severity	Therapy Options
<b>Severe Symptoms</b>	<ul style="list-style-type: none"> <li>- Chloroquine phosphate, 2 x 500 mg per day (days 1-3) followed by 2 x 250 mg (days 4-10) OR hydroxychloroquine dose of 1 x 400 mg (for 5 days)</li> <li>- Azithromycin, 1 x 500 mg (for 3 days)</li> <li>- Antivirus: oseltamivir, 2 x 75 mg OR favipiravir (Avigan) loading dose 2 x 1600 mg day 1 and then 2 x 600 mg (days 2-5)</li> <li>- Vitamin C is given IV during treatment</li> <li>- Other supportive drugs</li> <li>- Treatment of existing comorbidities</li> </ul>

## **B. SPECIAL ATTENTION OF DRUG ADMINISTRATION FOR COVID-19 IN INDONESIA**

The Drug Administration for patients with COVID-19 shall be conducted with proper rationale. According to WHO, "the rational use of drugs means that patients have access to drugs which are by clinical needs at doses according to individual needs over a certain period of time and provide the lowest risk to the individual and the community".<sup>41</sup>

The pandemic COVID-19 has caused panics in all levels of society including professional doctors. This state of panics and confusion tends to encourage doctors to administer drugs with minimum direction, especially since there has been no specific drug proven to be effective and safe for treating this disease.

This informatorium provides details of drugs that have been reported to be effective in various references, although it is not certain that all anti-COVID-19 drugs

will be effective and safe since there are still various obstacles in the research method. This informatorium also provides details regarding the dosage of drugs, how to use, side effects, and other information needed by the doctors who are in charge in giving treatment to the COVID-19 patients.

In order to optimize the results of treatment, certain instructions for the use of rational drugs in treating patients infected with COVID-19 are as follows:

1. There are many potentially effective drugs for treating COVID-19 infections (chloroquine, hydroxychloroquine, azithromycin, favipiravir, lopinavir-ritonavir, etc.). Although there are no comparative clinical trial results yet, choose a treatment regimen that is based on the literature which is most likely to be effective, safe, available, suitable for individual patients, and affordable in terms of price. Avoid giving a combination of several antiviral drugs at once because their safety is still disputable.
2. Pay close attention to the dosage regimen, method of administration, duration of treatment, drug interactions, and potential side effects related to drug use described in this informatorium.
3. Avoid the occurrence of polypharmacy treatment (the use too many types of drugs) as much as possible because polypharmacy will increase the frequency of drug side effects and the possibility of drug interactions. If there are negative effects due to this polypharmacy practice, it will be difficult for doctors to determine whether it is from the drugs or arises from the patient's illness. It is also difficult to determine which drug that becomes the real cause.
4. To reduce the likelihood of polypharmacy treatment, avoid treatment methods

"one drug for each complaint" as far as possible, especially for minor complaints which are not dangerous.

5. Up to the compilation process of this informatorium, there have been no drugs or vaccines that were proven effective in preventing infection by COVID-19.
6. Various high-dose vitamins and drugs that are claimed to increase the body's immune system have not been proven to be effective and safe, so there is no need to give high priority in the management of COVID-19 infections. The provision of vitamins in reasonable doses is adjusted to the individual needs of the patient.

The administration of certain drugs, especially drugs which are still in the research stage, the use of the off label in addition to having to be prescribed by a doctor (under the supervision of health workers) presents a greater risk in special populations such as pregnant and breastfeeding women, children, the elderly, and sufferers of chronic diseases such as diabetes and hypertension.

Some things to consider in the treatment of COVID-19 are as follows:

#### 1. Treatment of COVID-19 for pregnant and breastfeeding women

Changes in the immune system and physiology in pregnant women, in general, can increase the risk of complications of viral infections such as influenza. However, at present, there has not been enough evidence related to the severity of COVID-19 in the condition of pregnant women, given the limited data<sup>16,18</sup>. Besides, several studies conducted in the People's Republic of China related to the vertical transmission of intra-uterine pregnant women to the fetus, showed different results.<sup>21,42</sup>

From various references, the therapy or treatment of COVID-19 for pregnant and breastfeeding women must be carried out by a multidisciplinary team consisting of obstetric, perinatal, neonatal, and intensive care specialists. Therapy or treatment for pregnant and breastfeeding women with COVID-19 shall follow the recommended supportive therapy with the consideration of physiological changes in pregnant women.

Specifically for the use of symptomatic drugs and COVID-19 test drugs for pregnant women, caution should be given to information regarding each drug<sup>16</sup>, for instance:

- a. Ibuprofen for anti-fever/heat should not be used by 3<sup>rd</sup>-trimester pregnant women;
- b. The favipiravir test drug should not be used by pregnant women or who are suspected of being pregnant because of possible teratogenic effects on the fetus.

## 2. Treatment of COVID-19 for children

Based on COVID-19 case data globally, children are exposed to COVID-19 and its severity is very low compared to adults, especially the elderly. Therapy or treatment of COVID-19 for children is conducted according to the type and standard dosage of the drug set with due attention to precautionary information.<sup>43,44,45,46</sup> For example, hydroxychloroquine should not be used by children under 6 years of age (200 mg tablets not permitted at bodyweight <31 kg).

## 3. Treatment of COVID-19 for the elderly

In elderly patients under supervision or positive COVID-19 patients, it is necessary to conduct a focused assessment of patients to obtain a conventional medical history as well as an understanding of the values, priorities, and preferences

related to health management. In making decisions to overcome multi-morbidity and functional impairment, it is necessary to involve a multidisciplinary team consisting of doctors, nurses, pharmacists, and other health workers.

Physiological changes in the elderly can bring a decrease in an intrinsic capacity such as malnutrition, cognitive decline, and other conditions that need to be comprehensively monitored. Early detection of inappropriate drug administration can prevent the occurrence of drug side effects and drug interactions in drug administration for COVID-19. The elderly are more likely to get polypharmacy, due to the addition of new prescription drugs, reconciliation of inappropriate treatments, and lack of coordination in care thereby increasing negative health consequences.<sup>10</sup>

#### 4. Treatment of COVID-19 for patients with chronic diseases

Patients with chronic diseases such as diabetes and hypertension, especially in elderly patients, have been reported to increase risk factors for serious illness and even death when exposed to COVID-19. Therefore, although this patient may only experience mild symptoms, it is likely to experience a decrease in the condition so it needs to be put in a special care unit for close monitoring.<sup>11</sup>

For patients with diabetes, the administration of COVID-19 drugs such as chloroquine and hydroxychloroquine<sup>47</sup> needs to be carefully conducted. Besides, the use of diabetes medications, including the use of insulin, and monitoring of blood sugar levels must still be properly conducted<sup>48</sup>.

Based on the information from several sources, such as the EMA Drug Authority<sup>49</sup>, UK MHRA<sup>50</sup>, and the American College of Cardiology professional guide<sup>51</sup>, it is known that speculation about an increased risk of complications of COVID-19

infection in patients with hypertension, heart problems and diabetes using ACE-i (Angiotensin Converting Enzyme Inhibitor) and ARB (Angiotensin Receptor Blocker) still do not have data to support scientific research in humans. Therefore, people with diabetes and hypertension are still recommended to continue treatment according to doctor's advice to monitor their health conditions.

#### 5. The use of glucocorticoid drugs in COVID-19 patients

Specifically, all global references for COVID-19 therapy mention that they do not recommend the use of glucocorticoids in patients with COVID-19 with pneumonia since glucocorticoids are very strong immune-suppressants (inflammatory suppression) that cause delayed viral clearance based on the experience of use in patients with MERS-CoV infection, but its use can be considered in refractory shock or ARDS.

#### 6. The use of polypharmacy in COVID-19 patients

In addition to giving attention to risk factors, ensuring drug safety in polypharmacy is also one of the challenges related to drug safety. The conventional view of polypharmacy is the overuse of drugs, while the more appropriate view is to see the suitability/needs, since there are many cases of the simultaneous use of several drugs is considered necessary and useful<sup>52</sup>.

Although there is no standard definition, polypharmacy is often interpreted as a routine use of five or more drugs. These drugs include over-the-counter drugs, over-the-counter with limitation drugs, prescription drugs, and/or traditional and complementary medicines used by patients.

The following are things that can be put into consideration by health workers related to polypharmacy:

a. Polypharmacy is appropriate if:

- all drugs prescribed for certain therapeutic purposes have been agreed by the patient;
- therapeutic goals are being / will be achieved or are most likely to be achieved in the future;
- treatment has been optimized to minimize the risk of drug side effects; and
- the patient is motivated and able to take all the drugs

b. Polypharmacy is inappropriate if one or more prescribed drugs are no longer needed due to the following conditions:

- the indications are not supported by evidence,
- indications of completion/passing or too high a dose;
- one or more drugs fail to achieve the desired therapeutic goals;
- one or a combination of several drugs has given or made patients at high risk of experiencing side effects; or
- the patient does not want or is not able to consume one or more of these drugs.

Polypharmacy management related to decision making and determining the goals achieved in addition to involving health workers (doctors, nurses, pharmacists and others) also needs to involve patients, the patient's family/service providers to patients/caregivers. Good communication and sharing of accurate information are also very important and can be facilitated by patient medication records<sup>52</sup>.

Polypharmacy can increase the likelihood of drug interactions so that it may result in treatment efficacy not being achieved or the risk of serious or even fatal side effects<sup>53</sup>. For example, chloroquine and hydroxychloroquine are known to cause prolongation of the QT interval, so combining them with drugs that prolong the QT interval such as antiarrhythmic, tricyclic antidepressants, antipsychotics, and some anti-infections must be quite risky since it may increase the risk of arrhythmia<sup>54,55</sup>. Therefore, it is important to pay attention to information regarding drug warnings and interactions contained in the monograph of each COVID-19 drug (see CHAPTER IV).

## CHAPTER IV

### INFORMATORIUM OF COVID-19

#### A. ANTIVIRAL DRUGS

##### 1. LOPINAVIR + RITONAVIR

200/50 mg and 100/25 mg tablets

###### a) Indications

- **As a registered drug:** Second-line HIV / AIDS therapy in combination with other antivirals
- As a Test Drug: COVID-19 Therapy.

###### b) Contraindications

- Hypersensitivity to lopinavir, ritonavir, or drug components.
- Should not be given along with adrenoreceptor antagonists  $\alpha$ -1 (alfuzosin HCl), antianginal (ranolazine), antiarrhythmic (dronedarone), antibiotics (fusidic acid), antigout (colchicine in patients with liver / kidney damage), antihistamines (ranolazine), antiarrhythmics (dronedarone), antibiotics (fusidic acid), antigout (colchicine in patients with liver / kidney damage), antihistamines (astemizole, terfenadine) antipsychotics (blonanserin, lurasidone, pimozide), benzodiazepines (midazolam, triazolam), ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine), gastrointestinal motility (midazolam, triazolam), ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine), gastrointestinal motility (midazolam, triazolam), ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine), gastrointestinal motility (midazolam, triazolam), ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine), gastrointestinal motility (cisapride), herbal products (St. John's Wort / *Hypericum perforatum*),  $\beta$  long-acting (salmeterol), neuroleptic (pimozide), enzyme inhibitors PDE5 (sildenafil when used in the treatment of

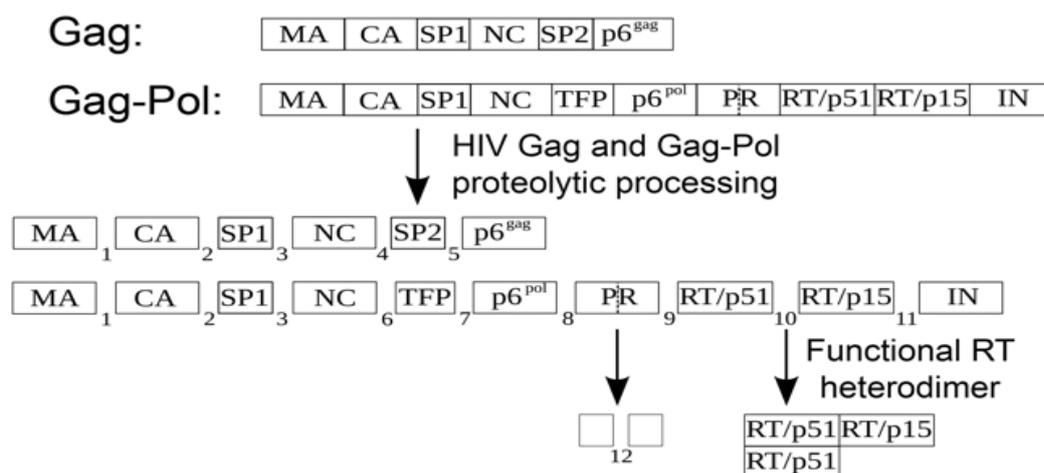
pulmonary arterial hypertension (PAH)).

- Patients with severe liver disorders

### c) Mechanism of Action

Lopinavir is a protease-inhibiting peptidomimetic of HIV-1 and HIV-2, which selectively inhibits the cutting of Gag and Gag-Pol polyproteins thereby preventing viral maturation (immature) and non-infectious.<sup>56,57</sup>

Ritonavir is an HIV protease peptidomimetic inhibitor that interferes with the HIV reproductive cycle<sup>58</sup>. Ritonavir is strongly inhibited by serum proteins but enhances the effect of other protease inhibitors through inhibition of degradation by the cytochrome P450<sup>59,60</sup> enzyme.



### d) Dosage

#### As a registered drug

Tablets must be swallowed, must not be chewed, broken, or crushed.

#### Adult:

- Patients who are just starting treatment: lopinavir / ritonavir tablets 400 mg / 100 mg (2 tablets 200 mg / 50 mg) 2 times daily with or without food, or 800 mg / 200 mg (4

tablets 200 mg / 50 mg) once a day with or without food, for no more than 10 days.

- Patients who have a history of previous therapy: lopinavir/ritonavir tablets 400 mg / 100 mg (2 tablets 200 mg / 50 mg) 2 times daily with or without food, for no more than 10 days.
- Joint therapy with other drugs:
  - Omeprazole and ranitidine: lopinavir/ritonavir can be combined with omeprazole and ranitidine without dose adjustment.
  - Efavirenz, nevirapine, amprenavir or nelfinavir: an increase in the dose of lopinavir / ritonavir up to 533 mg / 133 mg twice daily with food is recommended for use with efavirenz, nevirapine, amprenavir or nelfinavir. Lopinavir/ritonavir should not be given in a once-daily dosing regimen if given along with efavirenz, nevirapine, amprenavir or nelfinavir

#### Pediatric:

- Lopinavir/ritonavir should not be given once a day.
- Adult dose (lopinavir/ritonavir 400 mg / 100 mg twice daily) without administration of efavirenz, nevirapine, nelfinavir or amprenavir can be given to children weighing 35 kg or more, or with Body Surface Area (BSA) 1.4 m<sup>2</sup> or more and can swallow tablets.
- Giving WITHOUT efavirenz, nevirapine, nelfinavir or amprenavir follows the following guidelines based on the Body Surface Area (BSA):

<b>BSA (m<sup>2</sup>)</b>	<b>Tablet Qty (100 mg/ 25 mg) twice daily</b>
≥ 0,6 - < 0,9	2 (200 mg / 50 mg)
≥ 0,9 - < 1,4	3 (300 mg / 75 mg)
≥ 1,4	4 (400 mg / 100 mg)

- Giving WITHOUT efavirenz, nevirapine, nelfinavir, or amprenavir based on body weight follows the following guidelines:

<b>Body weight (kg)</b>	<b>Tablet Qty (100 mg/ 25 mg) twice daily</b>
15 – 25	2 (200 mg / 50 mg)
> 25 - 35	3 (300 mg / 75 mg)
> 35	4* (400 mg / 100 mg)

- Joint administration with efavirenz, nevirapine, nelfinavir, or amprenavir based on BSA follows the following guidelines:

<b>BSA (m<sup>2</sup>)</b>	<b>Tablet Qty (100 mg/ 25 mg) twice daily</b>
≥ 0,6 - < 0,8	2 tablets (200 mg / 50 mg)
≥ 0,8 - < 1,2	3 tablets (300 mg / 75 mg)
≥ 1,2 < 1,7	4* tablets (400 mg / 100 mg)
≥ 1,7	5 tablets (500 mg / 125 mg)

- Joint administration with efavirenz, nevirapine, nelfinavir or amprenavir based on body weight follows the following guidelines:

<b>Body weight (kg)</b>	<b>Tablet Qty (100 mg / 25 mg) twice daily</b>
15 – 20	2 (200 mg / 50 mg)
> 20 - 30	3 (300 mg / 75 mg)
> 30 – 45	4* (400 mg / 100 mg)
> 45	5 (500 mg / 100 mg)

\*alternative: 2 tablets of 200 mg / 50 mg can be given if you can swallow larger tablets

### **Dosage for COVID-19 test drug:**

- Adult: lopinavir / ritonavir tablet 400 mg / 100 mg (2 tablets 200 mg / 50 mg) twice daily, not more than 10 days.

- Pediatric: based on an adult dose, no more than 10 days.

<b>Body weight (kg)</b>	<b>Tablet Qty (100 / 25 mg) twice daily</b>
15 – 25	2 (200 mg / 50 mg)
> 25 - 30	3 (300 mg / 75 mg)
> 35	4* (400 mg / 100 mg)

\*alternative: 2 tablets of 200 mg / 50 mg can be given if you can swallow larger tablets

- Clinical trial results show the addition of 400 mg / 100 mg of lopinavir/ ritonavir given orally twice daily for 14 days did not show significant clinical improvement compared to standard treatment for COVID-19 patients in China<sup>61</sup>. This dosage is still recommended in therapy by WHO, International Pulmonologist’s Consensus on COVID-19, Japan, and Singapore. Further studies are needed on the effectiveness of this drug when combined with other antivirals.

**e) Warnings:**

- In diabetic patients, consideration should be given to monitoring blood sugar, due to post-marketing reports of diabetes exacerbations and hyperglycemia.
- The incidence of pancreatitis is observed in patients using the combination of lopinavir/ritonavir, and the risk is increased in patients with advanced HIV and patients with a history of pancreatitis.
- Lopinavir/ritonavir is metabolized in the liver, so it must be given with caution in patients with liver disorders.
- The reported increase in bleeding in patients, including spontaneous skin hematoma and hemarthrosis in patients with hemophilia type A and B.
- Special attention in drug administration for patients with heart structure disorders and patients using drugs that can extend the PR interval, such as verapamil and atazanavir.

**f) Side Effects:**

Diarrhea, nausea, vomiting, hypertriglyceridemia, hypercholesterolemia, fatigue including asthenia, abdominal pain, headache, dyspepsia, bloating, insomnia, paresthesia, anorexia, pain, depression, lipodystrophy, rash, myalgia, weight loss, abdominal enlargement, decreased libido, abnormal stools, vascular disorders, bronchitis, hypogonadism in men, amenorrhea, hypertension, chills, fever.

**2. FAVIPIRAVIR**

200 mg tablets

**a) Indications as a test drug:**

An indication for this drug is a new or recurrent pandemic influenza virus infection (limited use for treatment in cases where other antiviral drugs are not or less effective).<sup>62</sup>

Based on the favipiravir clinical trials for the COVID-19 drugs in Japan<sup>47</sup> and China<sup>63,64</sup>, the preliminary results have shown good effectiveness.<sup>65</sup>

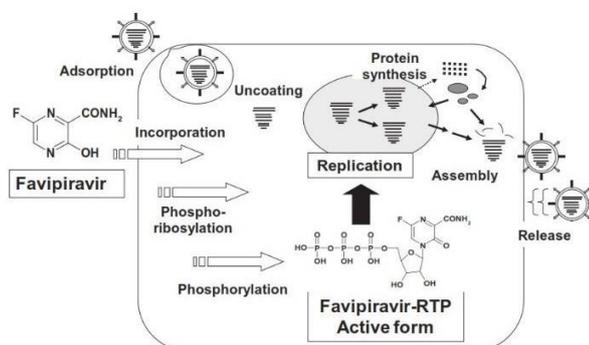
**b) Contraindications:**

1. Should not be used in the first trimester of pregnant women or who are planning a pregnancy.
2. Hypersensitivity to all components in favipiravir tablets

**c) Mechanism of Action:**

Favipiravir selectively inhibits RNA-dependent RNA polymerase (RdRp) from influenza viruses. Favipiravir is a prodrug that undergoes ribosylation and intracellular phosphorylation and is converted to the form of ribofuranosy

I phosphate (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase so that it inhibits RNA polymerase activity and inhibits the process of viral replication.<sup>65,66</sup>



#### d) Dosage:

Treatment of influenza virus disease<sup>25</sup>

In adults, the dose is 1600 mg twice daily on the first day, followed by 600 mg twice daily for the next four days. A total treatment for 5 days.

#### Dosage for COVID-19 test drug:

- Based on WHO<sup>25</sup>  
1600 mg dose on day 1 as a loading dose followed by 600 mg, twice daily starting day 2 until no more than 14 days.
- In Indonesia, according to PDV 40 COVID-19 Patient Procedure:  
Mild symptoms: if necessary, favipiravir 600 mg twice daily for 5 days.  
Moderate and severe symptoms: favipiravir loading dose 1600 mg 2 times daily 1 day and then 600 mg twice daily (days 2-5).

e) **Warnings**<sup>62</sup>:

The administration of favipiravir for the following patients must meet certain requirements:

- For women who are potentially pregnant, the pregnancy test results must confirm negative prior to the treatment. If pregnancy occurs during treatment, the treatment must be stopped immediately.
- If favipiravir is to be given to breastfeeding women, it is required to stop breastfeeding because the active metabolite of favipiravir in the form of hydroxylation is found in breast milk.
- Favipiravir is distributed in sperm. If the drug is given to male patients, explain the risks, and give the following instructions:
  - a. using the most effective contraceptive method with her partner during and for 7 days after treatment ends,
  - b. not having sexual relations with pregnant women.
- Although the causal relationship is still debatable, psychoneurotic symptoms such as abnormal behavior after the administration of favipiravir have been reported. If the treatment is needed for children and infants, certain precautions should be taken if abnormal behavior occurs. Therefore, the family must maintain or make other efforts at least 2 days if the treatment is carried out at home. Since similar symptoms related to influenza encephalopathy have been reported, the same actions must be taken.
- The administration of favipiravir must consider other requirements for patients with gout or who have a history of gout and hyperuricemia patients because it can increase uric acid levels and aggravate symptoms.
- Influenza virus infections can be accompanied by bacterial infections or can be masked by influenza-like symptoms. If there is a bacterial infection or a suspected

bacterial infection, antibiotics need to be given.

- The administration of favipiravir to elderly patients needs to be carefully conducted, accompanied by monitoring the general condition.
- There is no safety study of favipiravir in children.
- In an in vitro study, favipiravir inhibits hERG current in C<sub>max</sub> which is 3 times higher than C<sub>max</sub> in humans so that the risk of prolongation of the QT interval at a therapeutic dose is not high.

#### f) Drug Interactions<sup>62</sup>:

Favipiravir must be used with caution when given with the following drugs:

<b>Drugs</b>	<b>Symptoms</b>	<b>Mechanisms and Risk Factors</b>
Pyrazinamide	Blood uric acid increases. In the administration of pyrazinamide 1500 mg once a day and favipiravir 1200 mg / 400 mg twice daily, blood uric acid levels are 11.6 mg / dL when pyrazinamide is used alone, and 13.9 mg / dL when used in combination with favipiravir.	Uric acid reabsorption in the kidney tubules is additively enhanced. CYP2C8 inhibition increases repaglinide levels in the blood.
Repaglinide	Repaglinide levels in the blood may increase, and adverse reactions to repaglinide can occur.	CYP2C8 inhibition increases repaglinide levels in the blood.
Theophylline	Favipiravir levels in the blood may increase, and adverse reactions to favipiravir can occur.	Interaction with xanthine oxidase (XO) can increase blood levels of favipiravir.
Famciclovir, sulindac	The efficacy of famciclovir / sulindac can be reduced.	Aldehyde inhibition oxidase (AO) by favipiravir can reduce the active form of famciclovir /sulindac in the blood.
Chloroquine (CYP2C8 Substrate)	Potential interactions	The clinical significance is not known with certainty

Drugs	Symptoms	Mechanisms and Risk Factors
Oseltamivir	Potential interactions	The clinical significance is not known with certainty

### g) Side Effects:

At doses lower than the dose written in posology, undesirable effects are reported as listed in the following table:

	≥ 1%	0.5 - <1%	<0.5%
Hypersensitivity		Rash	Eczema, pruritus
Hepatic	Increase in AST (GOT), increase in ALT (GPT), increase $\gamma$ -GT		Increased ALP in blood, Increased bilirubin in the blood
Gastrointestinal tract	Diarrhea (4.79%)	Nausea, vomiting, stomachache	uncomfortable stomach, duodenal ulcer, hematochezia, stomach inflammation
Hematologist	A decrease in neutrophil count, decrease in leukocyte count		Increased white blood cell counts, decreased reticulocyte counts, Increased monocyte counts
Metabolic Disorders	Increased uric acid in the blood (4.79%), increase in triglycerides		A decrease in potassium levels in the blood
Airway			Asthma, oropharyngeal pain, rhinitis, Nasopharyngitis

	≥ 1%	0.5 - <1%	<0.5%
Others			Increased creatinine kinase levels in the blood (creatinine phosphokinase), presence of blood in urine, tonsillar polyps, pigmentation, dysgeusia, bruising, blurred vision, eye pain, vertigo, supraventricular extrasystoles

### 3. REMDESIVIR

100 mg tablets

#### a) Indications<sup>67</sup>:

As a test drug for the treatment of COVID-19, based on experience developing treatment of Ebola virus infection, SARS-CoV, MERS-CoV. From several in-vitro and in-vivo tests, Remdesivir shows strong antiviral activity and has also been shown to reduce pulmonary pathology (in-vitro testing). Remdesivir has the potential for clinical efficacy against filovirus, including the Ebola virus and SARS-CoV-2.

#### b) Contraindications<sup>67</sup>:

- Not recommended for sufferers of COVID-19 with moderate to severe kidney disorders.
- Not recommended for co-administration with other antivirals because antagonism, synergy, or no effect can occur.

### **c) Mechanism of Action** <sup>68,69</sup>:

Remdesivir is an adenine nucleotide analog with broad-spectrum antiviral activity against various RNA viruses, such as SARS, MERS, and Ebola.

Remdesivir undergoes efficient metabolic conversion in cells and tissues to active nucleoside triphosphate metabolites that inhibit RNA-dependent RNA polymerase (RdRp) viruses, but do not inhibit the patient's RdRp. Thus, remdesivir inhibits COVID-19 in the early stages of viral replication.

### **d) Dosage** <sup>24,66,67</sup>:

#### Adult:

- Day 1, 200 mg IV once a day (infused for > 30 minutes) as a loading dose.
- Day 2 to 10 are given 100 mg IV once a day (infused for > 30 minutes)

Pediatric with body weight <40 kg:

- Day 1, 5 mg / kg IV once a day (infused for > 30 minutes), as a loading dose,
- Day 2 to 10, 2.5 mg / kg IV once a day (infused for > 30 minutes).

### **e) Attention and Warnings:**

- As a test drug, remdesivir does not have clinical or pharmacokinetic (PK) safety data in patients with impaired renal function or liver function:
  - Remdesivir contains SBECD (sulfobutylether- $\beta$ -cyclodextrin) which is released through the kidneys and accumulates in impaired renal function, so monitoring of renal function needs to be carried out. If eGFR decreases by >50%, permanent cessation of Remdesivir treatment should be considered<sup>70</sup>.
  - Remdesivir can increase transient hepatic transaminases so monitoring of liver function tests is needed<sup>70</sup>.

- Use in pregnant and breastfeeding women: There are no data on clinical trial results in pregnant and breastfeeding women. Test results on mice and monkeys showed that remdesivir has an impact on kidney development in the fetus. Therefore, special consideration is needed on the use of remdesivir in pregnant and breastfeeding women.

#### **f) Drug Interactions:**

Data on remdesivir interactions with other drugs have not confirmed yet because there are no specific tests. However, based on the characteristics of similar drug groups, the use of several drugs can cause an increase or decrease in remdesivir level in the blood, or vice versa, for example in the use of remdesivir together with other antivirals, antibiotics (clarithromycin, rifampicin), phenytoin, phenobarbital, and products containing herbal ingredients of St. John's Wort.

#### **g) Side effects<sup>70</sup>:**

- Gastrointestinal disorders, hepatotoxic.
- From non-clinical data:

The risk of an effect on the central nervous system, respiratory and cardiovascular is low on the estimated level of therapy in humans.
- A dose of 150 mg IV once daily for 7-14 days in humans shows: there are no abnormalities in laboratory tests grade 3 or 4, an increase in ALT and AST degrees 1 or 2 without abnormalities in total bilirubin, alkaline phosphatase or albumin, and no effects on kidney function.

## 4. OSELTAMIVIR

75 mg capsules

### a) Indications

#### Influenza treatment<sup>71</sup>

- Used in adults and children aged 1 year or more who experience influenza symptoms, when influenza viruses are epidemic in the community.
- Benefits will occur when treatment starts within 2 days of the onset of symptoms.
- Indications are based on clinical studies of influenza that occur naturally with the main infection of influenza A.

#### Prevention of influenza<sup>71</sup>

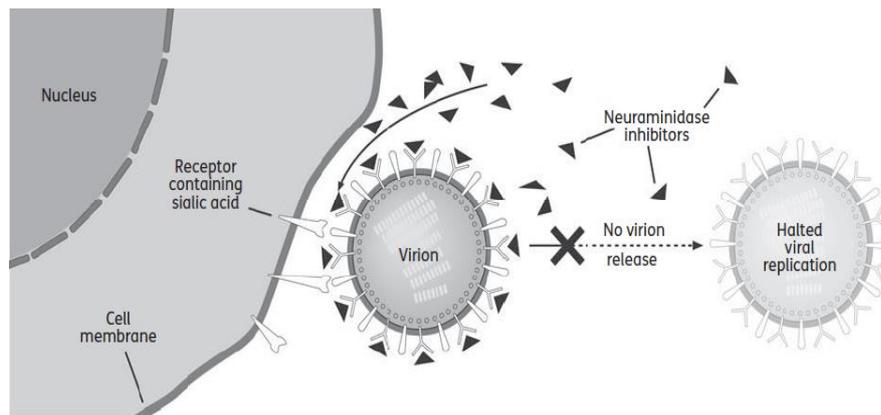
- Prevention of post-exposure in adults and adolescents aged 13 years or more after interacting with influenza patients when influenza viruses are endemic in the community.
- Determination of the use of oseltamivir for prevention is determined based on the conditions and population of cases that need protection, in situations of exclusion (such as disease incompatibility with vaccine availability and pandemic conditions), temporary prevention can be considered.
- Oseltamivir is not a substitute for the influenza vaccine.
- The use of antivirals for the treatment and prevention of influenza must be determined based on government recommendations taking into account the diversity of epidemiology and the impact of the disease on different geographical regions and patient populations.

### b) Contraindications<sup>71</sup>:

Hypersensitivity to oseltamivir phosphate and other additives.

**c) Mechanism of Action** <sup>71,72</sup>:

Oseltamivir phosphate is a pro-drug of oseltamivir carboxylate (OC) which is a selective and potent inhibitor of the influenza enzyme neuraminidase enzymes A and B, thus inhibiting influenza virus infection and in vitro replication. Viral neuraminidase enzymes play an important role in the release of newly formed virus particles from infected cells and the spread of virus transmission.



Gambar 3. Mekanisme kerja oseltamivir<sup>72</sup>

**d) Dosage**

Influenza treatment<sup>71</sup>

Treatment is carried out as soon as possible within 2 days of the onset of symptoms.

The dosage of Adult and Children  $\geq 13$  years: 75 mg twice daily for 5 days.

The dosage of Children 1-12 years is adjusted to the following bodyweight:

Weight	Dosage Recommendation
$\leq 15$ kg	30 mg twice daily
$>15$ kg to 23 kg	45 mg twice daily
$>23$ kg to 40 kg	60 mg twice daily
$>40$ kg	75 mg twice daily

Patients with impaired kidney function:

Influenza treatment:

<b>Creatinine clearance</b>	<b>Recommended dosage</b>
> 30 (mL / min)	75 mg twice daily
> 10 - ≤30 (mL / min)	30 mg twice daily or 30 mg suspension twice daily
≤ 10 (mL / min)	Not recommended
Dialysis patients	Not recommended

Influenza prevention:

<b>Creatinine clearance</b>	<b>Recommended dosage</b>
> 30 (mL / min)	75 mg twice daily
> 10 - ≤30 (mL / min)	75 mg twice daily or 30 mg suspension twice daily
≤ 10 (mL / min)	Not recommended
Dialysis patients	Not recommended

Treatment of COVID-19<sup>73</sup>

- In a retrospective study of 99 COVID-19 patients in China, oseltamivir was given at a dose of 75 mg orally every 12 hours. Evaluation results showed 58% of patients remained hospitalized, 31% recovered, and 11% died.
- There are various doses in several phases 3 clinical trials being carried out regarding the use of oseltamivir in COVID-19 patients, namely: 300 mg orally once daily, 75 mg orally once daily or twice daily for 14 days, and 4-6 mg / kg body weight orally once daily.
- Based on the Management of Patients with COVID-19 for Patients under Supervision with mild, moderate, and severe symptoms: 2 x 75 mg (for 5 days).
- Unlike the influenza virus, the COVID-19 virus does not require neuraminidase to

escape from the host cell. After replicating inside the host cell, the COVID-19 virus needs help from the protein E virus and the process of exocytosis to escape.<sup>74,75</sup>

- Because COVID-19 does not have the neuraminidase enzyme, oseltamivir is not effective for the COVID-19 virus. But oseltamivir can be given at the onset of COVID-19 symptoms that are similar to influenza symptoms. If oseltamivir is ineffective, it means that COVID-19 infection occurs, then oseltamivir must be immediately replaced with a drug for COVID-19<sup>24</sup>.

#### **e) Warnings <sup>71</sup>:**

- There has been no evidence of the benefits and safety of oseltamivir for:
  - prevention of influenza in children <12 years,
  - treatment and prevention of influenza in patients with immune system disorders,
  - influenza treatment in patients with chronic heart and/or respiratory disorders.
- Cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Steven Johnson's Syndrome, and erythema multiform were reported in post-marketing monitoring. Stop oseltamivir if serious hypersensitivity reactions occur.

#### **f) Drug interactions<sup>71</sup>:**

- No dose adjustment is needed if given with probenecid in patients with good kidney function.
- There are no pharmacokinetic interactions with amoxicillin.
- Pay more attention to the drug with a narrow therapeutic index (chlorpropamide, methotrexate, phenylbutazone).

#### **g) Side Effects<sup>71</sup>:**

The most commonly reported side effects are nausea, vomiting, abdominal pain, epistaxis, hearing loss, and conjunctivitis.

## **B. ANTIVIRAL DRUGS IN EMERGENCY**

### **1. CHLOROQUINE PHOSPHATE**

250 mg tablet

#### **a) Indications for emergency / limited use**

The use is limited to the emergency condition of the COVID-19 pandemic for the treatment of adult COVID-19 patients and adolescents who have a bodyweight of 50 kg or more who are hospitalized. [Note: Indications may change if there are recent data relating to the efficacy and safety of the drug in COVID-19 patients].

#### **b) Contraindications:**

- Patients with retinal or visual changes with any etiology.
- Patients who are hypersensitive to 4-aminokuinolin compounds.
- Patients with extended QT intervals at the baseline or have an increased risk of arrhythmia.

#### **c) Mechanism of Action:**

Chloroquine is anti-virus does phagolysosomal alkalization, thus inhibiting the phases of viral replication that depend on low pH, including the fusion and uncoating stages. Looking at its mechanism of action, chloroquine works in the early stages of infection by inhibiting the entry of the virus into the host cell. Chloroquine also has immunomodulatory activity, which can contribute to the anti-inflammatory response in patients with viral infections.

#### **d) Dosage:**

1. In emergency / limited use for COVID-19:

The optimal dosage and duration for COVID-19 are still unknown.

For limited use in the COVID-19 pandemic conditions, chloroquine phosphate is given to adult and adolescent patients with a bodyweight of 50 kg or more and is hospitalized at a dose of 1000 mg on day 1, then 500 mg per day for 4-7 days duration of treatment based on clinical evaluation results.

Note: The dosage and duration of treatment may change if there are up-to-date data regarding the efficacy and safety of the drug in COVID-19 patients.

2. In accordance with procedures for COVID-19 Patients under Supervision:

Mild and moderate symptoms: chloroquine phosphate 500 mg twice daily, for 5 days

Severe symptoms: Chloroquine phosphate 500 mg twice daily on day 1 to day 3, followed by 250 mg twice daily on day 4 to day 10.

**e) Warnings:**

Cardiovascular

- Extend the QT interval.
- Must be used with caution in patients with heart disease, extended QT, history of ventricular arrhythmias, bradycardia, uncorrected potassium or magnesium imbalance, and during treatment with drugs that prolong QT intervals, such as azithromycin and other antibacterials. Electrocardiogram monitoring is needed during drug administration.
- Myocarditis, pericarditis, and cardiomyopathy can increase the risk of arrhythmias. Cardiac injury monitoring is needed.

Hypoglycemia

Chloroquine has been reported to reduce clearance and insulin resistance, and cause loss of consciousness in patients with or without diabetes treatment.

### Hematology

Hemolysis in G6PD-deficient patients, pancytopenia, aplastic anemia, and neutropenia.

### Liver disorders

Because chloroquine phosphate is known to be concentrated in the liver, it must be used with caution in patients with hepatitis, liver disorders, alcoholism, or co-use with drugs known to be hepatotoxic.

### Kidney disorders

Chloroquine phosphate is known to be excreted by the kidneys and the risk of toxic reactions to this drug can be increased in patients with impaired kidney function.

### Central nerve system

Chloroquine phosphate can increase the risk of convulsions in patients with a history of seizures. Acute extrapyramidal disorders can occur. Psychosis, delirium, agitation, confusion, suicidal behavior and hallucinations can occur with the use of chloroquine phosphate.

### Psoriasis and porphyria

The use of chloroquine phosphate in patients with psoriasis can trigger severe psoriasis attacks. If used in patients with porphyria, the condition can be worse. Chloroquine phosphate should not be given under these conditions unless the benefits outweigh the risks.

### Retinopathy

Retinal damage occurs in some patients who use chloroquine phosphate in the long run.

## **f) Drug Interactions:**

### Digoxin

Can increase serum digoxin levels; so it needs to be monitored regularly.

### Antacids and kaolin

Antacids and kaolin can reduce the absorption of chloroquine phosphate. At least 4-hour intervals in the use of these drugs and chloroquine phosphate must be observed.

### Cimetidine

Cimetidine can inhibit the metabolism of chloroquine phosphate thereby increasing plasma levels. Concurrent use should be avoided.

### Insulin and other antidiabetic drugs

Since chloroquine phosphate can increase the effects of hypoglycemic treatment, decreasing the dose of insulin and other antidiabetic drugs is needed.

### Arrhythmogenic drugs

There may be an increased risk of ventricular arrhythmias if chloroquine phosphate is given along with other arrhythmogenic drugs, such as amiodarone, azithromycin or moxifloxacin.

### Ampicillin

In healthy subjects, chloroquine phosphate significantly reduced the bioavailability of ampicillin. At least 2-hour intervals between the use of ampicillin and chloroquine phosphate must be observed.

### Cyclosporine

After the initial use of chloroquine phosphate, there was a sudden increase in cyclosporine levels in serum. Therefore, close monitoring of cyclosporine levels in serum is recommended and, if necessary, the use of chloroquine is stopped.

### Mefloquine

Co-use of chloroquine phosphate with mefloquine can increase the risk of convulsions.

### Praziquantel

In a single-dose interaction study, chloroquine phosphate decreased the bioavailability of praziquantel.

### Tamoxifen

The use of chloroquine phosphate together with drugs that cause retinal toxicity, such as tamoxifen, is not recommended.

### Antiepileptic

Antiepileptic drug activity can be disrupted if given together with chloroquine phosphate.

### **Use during pregnancy**

In tests with animals, it shows toxicity to embryo-fetal development at a dose of about 3-16 times the maximum therapeutic dose based on body surface area ratio. Preclinical data indicate a potential risk of genotoxicity in several test systems. In humans, at recommended doses for prophylaxis and treatment of malaria, observational studies, and meta-analyses, including small-scale prospective trials of

chloroquine use in pregnancy, do not show an increase in birthrate or spontaneous abortion.

The balance of individual benefits must be assessed before giving chloroquine to pregnant women.

**g) Side Effects:**

- Eyes: irreversible retinal damage, blurred vision, difficulty in focus, and foggy vision.
- Nervous system: convulsions, psychosis, mild to severe headaches.
- Gastrointestinal: nausea, vomiting, diarrhea, and abdominal cramps.
- Hypersensitization reactions including urticaria and angioedema
- Bone marrow suppression
- Dermatology: changes in skin pigment, pruritis, hair loss, skin eruptions.
- Atrioventricular blocks; porphyria and psoriasis in sensitive individuals.

**2. HYDROXYCHLOROQUINE SULFATE**

200 mg tablets

**a) Indications**

Registered indications:

Treatment of systemic lupus erythematosus.

**Indications for emergency / limited use:**

Use is limited to the emergency condition of the COVID-19 pandemic for the treatment of adult COVID-19 patients and adolescents who have a bodyweight of 50 kg or more who are hospitalized. [Note: Indications may change if there are recent data relating to the efficacy and safety of the drug in COVID-19 patients].

## **b) Contraindications:**

- Patients with retinal or visual changes with any etiology.
- Patients who are hypersensitive to 4-aminoquinoline compounds.
- Patients with extended QT intervals at the baseline or have an increased risk of arrhythmia.

## **c) Mechanism of Action :**

Hydroxychloroquine as an antiviral performs phagolysosomal alkalinization, thus inhibiting the phases of viral replication that depend on low pH, including the fusion and uncoating stages. Hydroxychloroquine also has immunomodulatory activity, which can contribute to the anti-inflammatory response in patients with viral infections.

## **d) Dosage:**

### 1. Dosage for systemic lupus erythematosus:

- Adult (including elderly):

The minimum effective dosage must be given. Dosage should not exceed 6.5 mg/kg/day (calculated based on ideal body weight and not actual body weight) and between 200 mg or 400 mg per day. The dosage above 400 mg is not recommended.

- In patients who can receive 400 mg per day:

The initial dose is 400 mg in divided doses. The dose can be reduced to 200 mg if no improvement is seen. The maintenance dose must be increased to 400 mg per day if the response is reduced.

- Pediatric:

The minimum effective dose should be given and should not exceed 6.5 mg/kg/day based on ideal body weight. Therefore, a dose of 200 mg is not suitable for use in children with an ideal body weight of less than 31 kg.

## 2. Dosage on emergency / limited use for COVID-19

The optimal dose and duration of COVID-19 are unknown.

For limited use in the COVID-19 pandemic conditions, Hydroxychloroquine sulfate is given to adult and adolescent patients weighing 50 kg or more and are hospitalized at a dose of 800 mg on day 1, then 400 mg per day for 4-7 days total treatment duration based on clinical evaluation results.

Note: The dosage and duration of treatment may change if there are up-to-date data regarding the efficacy and safety of the drug in COVID-19 patients.

## 3. In accordance with Procedures of COVID-19 Patients under Supervision:

Symptoms of mild, moderate, and severe: Hydroxychloroquine sulfate 400 mg once a day, for 5 days.

### **e) Warnings:**

#### Cardiovascular

- Extend the QT interval.
- Must be used with caution in patients with heart disease, extended QT, history of ventricular arrhythmias, bradycardia, uncorrected potassium or magnesium imbalance, and during treatment with drugs that prolong QT intervals, such as azithromycin and other antibacterials. Electrocardiogram monitoring is needed during drug administration.
- Myocarditis, pericarditis, and cardiomyopathy can increase the risk of arrhythmias.

Cardiac injury monitoring is needed.

### Hypoglycemia

Hydroxychloroquine has been reported to reduce clearance and insulin resistance, and cause loss of consciousness in patients with or without diabetes treatment.

### Hematology

Hemolysis in G6PD-deficient patients, pancytopenia, aplastic anemia, and neutropenia.

### Liver disorders

Because hydroxychloroquine sulfate is known to be concentrated in the liver, it must be used with caution in patients with hepatitis, liver disorders, alcoholism, or co-use with drugs known to be hepatotoxic.

### Kidney disorders

Hydroxychloroquine sulfate is known to be excreted by the kidneys and the risk of toxic reactions to this drug can be increased in patients with impaired kidney function.

### Central nerve system

Hydroxychloroquine sulfate can increase the risk of convulsions in patients with a history of seizures. Acute extrapyramidal disorders can occur. Psychosis, delirium, agitation, confusion, suicidal behavior, and hallucinations can occur with the use of hydroxychloroquine sulfate.

### Psoriasis and porphyria

The use of hydroxychloroquine sulfate in patients with psoriasis can trigger severe psoriasis attacks. If used in patients with porphyria, the condition can be worse.

Hydroxychloroquine sulfate should not be given under these conditions unless the benefits outweigh the risks.

#### Retinopathy

Retinal damage occurs in some patients who use hydroxychloroquine sulfate in the long term

#### **f) Drug Interactions:**

##### Digoxin

Can increase serum digoxin levels so it needs to be monitored regularly.

##### Antacids and kaolin

Antacids and kaolin can reduce the absorption of hydroxychloroquine sulfate. At least 4-hour intervals in the use of these drugs and hydroxychloroquine sulfate must be observed.

##### Cimetidine

Cimetidine can inhibit the metabolism of hydroxychloroquine sulfate thereby increasing plasma levels. Concurrent use should be avoided.

##### Insulin and other antidiabetic drugs

Because hydroxychloroquine sulfate can increase the effects of hypoglycemic treatment, a decrease in insulin dosage and other antidiabetic drugs is needed.

##### Arrhythmogenic drugs

There may be an increased risk of ventricular arrhythmias if hydroxychloroquine sulfate is given together with other arrhythmogenic drugs, such as amiodarone, azithromycin, or moxifloxacin.

### Ampicillin

In healthy subjects, hydroxychloroquine sulfate significantly reduced the bioavailability of ampicillin. At least 2-hour intervals between the use of ampicillin and hydroxychloroquine sulfate must be observed.

### Cyclosporine

After the initial use of hydroxychloroquine sulfate, a sudden increase in cyclosporine levels in serum has been reported. Therefore, close monitoring is recommended for serum cyclosporine levels and, if necessary, the use of hydroxychloroquine is stopped.

### Mefloquine

Joint use of hydroxychloroquine sulfate with mefloquine can increase the risk of convulsions.

### Praziquantel

In a single-dose interaction study, hydroxychloroquine sulfate decreases the bioavailability of praziquantel.

### Tamoxifen

The use of hydroxychloroquine sulfate together with drugs that produce retinal toxicity, such as tamoxifen, is not recommended.

### Antiepileptic

Antiepileptic drug activity can be disrupted if given together with hydroxychloroquine sulfate.

### **Use during pregnancy**

In tests with animals, it shows toxicity to embryo-fetal development at a dose of about 3-16 times the maximum therapeutic dose based on body surface area ratio.

Preclinical data indicate a potential risk of genotoxicity in several test systems. In humans, at recommended doses for prophylaxis and treatment of malaria, observational studies, and meta-analyses, including small-scale prospective trials of the use of hydroxychloroquine in pregnancy, do not show an increase in birthrate or spontaneous abortion.

The balance of individual risk benefits must be assessed before giving hydroxychloroquine to pregnant women.

**g) Side Effects:**

Eye disorders:

- Retinopathy with changes in pigmentation and visual disturbances can occur (bull's eye appearance), but rarely if the recommended daily dose is not exceeded.
- Visibility disorders (visual field defects / paracentral scotomas), visual disturbances (visual acuity), decreased adaptation to the dark, abnormal color vision, blurred vision.
- Corneal changes including edema and vision are not clear, but maybe temporary and reversible at the interruption of treatment.
- Cases of maculopathy and macular degeneration may not be reversible.

Heart Disorders:

- Cardiomyopathy can cause heart failure and in some fatal cases.
- Chronic toxicity during conduction disorders (atrioventricular heart block) and reversible biventricular hypertrophy with drug termination.
- Hydroxychloroquine can extend the QT interval.
- Ventricular arrhythmias and Torsade de Pointes.

Immune system disorders: urticaria, angioedema, bronchospasm.

Skin and subcutaneous tissue disorders: skin rashes, pruritus, skin pigmentation disorders and mucous membranes, bullous eruptions including erythema multiforme, Stevens-Johnson's syndrome, and toxic epidermal necrolysis, a rash with eosinophilia and systemic symptoms (DRESS syndrome), photosensitivity, exfoliative dermatitis, and toxic epidermal necrolysis, rashes with eosinophilia and systemic symptoms (DRESS syndrome), photosensitivity, exfoliative dermatitis, acute exanthematous pustulosis in general (AGEP) which must be distinguished from psoriasis (hydroxychloroquine can trigger psoriasis attacks).

Gastrointestinal disorders: abdominal pain, nausea, diarrhea, vomiting that can be overcome by reducing the dose or termination of treatment.

Nerve system disorders: headache, dizziness, convulsions, extrapyramidal disorders such as dystonia, dyskinesia, tremor.

Psychiatric disorders: affect instability, anxiety, psychosis

Ear and labyrinth disorders: vertigo, tinnitus, hearing loss

Connective and musculoskeletal tissue disorders:

Sensorimotor disorders, skeletal muscle myopathy or neuromyopathy, and atrophy of proximal muscle tissue, which may be reversible after drug termination.

Blood and lymphatic system abnormalities: bone marrow depression, anemia, aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia, hemolysis in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

Metabolic and nutritional disorders: anorexia, hypoglycemia, porphyria, decreased appetite, and weight.

Hepatobiliary disorders: abnormal liver function tests, fulminant liver failure.

## **C. ANTIBIOTICS**

### **1. AZITHROMYCIN**

250 mg film capsule

500 mg film-coated tablet

Dry syrup 200 mg / 5 mL

500 mg / 10 mL infusion solution

#### **a) Indications:**

Azithromycin is indicated for the treatment of patients with mild to moderate infections caused by strains of sensitive microorganisms, such as upper respiratory infections (tonsillitis, pharyngitis), lower respiratory infections (acute bacterial exacerbations, chronic obstructive pulmonary disease, community pneumonia), skin infections and soft tissue, sexually transmitted diseases, urethritis, cervicitis associated with *Chlamydia trachomatis*, *Ureaplasma urealyticum* and *Neisseria gonorrhoeae*.

#### **b) Contraindications:**

Hypersensitivity to macrolide antibiotics (eg azithromycin, erythromycin) or ketolide groups, and other ingredients in the preparation of this drug.

#### **c) Dosage:**

1. As an antimicrobial as indicated
  - Uncomplicated genital chlamydia infection and non-gonococcal urethritis: 1000 mg as a single dose.

- For all indications: oral 500 mg once daily for 3 days. Alternative: 500 mg once daily on day 1 followed by 250 mg once daily on days 2-5.
  - Pediatric:
    - nodose information for children <6 months
    - Children > 6 months: 10 mg / kg of body weight once a day for 3 days, or 10 mg / kg of body weight on day 1 followed by 5 mg / kg of body weight on days 2-5.
2. In accordance with Procedures of COVID-19 Patients under Supervision:
- Mild, moderate, severe symptoms: azithromycin 500 mg once daily for 3 days.

**d) Warnings:**

Be avoided or used with caution in pregnancy, impaired liver function, hypersensitivity, and myasthenia gravis, patients with a history of the prolonged QT interval, patients who are taking antiarrhythmic drugs, antipsychotics, antidepressants or fluoroquinolones, patients with electrolyte disorders, bradycardia, cardiac arrhythmias, heart failure, and elderly patients because of this drug can extend the QT interval.

**e) Drug Interactions:**

1. The combined use of digoxin increases digoxin levels in the blood.
2. The use of nelfinavir can increase azithromycin levels in the blood, so it is necessary to monitor the side effects of azithromycin such as liver enzymes and hearing loss.
3. Joint use of oral anticoagulants such as warfarin can potentiate the effects of anticoagulants, so it is necessary to monitor INR.
4. The co-use of cyclosporine can increase cyclosporine levels. If co-administration of this drug is needed, cyclosporine levels should be monitored and the dose adjusted.
5. The co-use with chloroquine or hydroxychloroquine can prolong the QT interval and

can increase the risk of ventricular arrhythmias. This risk can be increased in patients with risk factors such as congenital long QT syndrome, heart disease, electrolyte disorders (hypokalemia, hypomagnesemia). Monitoring of the QT interval during treatment with symptoms of dizziness, fainting, palpitations, irregular heartbeat, shortness of breath, or syncope is necessary.

#### **f) Side Effects:**

Nausea, vomiting, abdominal pain, diarrhea; urticaria, rashes, and other allergic reactions; Reversible hearing loss has been reported after large doses; cholestatic jaundice and cardiac disorders (prolongation of the QT interval which can lead to arrhythmias and chest pain), anorexia, dyspepsia, flatulence, constipation, pancreatitis, hepatitis, fainting, dizziness, headaches, drowsiness, agitation, anxiety, hyperactivity, asthenia, paraesthesia, convulsions, mild neutropenia, thrombocytopenia, interstitial nephritis, acute renal failure, arthralgia, photosensitivity. The following are rare side effects: taste disturbances, pale tongue, and liver failure.

## **2. LEVOFLOKSASIN**

Levofloxacin tablets 500 mg

Levofloxacin coated film tablets 250 mg, 500 mg

Levofloxacin film-coated caplets 500 mg, 750 mg

Levofloxacin infusion 500 mg / 100 ml, 750 mg / 150 ml

### a) Indications<sup>76</sup>:

Mild, moderate, and severe infections caused by strain microorganisms that are susceptible to the disease as follows:

- Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*
- Acute bacterial exacerbations in chronic bronchitis due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella catarrhalis*
- Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, or *Streptococcus pneumoniae*.  
Additional treatment should be used according to clinical indications. If pneumonia is caused by *Pseudomonas aeruginosa*, it is recommended that levofloxacin be combined with anti-pseudomonal  $\beta$ -lactam.
- Community pneumonia due to *Staphylococcus aureus*, *Streptococcus pneumoniae* (including multi-drug-resistant strains [MDRSP]), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Legionella pneumoniae*, *Legionella pneumophila*
- Chronic bacterial prostatitis due to *Escherichia coli*, *Enterococcus faecalis*, or *Staphylococcus epidermidis*.
- Skin and soft tissue infections with complications.
- Urinary tract infections with complications

- Acute kidney infection.

**b) Contraindications<sup>76</sup>:**

Should not be used in patients who are hypersensitive to levofloxacin and other antimicrobial quinolone groups, epilepsy patients, patients with a history of tendon disease due to fluoroquinolone administration, children or adolescents, pregnant or breastfeeding women.

**c) Dosage<sup>76</sup>:**

- 250 mg or 500 mg tablets given orally every 24 hours as indicated by infection.
- Injection of 250 or 500 mg given slow infusion for more than 60 minutes every 24 hours or 750 mg given slow infusion for more than 90 minutes every 24 hours, as indicated by the infection.

The dosage recommendations above apply to patients with normal kidney function (creatinine clearance > 80 mL/min).

Oral doses should be given at least 2 hours before or 2 hours after antacids containing magnesium and/or aluminum, sucralfate, metal cations such as iron, multivitamin preparations containing zinc, didanosine, chewable tablets or powder for oral solutions (for children).

Patients with normal kidney function.

<b>Infection</b>	<b>Dosage Unit</b>	<b>Frequency</b>	<b>Duration</b>	<b>Daily Dosage</b>
Community pneumonia	500 mg	Every 24 hours	7 – 14 days	500 mg

<b>Infection</b>	<b>Dosage Unit</b>	<b>Frequency</b>	<b>Duration</b>	<b>Daily Dosage</b>
	750 mg	Every 24 hours	5 days	750 mg
Nosocomial pneumonia	750 mg	Every 24 hours	7 – 14 days	750 mg
Acute bacterial sinusitis	500 mg	Every 24 hours	7 – 14 days	500 mg
	750 mg	Every 24 hours	5 days	750 mg
Acute bacterial exacerbation of chronic bronchitis	500 mg	Every 24 hours	7 days	500 mg
	750 mg	Every 24 hours	3-5 days	750 mg
Chronic bacterial prostatitis	500 mg	Every 24 hours	28 days	500 mg
SSSI * with complications, UTI ** with complications, acute kidney infection	250 - 750 mg once a day depends on the type and pathogen that is estimated, usually 7-14 days depending on the severity of the disease			

\* intravenous to the oral route after several days), according to the patient's condition and doctor's policy

\*\* Skin and Skin Structure Infection

\*\*\*Urinary Tract Infection

Patients with impaired kidney function:

- Creatinine clearance > 50 mL/min: no dose adjustment
- Creatinine clearance 20-50 mL/min: initial dose 250 mg, then 125 mg every 24 hours, or initial dose 500 mg, then 250 mg every 24 hours.
- Creatinine clearance of 10-19 mL/min or <10 mL/min (including hemodialysis and CAPD): initial dose 250 mg, then 125 mg every 48 hours, or initial dose 500 mg thereafter 125 mg every 24 hours.
- Elderly patients and patients with impaired liver function (but normal kidney function) receive the same dose as normal adults.

**d) Warnings<sup>76</sup>:**

- Seizures, toxic psychosis, increased intracranial pressure, central nervous system stimulation which can trigger tremors, anxiety, mild headaches, confusion, hallucinations, paranoids, depression, nightmares, insomnia, and suicidal thoughts (rarely). The reaction can occur after the first dose. If the reaction occurs, the drug must be stopped.
- Careful giving to patients with central nervous system disorders, cerebral atherosclerosis, epilepsy, kidney dysfunction, can trigger seizures.
- Hypersensitivity and/or anaphylactic reactions. The reaction can occur after the first dose. Medication must be stopped if skin rashes or other symptoms of hypersensitivity occur.
- Pseudomembranous colitis (which is characterized by diarrhea after antibiotic administration) with mild to severe severity. In mild cases, drug administration

should be stopped, severe cases require administration of fluids and electrolytes, proteins, and antibiotics.

- Rupture of shoulder, hand, and Achilles tendons. The administration of the drug should be stopped if the patient experiences pain, inflammation, or rupture of the tendon.
- It is necessary to maintain adequate hydration in patients taking levofloxacin (to prevent the formation of urine with a high concentration).
- Careful administration in patients with impaired renal function (creatinine clearance  $\leq 80$  mL/min): adjusting drug dosage is needed to avoid levofloxacin accumulation.
- Moderate to severe phototoxicity reactions occur in patients who are exposed to direct sunlight while taking this drug. Exposure to excessive sunlight should be avoided. Treatment should be stopped if phototoxicity (skin eruption) occurs.
- In patients with diabetes, it is necessary to monitor blood sugar because the use of this drug causes hyperglycemia or symptomatic hypoglycemia.
- It is recommended that a periodic assessment of the kidney, liver, and hematopoietic function is carried out during treatment.

**e) Drug Interactions<sup>76</sup>:**

- Potential to form chelates if given with metal ions (Al, Cu, Zn, Mg, Ca), antacids containing Al or Mg and drugs containing Fe, thereby reducing the absorption of levofloxacin. The administration of these drugs must be at least 2 hours before or after administration of levofloxacin.

- Joint use of NSAIDs can increase the risk of CNS stimulation and seizures.
- Hyperglycemia or hypoglycemia if given with anti-diabetic drugs.
- Giving levofloxacin with warfarin can increase the effects of warfarin.

Co-administration of theophylline causes inhibition of theophylline metabolism resulting in an increase in theophylline levels in the blood, and an increased risk of theophylline side effects. Joint use of drugs that can prolong the QTC interval (e.g. anti-arrhythmia) can increase the risk of ventricular arrhythmia<sup>77</sup>.

#### **f) Side Effects<sup>76</sup>:**

- The incidence of side effects due to drugs during clinical trials phases 2 and 3 in North America is 6.2%. In patients receiving repeated doses of treatment, 3.7% stopped treatment due to side effects.
- In clinical trials, the following events are thought to be due to the drug in multiple doses: diarrhea 1.2%, nausea 1.2%, vaginitis 0.8%, flatulence 0.5%, pruritis 0.5%, rash 0.3 %, stomach pain 0.3%, genital moniliasis 0.3%, dizziness 0.3%, dyspepsia 0.3%, insomnia 0.3%, taste disorders 0.2%, vomiting 0.2%, anorexia 0, 1%, anxiety 0.1%, constipation 0.1%, edema 0.1%, fatigue 0.1%, headache 0.1%, increased sweat 0.1%, leukorrhea 0.1%, malaise 0, 1%, nervousness 0.1%, sleep disturbance 0.1%, tremor 0.1%, and urticaria 0.1%.
- In clinical trials, the most undesirable events (KTD) occur in > 3% of patients, regardless of the relationship with the drug, including nausea 6.6%, diarrhea 5.4%, headache 5.4%, constipation 3.1%.
- In some clinical trials, the following KTD occurs in 1-3% of patients: insomnia 2.9%, dizziness 2.5%, vomiting 2.1%, abdominal pain 2.0%, dyspepsia 2.0%, rash

1, 7%, vaginitis 1.8%, flatulens 1.6%, itching 1.6%, pain 1.4%, chest pain 1.1%, back pain 1.0%.

- The following KTD occurs in clinical trials between 0.5 - <1%: agitation, anorexia, anxiety, arthralgia, dry mouth, shortness of breath, edema, fatigue, fever, genital itching, increased sweating, nervousness, pharyngitis, rhinitis, disease skin, somnolent, taste changes.
- Additional KTD that occurs in clinical trials between 0.3% - <0.5%: heart failure, hypertension, leukorrhea, myocardial infarction, myalgia, purpura, tinnitus, tremor, urticaria.
- KTD with frequencies <0.3% that are considered medically important: abnormal coordination, nightmares, impaired liver function, platelet function, and kidney function, vision problems, acute kidney failure, worsening diabetes mellitus, aggressive reactions, anemia, angina pectoris, ARDS, arrhythmias, arthritis, asthma, bradycardia, cardiac arrest, cerebrovascular disorders, circulatory failure, coma, confusion, convulsions, coronary thrombosis, delirium, depression, diplopia, blood clot embolism, mental instability, circulatory failure, erythema, bleeding. The gastrointestinal tract, granulocytopenia, hallucinations, heart block, hepatic coma, hypoglycemia, hypotension, impaired concentration, increased lactate dehydrogenase (LDH), jaundice, leukocytosis, leukopenia, lymphadenopathy, manic reactions, mental deficiency, muscle weakness, pancreatic disorders, paralysis, paranoid, paranoid, postural hypertension, pseudomembranous colitis, rhabdomyolysis, sleep disorders, stupor, fainting, tachycardia, tendinitis, thrombocytopenia,

vertigo, weight loss, disturbance, and white blood cells.

- In clinical trials using repeated doses, ophthalmological disorders, including cataracts, and multiple lenticular opacity, have been found in patients treated with other quinolones. The relationship between drugs and these events is still uncertain.
- Crystalluria and cylindruria have been reported with other quinolones. The following laboratory abnormalities occur in 1.9% of patients receiving repeated doses of levofloxacin. It is not known whether these abnormalities are caused by medication or by the disease.
- Blood chemistry: decreased blood sugar levels and lymphocyte counts.
- Postmarketing side effects: Additional serious KTD reported from the experience of levofloxacin marketing patients outside the USA: allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal, abnormal EEG, encephalopathy, eosinophilia, erythema multiformis, hemolytic anemia, organ failure, paresthesias, Stevens-Johnson's Syndrome, tendon rupture, vasodilation.

### **3. MEROPENEM**

Injection Powder 0.5 g, 1 g

#### **a) Indications<sup>78</sup>:**

As a single therapy for adults and children, for the treatment of infections caused by sensitive bacterial strains, single or multiple, by microorganisms that are sensitive to meropenem:

- pneumonia and nosocomial pneumonia,
- urinary tract infection,
- intra-abdominal infection,
- gynecologic infection, such as endometritis
- skin infections and skin structure,
- meningitis,
- septicemia,
- empirical therapy for suspected infection in adult patients with neutropenia.

Meropenem is used as a single therapy or in combination with antiviral or antifungal agents.

Meropenem has been proven effective in single or combination therapy with other antimicrobials in the treatment of polymicrobial infections.

There is no experience in pediatric patients with neutropenia or primary or secondary immunodeficient patients.

**b) Contraindications<sup>79</sup>:**

Hypersensitivity to meropenem and antibiotics of the same class, patients with a history of anaphylactic reactions to beta-lactam antibiotics.

**c) Dosage:**

ADULT

- Skin and skin structure infections, pneumonia, urinary tract infections, gynecologic infections such as endometritis: intravenous injection 500 mg every 8 hours.
- Nosocomial pneumonia, peritonitis, suspected infection in neutropenic

patients, septicemia: 1 g intravenous injection every 8 hours.

- Meningitis: 2 g every 8 hours.

#### ADULT WITH KIDNEY DISORDERS

- For patients with creatinine clearance less than 51 mL/min, the dosage reduction rules:

<b>Creatinine clearance (mL / min)</b>	<b>Dose (depending on the type of infection)</b>	<b>Frequency</b>
26-50	Recommended dose (500 mg or 1 g or 2 g)	Every 12 hours
10-25	Recommended dose (500 mg or 1 g or 2 g)	Every 12 hours
<10	Recommended dose (500 mg or 1 g or 2 g)	Every 24 hours

#### ADULT WITH HEPATIC INSUFFICIENCY

No dose adjustment is needed in patients with hepatic insufficiency.

#### ELDERLY

No dose adjustment is needed in elderly patients with normal renal function or creatinine clearance values > 50 mL/min.

#### PEDIATRIC

- The recommended dosage for meningitis: 40 mg/kg of body weight every 8 hours.
- Age 3 months - 12 years: 10-20 mg/kg of body weight every 8 hours, depending on the type and severity of the infection, the sensitivity of the pathogen and the

patient's condition.

- For children weighing > 50 kg, the ADULT dose is given.
- There are no studies on children with impaired kidney function.

**d) Warnings <sup>72</sup>:**

- There is clinical and laboratory evidence of partial cross-allergenicity between carbapenem groups with antibiotics beta-lactam, penicillin, and cephalosporins. As with all beta-lactam antibiotics, hypersensitivity reactions are rarely reported. Before starting therapy with meropenem, patients need to be asked carefully about the presence/absence of a history of hypersensitivity reactions to beta-lactam antibiotics. Meropenem trihydrate must be used cautiously in patients with a history of hypersensitivity. If there is an allergic reaction to meropenem, the administration must be stopped and the patient is given appropriate treatment.
- As with other antibiotics, overgrowth of other insensitive organisms can occur, so every patient needs continuous observation.
- Transaminase and bilirubin levels must be monitored carefully if meropenem trihydrate is given to patients with liver disease.
- Not recommended for use in infections caused by methicillin-resistant staphylococci.
- Although rare, pseudomembranous colitis is reported in the use of meropenem trihydrate as in the case of antibiotic use in practice. The severity can vary from mild to life-threatening. Therefore, antibiotics must be prescribed with caution in individuals with a history of gastrointestinal complaints, especially colitis. It

is important to consider the diagnosis of pseudomembranous colitis in the case of patients who have diarrhea due to the use of meropenem trihydrate. Although research shows that the toxin produced by *Clostridium difficile* is a major cause of antibiotic-related colitis, other causes must still be considered.

- Joint administration of potentially nephrotoxic drugs must be carefully considered.
- Seizures and other CNS side effects have been reported on meropenem use, but usually occur in patients with CNS disorders (eg, brain lesions or history of seizures) or bacterial meningitis and/or in patients with impaired kidney function.
- Pregnancy category B.

The safety of meropenem in pregnancy is unknown. The only side effect observed in animal reproduction studies is the increased incidence of abortion in monkeys exposed to meropenem at a dose 13 times the human dose. Meropenem is given to pregnant women only if the therapeutic benefits outweigh the risks. Its use must be under direct supervision by a doctor.

- Breastfeeding mothers

Meropenem was detected in very small levels in the milk of test animals. Meropenem is given to nursing mothers only if the therapeutic benefits outweigh the risks.

- Pediatric

Safety and efficacy in infants <3 months have not been established. It has not been recommended the use of meropenem for children this age. There are no studies for children with impaired liver and kidney function.

There has been no information regarding effects on the ability to drive and run the engine, but it is not expected that adoption will affect the ability to drive and run the engine.

#### **e) Drug Interactions<sup>78</sup>**

- Probenecid competes with meropenem in active tubular secretion and thus inhibits renal excretion, causing an increase in the elimination half-life and plasma levels of meropenem. Because the potential and length of work of meropenem without probenecid are adequate, co-administration of probenecid with meropenem is not recommended.
- The potential effect of meropenem on protein binding from other drugs or metabolism has not been studied. The meropenem protein bond is quite low (around 2%), so it is unlikely that interactions will occur with other compounds based on protein binding.
- Meropenem can reduce serum levels of valproic acid to sub therapy levels.

#### **f) Side Effects<sup>78</sup>:**

Serious side effects are rarely found. The side effects reported are as follows:

- Local reactions at the injection site: inflammation, thrombophlebitis, pain at the injection site.
- Skin reactions: rashes, pruritus, urticaria. Rarely, severe skin reactions, such

as erythema multiforme, Stevens-Johnson's syndrome, and toxic epidermal necrolysis.

- Systemic allergic hypersensitivity reactions: rare. These reactions include angioedema and manifestations of anaphylaxis such as shock, hypotension, and respiratory depression.
- Gastrointestinal reactions: abdominal pain, nausea, vomiting, diarrhea, pseudomembranous colitis.
- Blood: thrombocytopenia, eosinophilia, thrombocytopenia, leukopenia, and neutropenia. A positive direct or indirect Coombs test and a partial reduction in thromboplastin time can occur.
- Liver function: increased levels of bilirubin serum, transaminases, alkaline phosphatase, and lactate dehydrogenase.
- Central nerve system: headache, paresthesia. Convulsions are rare and the causal relationship with meropenem is unclear.
- Other: oral and vaginal candidiasis.

#### **4. CEFOTAXIME**

Injection powder of 500 mg, 1 g, and 2 g

##### **a) Indications:**

Infections caused by bacteria that are sensitive to cefotaxime include:

- Lower respiratory tract infections (including pneumonia)
- Skin infections and skin structure
- Bone and joint infections

- Intra-abdominal infection
- Urinary tract infection
- Infection of female genitals
- Meningitis
- Septicemia
- Bacteremia
- Prevention of postoperative infections
- There are not enough clinical data to support the treatment of infections caused by *Salmonella typhi* and paratyphi A and B infections
- Cefotaxime is not effective against *Treponema pallidum* and *Clostridium difficile*
- In severe life-threatening infections, a combination of cefotaxime and aminoglycosides can be given without waiting for the results of sensitivity tests. The two preparations must be given separately, not mixed in one syringe.
- Infections due to *Pseudomonas aeruginosa* need another antibiotic that is effective against Pseudomonas.

**b) Contraindications:**

- Patients who are hypersensitive to cephalosporin class antibiotics.
- Patients who are hypersensitive to penicillin, the possibility of a cross allergic reaction must be considered.

**c) Dosage:**

- Dosage for adults and children > 12 years: 1 g every 12 hours
- Moderate to severe infections: 1-2 g every 6-8 hours.

- Severe or life-threatening infections: 2 g every 4 hours.
- Maximum dose: 12 g per day.
- Prevention of postoperative infections: 1 g IM or IV, given 30-90 minutes before to the surgical procedure.
- Sectio Caesarea: the first dose of 1 g is given IV immediately after the umbilical cord is clamped, then 1 g is given IM or IV at 6 and 12 hours after the first dose.
- Gonorrhoea without complications in adults: cefotaxime 1 g IM as a single dose.
- For less sensitive bacteria, the dose can be increased.
- Check for syphilis infection before treatment begins.

#### Pediatric:

- Infants and children <12 years: 50-100 mg/kg of body weight/day.
- The dose is divided at 6-12 hour intervals.
- For life-threatening infections, the daily dose is 150-200 mg/kg of body weight.
- Because the kidney cleansing in premature babies is not perfect, the dose per day should not be more than 50 mg/kg of body weight.

#### Patients with kidney disorders

- In creatinine clearance  $\geq 20$  ml/minute / 1.73 m<sup>2</sup>: no modification of the usual dosage is necessary.
- In patients with creatinine clearance <20 ml/min / 1.73 m<sup>2</sup>: dose and/or frequency of administration needs to be modified depending on the level of kidney damage. In these patients, reduce the dose to  $\frac{1}{2}$  the usual dosage .
- In hemodialysis patients: 0.5-2 g given in a single dose per day and given the dose after each dialysis period.

## Duration of treatment

Depending on the type of infection, but in general, the drug must be continued at least 48-72 hours after the patient has no fever or eradication of germs. In infections due to *Streptococcus pyogenes*: the drug must be continued for 10 days to reduce the risk of rheumatic fever and glomerulonephritis.

### **d) Warnings:**

- In treatment with cefotaxime, such as other cephalosporin antibiotics, allergic reactions cannot be avoided.
- Long-term use can lead to the growth of some insensitive organisms, especially candida and pseudomonas. Vaginitis and moniliasis can occur in <1% of patients. During cefotaxime use, resistant strains of some organisms can develop, especially enterobacter, *Pseudomonasaeruginosa*, and serratia. Careful observation of cefotaxime should be made. If superinfection occurs with cefotaxime, appropriate treatment must be taken.
- In patients with a history of gastrointestinal disease, cefotaxime can cause colitis.
- The safety of cefotaxime use during pregnancy is unknown, so the use of this drug during pregnancy is only when it is necessary.
- Reproduction studies on mice and rats at a dose 30 times the human dose, did not show fertility problems or fetal damage.
- Cefotaxime should be used with caution in breastfeeding women because cefotaxime is distributed into breast milk.

- Like other cephalosporin antibiotics, cefotaxime causes false positive results on urine glucose testing with cupri sulfate solution (Benedict's reagent, Clintest®) cefotaxime will also increase creatinine levels in serum or urine. The use of cefotaxime can lead to positive results on the Coombs' test.
- Examination of kidney function should be done if cefotaxime is combined with the aminoglycoside group. If a larger dose is needed, use 2 g of injection dry powder, while for infants, premature babies and children use 500 mg.

#### **e) Drug Interactions:**

- In vitro studies show that the antibacterial activity of cefotaxime and aminoglycosides is additive / synergistic towards several organisms including some strains of *Pseudomonas aeruginosa* and *S. marcescens*. However, the nature of synergism cannot be predicted and the nature of antagonism can also occur if cefotaxime is combined with aminoglycosides.
- The administration of probenecid will increase levels of cefotaxime in serum.

#### **f) Side Effects:**

- Gastrointestinal disorders: anorexia, diarrhea, nausea, vomiting, abdominal pain and colitis.
- In the case of intestinal inflammation caused by cefotaxime, it will endanger the lives of the patient, so that cefotaxime should be stopped immediately and appropriate initial treatment must be given. It's best to avoid giving drugs that can inhibit intestinal peristalsis.
- Haematological changes: neutropenia, leukopenia, granulocytopenia,

thrombocytopenia. On treatment for more than 10 days: perform monitoring blood count.

- Hypersensitivity reactions: rashes (maculopapular or erythematous), pruritus, fever and eosinophilia.
- In interstitial nephritis anaphylactic shock can occur which threatens the life of the patient and requires emergency measures to overcome it.
- Local effects: occur at the injection site. IV administration of cefotaxime can cause phlebitis and thrombophlebitis. IM administration can cause pain, induration, and tenderness at the injection site.
- Effects on the kidney: temporary increase in serum creatinine and / or BUN levels, or alanine aminopeptidases in urine (an indication of temporary tubular damage).
- Other side effects (rare): temporary increase in levels of SGOT, SGPT, LDH, bilirubin and alkaline phosphatase in serum. Headache, agitation, confusion, fatigue and night sweats.

## **D. NON-OPIOID ANALGESICS**

### **1. PARASETAMOL (ASETAMINOFEN)**

Tablets of 100 mg, 125 mg, 325 mg, 500 mg, 600 mg and 650 mg

Caplets of 500 mg, 600 mg, 650 mg

500 mg film-coated caplet

Suppositoria of 80 mg, 125 mg, 160 mg, 240 mg, 250 mg

Drop of 60 mg / 0.6 mL, 80 mg / 0.8 mL, 100 mg / mL

Syrup of 100 mg / mL, 120 mg / 5 mL, 120 mg, 125 mg, 160 mg / 5 mL, 250 mg / 5 mL

Infusion of 10 mg / mL

**a) Indications:**

- To reduce the fever that accompanies the flu; and fever after immunization.
- Relieve pain in minor aches such as headaches, toothaches and muscle aches.

**b) Contraindications:**

Do not use it on sufferers who suffer from hypersensitive liver damage to paracetamol.

**c) Dosage:**

- 3-4 times a day. The minimum dosage interval is 4 hours and does not exceed 4 x in 24 hours.
- Adults: 500 mg -1000 mg, 3-4 times daily; Children 6-12 years, 250 mg - 500 mg, 3-4 times daily.

**d) Warning:**

- If you still have a fever for more than 2 days (48 hours) or if you still feel pain for more than 5 days, contact your doctor.
- Paracetamol is reported to have the potential effect of oral anticoagulant drugs.
- Call a doctor before using this medicine if you are pregnant or breastfeeding.  
Be careful using this drug in people with kidney disease.
- The use of this drug in patients who consume alcohol can increase the risk of damage to liver function.
- Use of high doses can cause liver damage.
- Not recommended for use with other drugs that contain paracetamol.

#### **e) Drug Interactions:**

- Anticoagulants: long-term use of paracetamol can increase the effects of coumarin anticoagulants
- Cytotoxic: paracetamol can inhibit intravenous busulfan metabolism (monitor for 72 hours of co-administration with paracetamol)
- Hypolipidemic: decreased absorption of paracetamol due to cholestiramine
- Metoclopramide: Increased absorption of paracetamol due to metoclopramide

Cholesterol is reduced in the absorption of paracetamol.

- Paracetamol can inhibit the metabolism of busulfan given intravenously (it is recommended to give busulfan carefully within 72 hours on co-administration with paracetamol).

#### **f) Side Effects:**

The use of high doses can cause liver damage, hypersensitivity reactions such as redness or itching of the skin. Stop using the drug and contact your doctor immediately if you experience any side effects.

### **E. SELECTIVE BETA-1 ADRENORECEPTOR AGONISTS**

In the case of COVID-19 patients, albuterol (salbutamol) is used as supportive therapy for patients who need bronchodilator therapy, including COVID-19 patients with indications of other diseases such as asthma, COPD or experiencing bronchospastic reactions. The dosage form used is inhalers (Metered Dose Inhalers / MDI) as a substitute for nebulizers to prevent transmission<sup>79,80</sup>.

## 1. SALBUTAMOL SULPHATE

Tablets of 2 mg and 4 mg

Caplets of 2 mg and 4 mg

Capsules of 2 mg and 4 mg

Syrup of 2 mg / 5 mL

Aerosol of 100 mcg

Inhalation fluid of 100 mcg

Injection fluid of 500 mcg / mL

Inhalation powder of 200 mcg

### **a) Indications:**

Bronchial spasms in all types of bronchial asthma, chronic bronchitis, and emphysema.

Routine management of chronic bronchospasm that is unresponsive to conventional therapy.

Treatment of acute severe asthma (asthmatics status).

### **b) Contraindications:**

Patients who are hypersensitive to this drug.

Salbutamol should not be used in the treatment of abortion during the first and second trimester of pregnancy.

### **c) Dosage:**

#### Tablet

Adult (> 12 years): 1-2 tablets, 3-4 times daily.

The dose can be increased gradually.

For the elderly, a lower initial dose is given.

Children aged 2-6 years: ½ - 1 tablet, 3-4 times daily.

Children aged 6-12 years: 1 tablet, 3-4 times daily

### Syrup

Adult (> 12 years): 3-4 times a day 5-10 mL a day.

Children aged 2-6 years: 3-4 times a day 2.5-5 mL a day

Children aged 6-12 years: 3-4 times daily 5 mL.

### Inhalation liquid

Adults and children: the appropriate initial dose through inhalation is 2.5 mg. the dose can be increased to 5 mg, the therapy is repeated 4 times a day. In adults, higher doses up to 40 mg per day, can be given under strict medical supervision at the hospital for treatment of severe airway obstruction. The clinical effect of salbutamol that is stimulated in infants under 18 months is uncertain.

While hypoxia can occur, additional oxygen therapy must be considered.

### **d) Warnings:**

- Special attention is given to patients with thyrotoxicosis, hypertension, cardiovascular disorders, hyperthyroidism, and diabetes mellitus.
- Although there is no evidence of teratogenicity, salbutamol should be used during the first trimester of pregnancy only if necessary.
- Caution for use in breastfeeding women because of the possibility of excretion through milk.
- Special attention in children <2 years of age since the safety is not confirmed.
- If administered intravenously in diabetic patients, blood sugar levels need to

be monitored.

- Inhalation liquids should be used with caution in patients who are known to have received large doses of other sympathomimetic drugs.
- The combination of salbutamol nebulation with anticholinergic nebulation must be used with caution.
- Potentially serious hypokalaemia can occur from  $\beta 2$ -agonist therapy, especially from parenteral administration and nebulation.
- Special attention is recommended in severe acute asthma because its effects can be enhanced by co-administration of xanthine derivatives (example: theophylline), steroids, or diuretics and by hypoxia. It is recommended that potassium serum levels be monitored in this situation.

**e) Drug Interactions:**

- The effect of salbutamol is inhibited by  $\beta 2$  antagonists.
- Joint administration of monoamine oxidase can cause severe hypertension.
- Salbutamol and non-selective beta-blockers such as propranolol, may not be given together.

**f) Side Effects:**

- Tremors (especially in the hands), tension, headaches, muscle cramps, palpitations.
- Tachycardia, arrhythmias, peripheral vasodilation, sleep disorders, and behavior.
- Paradoxical bronchospasm, urticaria, angioedema, hypotension, collapse.
- Hypokalaemia at high doses.

- Pain in an intramuscular injection.
- Hypoxemia, metabolic effects (increase in free fatty acids, glucose, lactate, pyruvate, insulin).

## **F. CENTRAL NERVE SYSTEM DRUGS - BENZODIAZEPINE CLASS**

### **1. MIDAZOLAM**

Midazolam Injection Fluid 1 mg / mL, 5 mg / mL

#### **a) Indications:**

- Premedication before induction of anesthesia (IM administration)
- Basal sedation before a diagnostic or surgical procedure is performed under local anesthesia (IV administration)
- Induction of conscious anesthesia. As an inducing agent under inhalation anesthesia or a sleep induction component in combination with anesthesia, including total anesthesia (IV injection) <sup>81</sup>.

#### **b) Contraindications:**

Hypersensitivity to benzodiazepines, acute pulmonary insufficiency, respiratory depression.

#### **c) Dosage:**

- Premedication before induction of anesthesia:

Intramuscular administration: In patients who experience pain before surgery, single administration, or combination with anticholinergics and possibly analgesics.

Adult: 0.07-0.10 mg / kg of body weight IM. Adapted to the age and condition of patients. The usual dose is 5 mg.

Elderly and weak patients: 0.025 - 0.05 mg / kg of body weight IM. This dose should be given 30 minutes before induction of anesthesia.

#### - Intravenous basal sedation

For basal sedation in diagnostic or surgical procedures performed under local anesthesia.

Starting dose: 2.5 mg, 5-10 minutes before the start of surgery. Furthermore, a dose of 1 mg can be given if needed. Usually, no total dose of more than 5 mg is needed to achieve the desired effect.

In cases of severe illness, especially if the general condition of the patient is weak or elderly, the initial dose should be reduced to 1 - 1.5 mg. No total dosage of more than 3.5 mg is needed to achieve the desired effect.

#### - Induction of conscious anesthesia

The induction dose of anesthesia is 10 mg IV.

In general, a sufficient level of unconsciousness is reached after 2-3 minutes. The dose is reduced in the elderly (over 55 years).

Maintenance dose: for maintenance can be followed by IV injection of low doses. Doses and intervals differ depending on the individual reaction. Additional doses are given only if a thorough evaluation has been carried out and shows the need for a sedation effect.

### **In positive COVID-19 patients:**

#### - Acute respiratory distress

Given also with morphine: 1-2 mg subcutaneous, maximum 4 times per hour.

The elderly is a group at high risk for COVID-19 infection. Because of the COVID-19 pandemic, in Europe, The Association for Geriatric Palliative Medicine (FGPG) recommends the integration of a palliative care approach for the elderly at home or in a patient setting. Midazolam is one drug that can be used to treat one of the symptoms in this COVID-19 patient.<sup>82</sup>

#### - Anesthesia for tracheal intubation

Tracheal intubation is a procedure that does not require general anesthesia. Midazolam is given as one of the anesthetics for this procedure: 1.0 mg/kg/hour by IV bolus (can also be given orally, IM or rectally, oral form especially for sedation of children).

Tracheal intubation is one of the independent risk factors for respiratory infections. Researchers in China conducted a retrospective analysis of anesthesia, intubation methods, complications, body temperature, and nucleic acid test results in 12 patients with pneumonia-COVID-19. Tracheal intubation was performed on a positive pressure hood filter and using the appropriate PPE. All patients successfully performed tracheal intubation with bronchoscopy without serious complications. Anesthesia is given: midazolam, propofol, morphine/fentanyl. Nine health workers who did intubation did not have a fever, and the nucleic acid test from throat swabs was negative.<sup>83</sup>

#### **d) Warning:**

- Providing parenteral to high-risk patients, the elderly, patients with chronic kidney failure, or impaired liver function.
- Premature babies and newborns

- Pregnancy (category B) and breastfeeding women

**e) Drug Interactions:**

- Co-administration with cimetidine (not ranitidine) has been reported to reduce midazolam clearance.
- Midazolam enhances the central sedative effect of neuroleptics, tranquilizers, antidepressants, sleep inducers, analgesics, and anesthetics (this potential can be therapeutically beneficial in certain cases so it is of particular concern to high-risk patients)
- Potentiation with alcohol can have an unexpected effect (do not consume alcoholic drinks at least 12 hours after administration of parenteral midazolam).

**f) Side Effects:**

- Slightly decreases arterial blood pressure, pulse, and breathing.
- Severe cardio-respiration, including respiratory depression, apnea, sudden cardiac / respiratory arrest, is rare (events such as this are more likely to occur in the elderly and patients with respiratory insufficiency or impaired cardiac function, especially in high doses).
- Nausea, vomiting, headache, dizziness, drowsiness, ataxia, hallucinations, episodes of amnesia, allergic reactions such as rashes, pruritus.
- Benzodiazepines reduce cerebral blood flow and brain metabolism, but less than barbiturates.

## **G. EXPECTORANT**

### **1. ACETHYLSTEIN**

Capsules of 200 mg

Film caplets of 200 mg

Effervescent tablets of 600 mg

Granules of 100 mg, 200 mg

Dry syrup of 100 mg / 5 mL

Inhalation fluid of 100 mg / mL

Fluid infusion of 200 mg

#### **a) Indications:**

Expectorate the thick mucus in the bronchus and lungs, such as acute, chronic, and chronic bronchitis, recurring bronchiectasis, emphysema, mucoviscidosis, so that they can be easily spotted out.

#### **b) Contraindications:**

Hypersensitivity to acetylcysteine.

#### **c) Dosage:**

- Adults and children > 14 years: 1 Capsule 2-3 times daily (equivalent to 400 - 600 mg N-acetylcysteine per day)  
For children 6-14 years: 1 capsule 2 times daily (equivalent to 400 mg of N-acetylcysteine per day).
- In the case of mucoviscidosis:

Children > 6 years: 1 capsule 3 times daily (equivalent to 600 mg of N-acetylcysteine per day).

For children <6 years of age considered for other suitable preparations.

- The capsules are given after meals, with some water.

**d) Warning:**

- During treatment, people with asthma must be monitored; the treatment is terminated if there are signs of bronchospasm.
- The smell of sulfur is not a sign of damage to the drug. It is the nature of nutritious substances.
- In patients with a history of gastritis, it should be given after meals.
- Drug administration to pregnant and breastfeeding women

In some studies, both in animals and humans show that acetylcysteine administration does not cause teratogenic effects or dangerous side effects, but during pregnancy and breastfeeding acetylcysteine administration must be under a doctor's supervision.

- The drug administration for infants who are still breastfed and infants <1 year, acetylcysteine can be used only in life-threatening events and always under strict medical control. The dosage for newborns has not been confirmed according to any available reference.

**e) Drug Interactions:**

- Joint administration of cough suppressants (antitussives) can cause a dangerous cessation of secretions, as cough decreases.
- Use with tetracycline HCl must be administered separately at intervals of at least 2 hours.

- Co-administration of nitroglycerin might cause an increase in the vasodilation and blood flow effects of nitroglycerin.

**f) Side Effects:**

- Cirrhosis, nausea, vomiting, and diarrhea are rare.
- Stomatitis, dizziness, and buzzing ears (tinnitus).
- Allergic reactions, such as itching, urticaria, cutaneous eruption (exanthema, rash), difficulty breathing (bronchospasm), rapid heart rate, and drop in blood pressure.
- Bronchospasm in patients with hyper-reactive bronchi, called "Hyper Responder" (i.e. in patients with increased sensitivity due to various stimuli).

**H. VITAMIN**

**1. ASCORBIC ACID (VITAMIN C)**

Tablets of 25 mg, 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg

Injection of 100 mg/mL and 200 mg/mL.

**a) Indications:**

Treatment of ascorbic acid deficiency.

In the case of sepsis in cases of COVID-19 infection, high doses of ascorbic acid as an antioxidant against immune cells and as an antioxidant against lung epithelial cells.<sup>84</sup>

**b) Contraindications:**

Hypersensitivity to ascorbic acid, hyperoxaluria.

**c) Dosage:**

Following the procedures of COVID-19 Patients under Supervision.

Without symptoms and mild symptoms: 100-200 mg orally 3 times daily for 14 days.

Moderate and Severe Symptoms: 400 mg IV once a day with slow injection (can cause temporary dizziness).

The time of administration of high-dose ascorbic acid in the treatment of COVID-19 needs to be considered when the administration is in the initial period of the disease in a short time 50 mg/kg of body weight every 6 hours IV for 4 days.

**d) Attention and warning:**

- The use of large doses can cause an increase in levels of oxalic acid in the urine and precipitation of calcium oxalate may occur in the kidneys.
- Patients with a history of kidney failure or kidney stones.
- Use in patients with glucose-6- phosphate dehydrogenase (C6PD) deficiency can cause hemolysis.
- Ascorbic acid must be given at minimum doses in patients with excess iron because ascorbic acid can increase iron absorption. Large doses of ascorbic acid can be dangerous, especially in patients with hemochromatosis, thalassemia, polisitemia , leukemia, or sideroblastic anemia.
- The safety of use in pregnant and breastfeeding women is not yet known, so it can only be given if the clinical benefits outweigh the risks.
- Large doses of ascorbic acid can also cause sickle cells.

**e) Drug Interactions:**

- Joint administration of anticoagulants causes reduced anticoagulant effects.
- Joint administration of aspirin causes the effect of decreased ascorbic acid, high-dose ascorbic acid (> 2000 mg/day) can increase aspirin levels in the blood to reach toxic levels.

- Sharing with barbiturates can extend the effect of barbiturates.
- The administration of birth control pills with high-dose ascorbic acid (1000 mg/day) causes an increased risk of pregnancy, bleeding is a sign of interaction. The administration of ascorbic acid at a dose of 250-500 mg can reduce this interaction.
- Co-administration of quinidine can result in an extension of quinidine employment.
- Co-administration of quinine can result in an extension of quinine's service period.
- Sharing with primidone can cause primidone extended periods.
- Joint testing of glucose levels in urine in diabetics can lead to the possibility of error in test results.
- Drugs that induce tissue desaturation of ascorbic acid including aspirin, the nicotine from cigarettes, alcohol, some appetite suppressants, iron, phenytoin, some anti-convulsant drugs, estrogen components, or oral contraceptives and tetracycline.
- Ascorbic acid may reduce the activity of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin
- Ascorbic acid may reduce amphetamine and other drugs that are affected by gastric acidification such as fluphenazine.

**f) Side Effects:**

- In large doses:
  - Oral administration causes gastrointestinal disturbances (nausea, vomiting, stomach cramps)
  - IV administration results in acidosis
  - IV administration quickly causes dizziness and short fainting.
- Tired, headache, insomnia, redness, burning sensation on the face and neck.

## **2. ALPHA TOCOPHEROL ACETATE (VITAMIN E)**

Film coated tablets, a combination of Metamizole sodium monohydrate / Cyanocobalamin / Thiamin nitrate / Pyridoxine hydrochloride / Alpha tocopherol acetate: 324 mg / 100 mg / 100 mg / 50 mg / 30.0 IU.

### **a) Indications:**

The daily requirement of vitamin E has not been confirmed but maybe around 3-15 mg daily. There is little evidence that oral vitamin E supplements are needed in adults, even if secondary malabsorption of fat is caused by cholestasis. Vitamin E supplementation is given to children with fat malabsorption such as cystic fibrosis and cholestasis. In children with abetalipoproteinemia, abnormal (low) vitamin E levels are associated with neuromuscular abnormalities, which usually only indicate a response to parenteral vitamin E administration.

### **b) Warning:**

Predisposing to thrombosis: increased risk of necrotising enterocolitis in preterm infants weighing less than 1.5 kg.

### **c) Side Effects:**

Diarrhea and abdominal pain at doses of more than 1000 mg every day.

## REFERENCES

1. World Health Organization (WHO). 2020. [https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-\(covid-2019\)-and-the-virus-that-causes-it](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it). Published 11 February 2020. Accessed 23 March 2020.
2. Centers for Disease Control and Prevention (CDC). 2020. <https://www.cdc.gov/coronavirus/2019-ncov/prepare/transmission.html>. Published 4 March 2020. Accessed 23 March 2020.
3. World Health Organization (WHO). 2020. <https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-COVID-19-implications-for-ipc-precaution-recommendations>. Published 27 March 2020. Accessed 29 March 2020.
4. National Health Committee of the People's Republic of China. Interpretation of New Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Version 6). <http://www.nhc.gov.cn/yzygj/s7652m/202002/54e1ad5c2aac45c19eb541799bf637e9>. Published 19 February 2020. Accessed 21 March 2020.
5. Kementerian Kesehatan Republik Indonesia. 2020. <https://covid19.kemkes.go.id/situasi-infeksi-emerging/info-coronavirus/situasi-terkini-perkembangan-coronavirus-disease-COVID-19-22-March-2020/#.XnhNAYgzaUI>. Published 22 March 2020. Accessed 23 March 2020.
6. World Health Organization (WHO). 2020. <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-COVID-19---11-march-2020>. Published 11 March 2020. Accessed 23 March 2020.
7. Centers for Disease Control and Prevention (CDC). 2020. Information for Clinicians on Therapeutic Options for COVID-19 Patients. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html>.

Published 21 March 2020. Accessed 23 March 2020.

8. "Solidarity" clinical trial for COVID-19 treatments. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>. Published 20 March 2020. Accessed 8 April 2020.
9. World Health Organization (WHO). 2020. A coordinated Global Research Roadmap. <https://www.who.int/blueprint/priority-diseases/key-action/Roadmap-version-FINAL-for-WEB.pdf?ua=1>. Published 4 March 2020. Accessed 23 March 2020.
10. WHO Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance version 1.2, 13 March 2020.
11. CDC Interim Clinical Guidance for Management of Patients with Confirmed Corona Disease (COVID-19), updated 7 March 2020.
12. Tiangbo Liang. 2020. Handbook of COVID-19 Prevention and Treatment in China. Jack Ma Foundation.
13. World Health Organization (WHO). 2020. <https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/>. Accessed 26 March 2020.
14. World Health Organization (WHO). 2020. <https://www.who.int/blueprint/priority-diseases/key-action/multicenter-adaptive-RCT-of-investigational-therapeutics-for-COVID-19.pdf?ua=1>. Accessed 26 March 2020.
15. World Health Organization (WHO). 2016. <https://www.who.int/ethics/publications/infectious-disease-outbreaks/en/>. Accessed 26 March 2020.
16. World Health Organization (WHO). 2020. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management>. Published February 2020. Accessed 26 March 2020.

17. European Medicine Agency. EMA gives advice on the use of Non-Steroidal Anti Inflammatories for COVID-19 <https://www.ema.europa.eu/en/news> (accessed 18 March 2020)
18. US FDA (accessed 19 March 2020) FDA advises patient on the use of NSAID for COVID-19  
<https://www.fda.gov/drugs/drug-safety-availability/fda-advises-patients-use-nsaids-covid-19>
19. WHO public information (19 March 2020) : WHO does not recommend against the use of Ibuprofen for COVID-19 symptoms <https://twitter.com/WHO/status/1240409217997189128>
20. UNFPA, [http://www.unfpa.org/press/unfpa-statement-novel-coronavirus-\(COVID-19\)-and-pregnancy](http://www.unfpa.org/press/unfpa-statement-novel-coronavirus-(COVID-19)-and-pregnancy), 5 March 2020 (accessed 29 March 2020)
21. Zhou, Wang. 2020. Buku Panduan Pencegahan Corona Virus, RRT, Wuhan CDC.
22. European Medicine Agency (EMA). 2020. EMA provides recommendations on compassionate use of remdesivir for COVID-19. <https://www.ema.europa.eu/en/news/ema-provides-recommendations-compassionate-use-remdesivir-covid-19>.
23. European Medicine Agency (EMA). 2020. Conditions of use, conditions for distribution, and patients targeted and conditions for safety monitoring addressed to member states for remdesivir available for compassionate use.
24. Joseph, T. dan Moslehi, MA. 2020. International Pulmonologist's Consensus on COVID-19. Amrita Institute of Medical Sciences: India.
25. World Health Organization (WHO). 2020. Table of therapeutics in WHO A coordinated Global Research Roadmap. [https://www.who.int/blueprint/priority-diseases/key-action/Table\\_of\\_therapeutics\\_Appendix\\_17022020.pdf?ua=1](https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1). Published 21 March 2020. Accessed 26 March 2020.
26. Rebetol Final Printed Labeling, Schering Corporation, USA.

27. Instruction for the Medical Use of Arbidol. Good Earth Medicine LLC.
28. Gui Qiang Wang, MD. Diagnosis and Treatment Protocol of COVID 19 (Trial Version 7), Updated on March 3, 2020. National Health Commission & State Administration of Traditional Chinese Medicine.
29. FDA News Release Coronavirus (COVID-19) Update: Daily Roundup March 30, 2020. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-30-2020>. Published 30 March 2020. Accessed 31 March 2020.
30. National Institute of Allergy and Infectious Disease. NIH Clinical Trial of Remdesivir to Treat COVID-19 Begins. <https://www.niaid.nih.gov/news-events/nih-clinical-trial-remdesivir-treat-COVID-19-begins>. Published 25 February 2020. Accessed 26 March 2020.
31. Fact Sheet for Health Care Providers, Emergency Use Authorization (EUA) of Hydroxychloroquine Sulfate Supplied from the Strategic National Stockpile for Treatment of COVID-19 in Certain Hospitalized Patients. Published 28 March 2020.
32. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Chloroquine Phosphate Supplied from the Strategic National Stockpile for Treatment of COVID-19 in Certain Hospitalized Patients. Published pada tanggal 28 March 2020
33. United States Food and Drug Administration (US FDA). 2020. Coronavirus (COVID-19) Update: FDA continues to facilitate the development of treatments. <https://www.fda.gov/news-events/press-announcements/coronavirus-COVID-19-update-fda-continues-facilitate-development-treatments>. Published 19 March 2020. Accessed 26 March 2020.
34. NIH US National Library of Medicine. 2020. Study to evaluate the safety and antiviral activity of Remdesivir (GS-5734TM) in participants with moderate COVID-19 compared to standard of care

- treatment.<https://clinicaltrials.gov/ct2/show/NCT04292730>. Accessed 26 March 2020.
35. NIH US National Library of Medicine. 2020. Adaptive COVID-19 treatment trial (ACTT). <https://clinicaltrials.gov/ct2/show/NCT04280705>. Accessed 26 March 2020.
  36. Gautret, P. et al. 2020. Hydroxychloroquine and azithromycin as a treatment of COVID - 19: results of an open - label non - randomized clinical trial. *International Journal of Antimicrobial Agents*.
  37. Gao J, Tian Z, dan Yang X. 2020. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*,14(1):72-73.
  38. Ministry of Health, Labour, and Welfare. Concept of antiviral drug treatment for COVID-19, 1st edition. [https://www.mhlw.go.jp/site\\_kensa\\_ku\\_english.html?q=covid%20drug](https://www.mhlw.go.jp/site_kensa_ku_english.html?q=covid%20drug). Accessed 26 March 2020.
  39. Hock, Saw Swee. 2020. COVID-19 Science Report: Therapeutics. Singapore:School of Public Health (NUS).
  40. PDPI. 2020. Tata Laksana Pasien COVID-19. Jakarta:PDPI
  41. [https://www.who.int/medicines/areas/rational\\_use/en/](https://www.who.int/medicines/areas/rational_use/en/) Accessed pada 31 March 2020
  42. Huijun chen, Juajun Guo, Chen Wang et.al. the Lancet 2020, 395:809-15 Clinical Characteristics & Intra Uterine Vertical Transmission potential of COVID-19 Infection in 9 pregnant women : a Retrospective Review of Medical Record, corrected version March 23, 2020
  43. Wu Z, McGoogan JM, Characteristics and Important Lessons From the COVID-19 Outbreak in China: Summary of a Report of 72314 cases from the Chinese CDC, *JAMA* 2020.
  44. The US CDC, Severe Outcomes among Patients with COVID-19, Feb 12-March

- 16, 2020 <https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2>. Accessed 19 March 2020).
45. Cai J, Xu J, Lin D, et al A Case Series of Children with 2019 n-Corona Infection : Clinical and Epidemiological Features, Clin Infect Dis,2020.
  46. Liu W, Zhang Q, Chen J, et al Detection of COVID-19 in Children in Early January 2020 in Wuhan, China. N.England J Med, 2020.
  47. Smith, T., Bushek, J., dan Prosser, T. 2020. COVID-19 Drug Therapy – Potential Options. Clinical Drug Information – Clinical Solutions. Accessed 28 March 2020.
  48. <https://www.idf.org/our-network/regions-members/europe/europe-news/196-information-on-corona-virus-disease-2019-COVID-19-outbreak-and-guidance-for-people-with-diabetes.html>, Accessed 31 March 2020.
  49. European Medicines Agency (27 March 2020): EMA advises continued use of medicines for hypertension, heart or kidney diseases during COVID-19 pandemic. <https://www.ema.europa.eu/en/news/ema-advises-continued-use-medicines-hypertension-heart-kidney-diseases-during-covid-19-pandemic>
  50. UK Medicine and Healthcare products Regulatory Agency (27 March 2020) Coronavirus (COVID-19) and high blood pressure medication. <https://www.gov.uk/government/news/coronavirus-covid-19-and-high-blood-pressure-medication>
  51. American College of Cardiology (17 March 2020). HFSA/ACC/AHA Statement Addresses Concerns Re : Using RAAS Antagonists in COVID-19 <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-incovid-19>
  52. WHO Technical Report, Medication Safety in Polypharmacy, WHO/UHC/SDS/2019.11. Accessed 31 March 2020
  53. [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf). Accessed 31 March 2020.

54. <https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/guidelines/specific-antiviral-therapy-in-the-clinical-management-of-acute-respiratory-infection-with-sars-cov-2-COVID-19.pdf>. Accessed 31 March 2020.
55. <https://www.apsf.org/ddi/summary-of-chloroquine-and-hydroxychloroquine-drug-drug-interactions/>. Accessed 31 March 2020.
56. Könnnyű B, Sadiq SK, Turányi T, Hírmondó R, Müller B, Kräusslich H-G, et al. (2013) Gag-Pol Processing during HIV-1 Virion Maturation: A Systems Biology Approach. PLoS Comput Biol 9(6): e1003103. <https://doi.org/10.1371/journal.pcbi.1003103>. Accessed 30 March 2020.
57. <https://pubchem.ncbi.nlm.nih.gov/compound/Lopinavir>. Accessed 30 March 2020.
58. <https://www.drugbank.ca/drugs/DB00503>. Accessed 30 March 2020.
59. <https://pubchem.ncbi.nlm.nih.gov/compound/392622>. Accessed 30 March 2020.
60. [https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI\\_Thesaurus&ns=NCI\\_Thesaurus&code=C1609](https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=NCI_Thesaurus&code=C1609). Accessed 30 March 2020.
61. Bin Cao, M.D., Yeming Wang, M.D., Danning Wen, M.D., et al. 2020. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. (<https://www.nejm.org/doi/full/10.1056/NEJMoa2001282>). Accessed 30 March 2020.
62. AVIGAN Leaflet Toyama Chemical. Co., Ltd.
63. Chang, C, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv.
64. Cai, Q., et al. 2020. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering.
65. Furuta, Y., et al. 2009. T-705 (favipiravir) and related compounds: Novel broad-spectrum inhibitors of RNA viral infections. J. of Antiviral Resch., 82(3):95-102.

66. Dong, L., Hu, S., dan Gao, J. 2020. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther.*, 14(1):58-60.
67. World Health Organization (WHO). Summaries of evidence from selected experimental therapeutics, as of October 2018, RnD Blueprint, WHO. <https://www.who.int/ebola/drc-2018/summaries-of-evidence-experimental-therapeutics.pdf?ua=1>. Accessed 27 March 2020.
68. Remdesivir for Potential Treatment of COVID-19, Clinical Trials. <https://www.clinicaltrialsarena.com/projects/remdesivir/>. Accessed 27 March 2020.
69. World Health Organization (WHO). Summaries of evidence from selected experimental therapeutics, as of October 2018, RnD Blueprint, WHO. <https://www.who.int/ebola/drc-2018/summaries-of-evidence-experimental-therapeutics.pdf?ua=1>. Accessed 27 March 2020.
70. Bergin, C., et al. 2020. Specific Antiviral Therapy in the Clinical Management of Acute Respiratory Infection with SARS-CoV-2 (COVID-19), version 1.0. Health Service Executive.
71. Approved label Tamiflu®
72. Davis, Brian E. 2010. Pharmacokinetics of oseltamivir: an oral antiviral for the treatment and prophylaxis of influenza in diverse populations. *J Antimicrob Chemother*; 65 Suppl 2: II5 –10
73. AHFS: Assessment of Evidence for COVID-19-Related Treatments: Updated 3/30/2020.
74. Fehr AR and Perlman S. 2015. Coronaviruses: An Overview of Their Replication and Pathogenesis. *Methods Mol Biol.*; 1282:1-23.
75. Dou D, Revol R, Ostbye H, Wang H, Daniels R. 2018. Influenza A Virus Cell Entry, Replication, Virion Assembly and Movement. *Front. Immunol.* 9:1581.
76. Leaflet Cravit® IV. Approved label Badan POM (Dit. Registrasi Obat).

77. Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 2020;43 E019.
78. Leaflet Meropenem Trihydrate Serbuk Injeksi IV. Approved label Badan POM. (Directorate of Drug Registration).
79. Inhalation Therapy for Suspected COVID-19 Patients. <https://www.munsonhealthcare.org/media/file/Physician%20Services/COVID19/Communications/Inhalation%20Therapy%20for%20Suspected%20COVID-19%20Patients.pdf>. Accessed 27 March 2020
80. Albuterol Inhaler Shortage Due to COVID-19 Could Impact People With Asthma. <https://community.aafa.org/blog/albuterol-inhaler-shortage-due-to-covid-19-could-impact-people-with-asthma>. Accessed 27 March 2020.
81. Approved label midazolam.
82. Kunz Rolanda dan Minder Markus, COVID-19 pandemic: palliative care for elderly and frail patients at home and in residential and nursing homes, <https://doi.org/10.4414/smw.2020.20235>. Accessed 31 March 2020.
83. Cai SJ, et al, Analysis of bronchoscope-guided tracheal intubation in 12 cases with COVID-19 under the personal protective equipment with positive pressure protective hood, *Chinese Journal of tuberculosis and respiratory diseases*, 2020 Mar 5;43(0):E033. doi: 10.3760/cma.j.cn112147-20200222-00153. Accessed 31 March 2020.
84. Erol, adnan. 2020. High-dose intravenous vitamin C treatment for COVID-19 (a mechanistic approach).

## APPENDIX

### A. LIST OF DRUGS

<b>ANTIVIRAL THERAPY</b>
<b>Lopinavir+Ritonavir</b> 1) Aluvia Tablet-coated Salve, Lopinavir/Ritonavir: 100 mg/25 mg, 200 mg/50 mg, PT Abbott Indonesia.
<b>Oseltamivir</b> 1) Oseltamivir capsule, 75 mg, PT Indofarma; PT Boehringer Ingelheim
<b>ANTIVIRAL TEST DRUGS</b>
<b>Chloroquine Phosphate</b> 1) Chloroquin Phosphate Tablet, 250 mg, PT Kimia Farma; PT. Novapharin; PT. Dexe Medica
<b>Hydroxychloroquine Sulfate</b> 1) Hydroxychloroquine sulfate, 200 mg, PT Imedco Djaja; PT. Kimia Farma ,; PT. Dexe Medica
<b>ANTIBIOTICS</b>
<b>Azithromycin</b> 1) Azithromycin Membrane-coated Caplets; 250 mg; Pfizer Indonesia. 2) Azithromycin Film-coated Tablets; 500 mg; Pfizer Indonesia; Otto Pharmaceutical Indonesia; Tempo Scan Pacific; Kimia Farma; Pyridam Farma; HexPharm; Guardian Pharmatama; Novell Pharmaceutical Laboratories; Dexe Medica; Etercon Pharma; Pharos Indonesia; Sanbe

Farma; Bernofarm; Dankos Farma; Dipa Pharmalab Intersains; Interbat Indonesia; Promedrahardjo Pharmaceutical Industry; Ferron Pharmaceuticals.

- 3) Azithromycin Capsules; 250 mg; Pratapa Nirmala, Interbat.
- 4) Azithromycin dry syrup; 200 mg / 5 mL; Pfizer Indonesia, Dexa Medica, Ferron Pharmaceutical, Tempo Scan Pacific, Guardian Pharmatama.
- 5) Azithromycin powder for infusion solution; 500 mg / 10 mL; Pfizer Indonesia, Bernofarm, Natura Laboratoria Prima.
- 6) Azithromycin injection powder; 500mg; Novell Pharmaceutical Laboratories.

### **Levofloxacin**

- 1) Levofloxacin Infusion; 500 mg / 100 mL; PT. Lapi-Indonesia; PT. Pratapa Nirmala; PT. Caprifarmindo Labs; PT Ikapharmindo Putramas; PT. Sanbe Farma; PT. Novell Pharmaceutical; PT Pertiwi Agung; PT. Mahakam Beta Farma; PT. Pharos Indonesia; PT. Promedrahardjo Pharmaceutical Industry; PT. Mestika Farma; PT. Gracia Pharmindo; PT. Hexpharm; PT. Bernofarm; PT Kalbe Farma; PT. Interbat.
- 2) Levofloxacin Hemihydrate Infusion; 750 mg / 150 mL; PT. Bernofarm; PT Pertiwi Agung; PT. Kalbe Farma.
- 3) Levofloxacin Hemihydrate Film-coated Tablet; 250 mg; PT. Kalbe Farma.
- 4) Levofloxacin Hemihydrate Film-coated Tablet; 500 mg; PT Lapi; PT Kalbe Farma; PT. Sanbe Farma; PT. Futamed Pharmaceutical; PT Pertiwi Agung; PT Pharos Indonesia; PT. Hexpharm; PT. Bernofarm; PT Zenith

Pharmacist Factory

- 5) Levofloxacin Hemihydrate Membrane-coated Caplets; 500 mg; PT Pratapa Nirmala; PT. Mahakam Beta Farma; PT. Mestika Farma; PT. Yarindo; PT. Interbat; PT. Novell Pharmaceutical; PT. Gracia Pharmindo.
- 6) Levofloxacin Hemihydrate Membrane-coated Caplets; 750 mg; PT. Kalbe Farma; PT Pratapa Nirmala; PT Pharos Indonesia.
- 7) Levofloxacin Tablet; 500 mg; PT. Caprifarmindo Labs; PT. Harsen; PT. Indofarma; PT. Bernofarm; PT. Promedrahardjo Pharmaceutical Industry.

**Meropenem**

- 1) Meropenem Injection Powder: 0.5 G / 0.5 G, PT. Caprifarmindo Labs; PT. Dankos Farma; PT. Bernofarm; PT. Mahakam Beta Farma; PT Yarindo Pharmatama; PT. Hexpharm; PT. Novell Pharmaceutical; PT Sanbe Farma; PT. Pratapa Nirmala.
- 2) Meropenem Injection Powder; 0.6403-0.75075 G / 0.5 G; PT. Pertiwi Agung.
- 3) Meropenem Injection Powder; 1 G / 1 G; PT. Caprifarmindo Labs; PT. Mahakam; PT. Dankos Farma; PT. DIPA Pharmalab; PT Sanbe Farma; PT Erlimpex; PT. Metiska Farma; PT. Yarindo; PT. Pratapa Nirmala; PT. Lapi Indonesia.
- 4) Meropenem; 1,2806-1,50045G / 1G; PT. Interbat.
- 5) Meropenem Trihydrate Injection Powder; 1,371 G / 1 G; PT. Gracia Pharmindo
- 6) Meropenem Trihydrate Injection Powder: 1.38 G / 1 G, PT. Rama Emerald

Multi Success.

7) Meropenem Injection Powder: 1.32 G / 1 G, PT Llyold Pharma Indonesia

8) Meropenem Trihydrate: 728 mg / 500 mg, PT. Mahakam Beta Farma.

### **Cefotaxime**

1) Cefotaxime Injection Powder; 500 mg / vial; PT. Holi Pharma; Meprofarm Indonesia.

2) Cefotaxime Injection Powder; 1000 mg / vial; PT. Gracia Pharmindo; PT. Pratapa Nirmala; PT. Phapros Indonesia; PT. Sanbe Farma; PT. Natura Laboratorium Prima Indonesia; PT. LAPI Indonesia; OTTO Pharmaceuticals Inds; PT. DEXA medica; PT. Rama Emerald Multi Success; PT. Yarindo Farmatama; Meprofarm Indonesia; Interbat Indonesia; Pyridam Farma; PT. Kimia Farma.

### **NON-OPIOID ANALGESICS**

#### **Paracetamol (Acetaminophen)**

1) Paracetamol Syrup 100 mg / mL; Vitabiotics Healthcare – Indonesia

2) Paracetamol Syrup; 120 mg / 5 mL; Afi Farma - Indonesia; Afiat - Indonesia; Molex Ayus - Indonesia; Pim Pharmaceuticals; Lucas Djaja; Ciubros Farma - Indonesia; Hexpharm - Indonesia; Dasa Esa Farma Pharma and Chemical Factory - Indonesia; Actavis - Indonesia; Mudita Karuna - Indonesia; Erela - Indonesia; Erlimpex - Indonesia; Errita Pharma - Indonesia; Ifars - Indonesia; Holi Pharma - Indonesia; Gratia Husada Pharma - Indonesia; Ikapharmindo Putramas; Berlico Mulia Farma; Itrasal - Indonesia; Solas Langgeng Sejahtera - Indonesia; Intijaya Meta Ratna

Farma - Indonesia; Novapharin - Indonesia; Candra Nusantara Jaya - Indonesia; Bromo Pharmaceutical Industries - Indonesia; Mutifa Pharmaceutical Industry - Indonesia; Mulia Farma Suci - Indonesia; Otto Pharmaceuticasl Inds. - Indonesia; Yekatria Farma - Indonesia; Interbat - Indonesia; Caprifarmino Labs - Indonesia; Tempo Scan Pacific Tbk - Indonesia; Kimia Farma, Bandung - Indonesia; United Farmatic Indonesia - Indonesia; Phapros - Indonesia; Indofarma - Indonesia; Tropica Mas - Indonesia; Promedrahardjo Pharmaceutical Industry - Indonesia; Mega Esa Farma - Indonesia; Graha Farma - Indonesia; Imfarmind Pharmaceutical Industry - Indonesia; Taisho Pharmaceutical Indonesia Tbk - Indonesia; Coronet Crown - Indonesia; Bernofarm - Indonesia; Novell Pharmaceutical Lab. - Indonesia; Pyridam Farma - Indonesia; Rama Emerald Multi Sukses - Indonesia; Samco Farma - Indonesia; Aditama Raya Farmino - Indonesia; Taisho Pharmaceutical Co. Ltd., Japan; Trifa Raya Laboratories - Indonesia; Tropica Mas - Indonesia; Universal Pharm. Industries - Indonesia; Zenith Pharma Factory; Bufa Aneka - Indonesia; First Medipharma - Indonesia; Imedco Djaja - Indonesia; Sanbe Farma.

3) Paracetamol Syrup; 160 mg / 5 mL; Tempo Scan Pacific Tbk - Indonesia; Supra Ferbindo Farma - Indonesia; Ifars - Indonesia; Gratia Husada Pharma - Indonesia; Mulia Farma Suci - Indonesia; Sterling Products Indonesia - Indonesia; Taisho Pharmaceutical Indonesia Tbk - Indonesia; Konimex - Indonesia; Corsa Industries Ltd - Indonesia; Graha Farma - Indonesia; Finusolprima Farma International - Indonesia.

- 4) Paracetamol Syrup; 250 mg / 5 mL; Finusolprima Farma International; Lucas Djaja; Marin Liza Pharmacy - Indonesia; Metiska Farma - Indonesia; Taisho Pharmaceutical Co. Ltd., Japan; Taisho Pharmaceutical Indonesia Tbk - Indonesia; Triyasa Nagamas Farma.
- 5) Paracetamol Drops; 60 mg / 0.6 mL; Afi Farma - Indonesia; Erlimpex - Indonesia; Gratia Husada Pharma - Indonesia; Ifars - Indonesia; Intijaya Meta Ratna Farma - Indonesia; Metiska Farma - Indonesia; Otto Pharmaceuticasl Inds. - Indonesia; Pyridam Farma - Indonesia; Sanbe Farma; Tempo Scan Pacific Tbk - Indonesia; Darya-Varia Laboratoria Tbk - Indonesia; Novell Pharmaceutical Laboratories - Indonesia.
- 6) Paracetamol Drops; 80 mg / 0.8 mL; Taisho Pharmaceutical Indonesia Tbk - Indonesia.
- 7) Paracetamol Drops; 100 mg / mL; Ifars - Indonesia; Berlico Mulia Farma; Bernofarm - Indonesia; Bromo Pharmaceutical Industries - Indonesia; Coronet Crown - Indonesia; Indofarma - Indonesia; Mega Esa Farma - Indonesia; Molex Ayus - Indonesia; Pharos Indonesia - Indonesia; Samco Farma - Indonesia; Sterling Products Indonesia - Indonesia; Supra Ferbindo Farma - Indonesia; Taisho Pharmaceutical Indonesia Tbk - Indonesia; Mecosin Indonesia - Indonesia; Rama Emerald Multi Sukses - Indonesia.
- 8) Paracetamol Elixir; 120 mg / 5 mL; Harsen - Indonesia; Mecosin Indonesia - Indonesia.
- 9) Paracetamol Suspension; 100 mg / mL; Sterling Products Indonesia -

Indonesia.

- 10) Paracetamol Suspension; 120 mg / 5 mL; Guardian Pharmatama, Citeureup - Indonesia; Pharos Indonesia - Indonesia.
- 11) Paracetamol Suspension; 160 mg / 5 mL; Medifarma Laboratories - Indonesia; Prima Medika Laboratories - Indonesia.
- 12) Paracetamol Suspension; 250 mg / 5 mL; Actavis - Indonesia; Pharos Indonesia - Indonesia; Sterling Products Indonesia - Indonesia; Supra Ferbindo Farma - Indonesia; Darya-Varia Laboratoria Tbk - Indonesia; Errita Pharma - Indonesia; Tempo Scan Pacific Tbk - Indonesia.
- 13) Powder Paracetamol; 150 mg; Ciubros Farma - Indonesia; Bromo Pharmaceutical Industries - Indonesia.
- 14) Paracetamol Granules; 500 mg; Medifarma Laboratories - Indonesia.
- 15) Paracetamol Caplets; 500 mg; Actavis - Indonesia; Aditama Raya Farmino - Indonesia; Balatif - Indonesia; Berlico Mulia Farma; Bernofarm - Indonesia; Bufa Aneka - Indonesia; Candra Nusantara Jaya - Indonesia; Ciubros Farma - Indonesia; Erela - Indonesia; Errita Pharma - Indonesia; Faratu - Indonesia; First Medifarma - Indonesia; Gratia Husada Farma - Indonesia; Guardian Pharmatama, Citeureup - Indonesia; Holi Pharma - Indonesia; Ifars - Indonesia; Imfarmind Pharmaceutical Industry - Indonesia; Intijaya Meta Ratna Farma - Indonesia; Itrasal - Indonesia; Konimex - Indonesia; Lloyd Pharma Indonesia; Mecosin Indonesia - Indonesia; Mega Esa Farma - Indonesia; Mulia Farma Suci - Indonesia; Novapharin - Indonesia; Nufarindo - Indonesia; Oryza Farma Indonesia -

Indonesia; Dasa Esa Farma Pharma and Chemical Factory - Indonesia; Pertiwi Agung - Indonesia; Phapros - Indonesia; Pim Pharmaceuticals - Indonesia; Pim Pharmaceuticals - Indonesia; Rama Emerald Multi Sukses - Indonesia; Samco Farma - Indonesia; Sandai Farma - Indonesia; Satria Bumi Kerta - Indonesia; Sejahtera Lestari Farma; Solas Langgeng Sejagtera - Indonesia; Sterling Products Indonesia - Indonesia; Trifa Raya Laboratories - Indonesia; Triman - Indonesia; Tropica Mas - Indonesia; Universal Pharm. Industries - Indonesia; Yekatria Farma - Indonesia.

16) Paracetamol Caplets; 600 mg; Bernofarm - Indonesia.

17) Paracetamol Caplets; 650 mg; Erela - Indonesia; Erlimpex - Indonesia; Errita Pharma - Indonesia; Finusolprima Farma International; Graha Farma - Indonesia; Ifars Pharmaceutical Laboratories - Indonesia; Mecosin Indonesia - Indonesia; Molex Ayus - Indonesia; Mulia Farma Suci - Indonesia; Zenith Pharma Factory - Indonesia; Pyridam Farma Tbk - Indonesia; Samco Farma - Indonesia; Sampharindo Perdana - Indonesia; Sunthi Sepuri - Indonesia; Tempo Scan Pacific Tbk - Indonesia.

18) Paracetamol Membrane-coated Caplets; 500 mg; Naval Pharmacy Institute Drs Mochamad.

19) Paracetamol Tablets; 125 mg; Dankos Farma - Indonesia.

20) Paracetamol Tablets; 325 mg; Konimex - Indonesia; Medifarma Laboratories - Indonesia; Pt Taisho Pharmaceutical - Indonesia; Taisho Pharmaceutical Indonesia Tbk - Indonesia.

21) Paracetamol Tablets; 500 mg; Artois Pharmaceutical (Artopharma) -

Indonesia; Chess Da'wah Crane Pharmacy - Indonesia; Coronet Crown - Indonesia; Corsa Industries Ltd - Indonesia; Finusolprima Farma International; Harsen - Indonesia; Hexpharm - Indonesia; Indofarma - Indonesia; Interbat - Indonesia; Kaliroto - Indonesia; Kimia Farma, Medan - Indonesia; Medifarma Laboratories - Indonesia; Meprofarm - Indonesia; Metiska Farma - Indonesia; Mutifa Pharmaceutical Industry - Indonesia; Nicholas Lab Indonesia - Indonesia; Novell Pharmaceutical Laboratories - Indonesia; Zenith Pharma Factory - Indonesia; Pt Taisho Pharmaceutical - Indonesia; Pyridam Farma - Indonesia; Sanbe Farma; Sunthi Sepuri - Indonesia; Tempo Scan Pacific Tbk - Indonesia.

22) Paracetamol Tablets; 600 mg; Medifarma Laboratories - Indonesia; Yekatria Farma - Indonesia.

23) Paracetamol Tablets; 650 mg; Sanbe Farma.

24) Paracetamol Film-coated Tablets; 500 mg; Armoxindo Farma - Indonesia.

25) Paracetamol Effervescent Tablets; 500 mg; Sanbe Farma.

26) Paracetamol Tablets Effervescent; 1000 mg; Sanbe Farma.

27) Paracetamol Enema; 250 mg / 4 mL; Actavis - Indonesia.

28) Paracetamol Enema; 125 mg / 2.5 mL; Actavis - Indonesia.

29) Paracetamol Suppositories; 80 mg; Combiphar - Indonesia; Meprofarm - Indonesia.

30) Paracetamol Suppositories; 125 mg; Interbat - Indonesia; Oryza Farma Indonesia - Indonesia.

31) Paracetamol Suppositories; 160 mg; Combiphar - Indonesia; Meprofarm -

Indonesia.

32) Paracetamol Suppositoria; 240 mg; Combiphar - Indonesia.

33) Paracetamol Suppositoria; 250 mg; Interbat - Indonesia; Oryza Farma Indonesia - Indonesia.

34) Paracetamol Infusion; 10 mg / mL; Darya Varia Laboratoria - Indonesia; Etercon Pharma - Indonesia; Hexpharm - Indonesia; Ikapharmindo Putramas; Kalbe Farma - Indonesia; Meprofarm - Indonesia; Novell Pharmaceutical Lab. - Indonesia; Pratapa Nirmala - Indonesia; Sanbe Farma - Indonesia; Yarindo Farmatama - Indonesia.

35) Paracetamol Infusion; 1 G / 100 mL; Bernofarm - Indonesia; Hexpharm - Indonesia; Infion - Indonesia; Kalbe Farma - Indonesia; Mersifarma Tirmaku Mercusana - Indonesia; Sanbe Farma; Natura Laboratoria Prima - Indonesia; Mahakam Beta Farma - Indonesia.

## **BETA-2 SELECTIVE ADRENOSEPTOR AGONISTS**

### **Salbutamol**

1) Salbutamol Sulfate Tablet; 2 mg; PT. Armoxindo Farma; PT. Graha Farma; PT. Dankos Farma; PT. Yarindo Farmatama; PT. First Meditama; PT. Kimia Farma; PT. Phapros; PT. Glaxo Wellcome Indonesia.

2) Salbutamol Sulfate Tablet: 4 mg, PT. Sanbe Farma; PT. Armoxindo Farma; PT. Graha Farma; PT. Molex Ayus; PT. Dankos Farma; PT. Indofarma; PT. First Meditama; PT. Kimia Farma; PT. Phapros; PT. Yarindo Farmatama; PT. Sampharindo Perdana; PT. Pharos Indonesia.

3) Salbutamol Sulfate Caplets; 4 mg; PT. Ifars; PT. Itrasal.

- 4) Salbutamol Sulfate Capsule: 2 mg, PT. Lapi.
- 5) Salbutamol Sulfate Capsules: 4 mg, PT. Lapi.
- 6) Salbutamol Sulfate Syrup; 2 mg / 5 mL; PT. Sanbe Farma; PT. Konimex; PT. Lapi; PT. Sampharindo Perdana; PT. Dankos Farma; PT. Indofarma; PT. Glaxo Wellcome Indonesia.
- 7) Salbutamol Sulfate Aerosol; 100 mcg; PT. Bernofarm; PT. Imedco Djaja.
- 8) Salbutamol Sulfate Inhaler Fluid; 100 mcg; PT. Dipa Pharmalab Intersains; PT. Dexa Medica; PT. Glaxo Wellcome Indonesia.
- 9) Salbutamol Fluid Inhalers; 1 mg / mL; PT. Pratapa Nirmala; PT. Ferron Par Pharmaceuticals; PT. Dexa Medica.
- 10) Salbutamol Sulfate Inhaler Fluid; 1,205 mcg; PT. Novell Pharmaceutical.
- 11) Salbutamol Sulfate Inhaler Fluid; 2.5 mg; PT. Lapi.
- 12) Salbutamol Sulfate Injection Fluid; 500 mcg / mL; PT. Lapi.
- 13) Salbutamol Sulfate Powder Inhalers; 200 mcg; PT. Glaxo Wellcome Indonesia.

## **CENTRE NERVE SYSTEM DRUG – BENZODIAZEPINES CLASS**

### **Midazolam**

- 1) Midazolam Injection Fluid; 1 mg / mL; PT Pratapa Nirmala; PT Kalbe Farma; PT Novell Pharmaceutical; PT Pharos Indonesia; PT Ethica Industri Pharmaceutical.
- 2) Midazolam Hydrochloride Injection Fluid; 5 mg / mL; PT Combiphar; PT Kalbe Farma; PT Novell Pharmaceutical; PT Ethica Industri

Pharmaceutical.

## **EXPECTORANT**

### **Acetylcysteine**

- 1) Acetylcysteine Capsules; 200 mg; Erela - Indonesia; Etercon Pharma - Indonesia; Ethica - Indonesia; Guardian Pharmatama, Tangerang - Indonesia; Indofarma - Indonesia; Lapi Laboratories - Indonesia; Mahakam Beta Farma - Indonesia; Mersifarma Tirmaku Mercusana - Indonesia; Nulab Pharmaceutical Indonesia; Pharos Indonesia - Indonesia; Pratapa Nirmala - Indonesia; Pyridam Farma Tbk - Indonesia; Sampharindo Perdana - Indonesia; Simex Pharmaceutical Indonesia - Indonesia; Yarindo Farmatama - Indonesia.
- 2) Acetylcysteine Membrane-coated Caplets; 200 mg; PT Nufarindo.
- 3) Acetylcysteine Granules; 100 mg; PT Erela.
- 4) Acetylcysteine Granules; 200 mg; PT Erela.
- 5) Acetylcysteine Tablet Effervescens; 600 mg; Tunggal Idaman Abdi - Indonesia; Temmler Pharma GmbH, Germany; Caprifarmindo Laboratories - Indonesia.
- 6) Acetylcysteine Dry Syrup; 100 mg / 5 mL; Erela - Indonesia; Ethica - Indonesia; Pharos Indonesia - Indonesia.
- 7) Acetylcysteine Inhalation Liquid; 100 mg / mL; Pratapa Nirmala - Indonesia; Dexa Medica - Indonesia; Ferron Par Pharmaceuticals - Indonesia; Beta Pharmacon - Indonesia; Single Desire Abdi-Indonesia.
- 8) Acetylcysteine Infusion Fluid; 200 mg; Tunggal Idaman Abdi - Indonesia;

Pratapa Nirmala - Indonesia.

## **VITAMIN**

### **Ascorbic Acid (Vitamin C)**

- 1) Ascorbic Acid Injection Fluid; 100 mg / mL; PT Ethica; PT Mahakam Beta Farma; Ipha Laboratories - Indonesia.
- 2) Ascorbic Acid Injection; 200 mg / mL; PT Mahakam Beta Farma; PT Harsen; PT Sanbe Farma.
- 3) Ascorbic Acid Tablets; 25 mg; PT. Mega Esa Farma - Jakarta; PT. Imfarmind Pharmaceutical Industry - Indonesia; PT. Yekatria Farma - Indonesia; PT. Pim Pharmaceuticals - Indonesia.
- 4) Ascorbic Acid Tablets; 50 mg; PT. Kimia Farma Tbk - Indonesia; PT. Balatif - Indonesia; PT. Afiat Pharmaceutical and Trading Industry Company; PT. Triman - Indonesia; PT. Supra Ferbindo Farma - Indonesia; PT. Imfarmind Pharmaceutical Industry - Indonesia; PT. Trifa Raya Laboratories - Indonesia; PT. Yekatria Farma - Indonesia.
- 5) Ascorbic Acid Tablets; 100 mg; PT. Millennium Pharmacon International - Indonesia; PT. Kimia Farma - Indonesia.
- 6) Ascorbic Acid Tablets; 250 mg; PT. Kimia Farma Tbk - Indonesia; PT. Tempo Scan Pacific Tbk - Indonesia; PT. Imfarmind Pharmaceutical Industry - Indonesia; PT. Afiat Pharmaceutical and Trading Industry Company; PT. Phapros - Indonesia.
- 7) Ascorbic Acid Tablets; 500 mg; PT. Guna Nutrindo Sehat - Indonesia.
- 8) Ascorbic Acid Tablets; 1000 mg; PT. Guna Nutrindo Sehat - Indonesia.

**Alpha Tocopherol Acetate (Vitamin E)**

- 1) Arsinal Film-coated Tablet, Metamizole sodium monohydrate / cyanocobalamin / Thiamin nitrate / Pyridoxine Hydrochloride / Alpha Tocopherol Acetate combination: 324 mg / 100 mg / 100 mg / 50 mg / 30.0 IU, PT. Meprofarm

## B. DRUG INTERACTION

### 1. LOPINAVIR / RITONAVIR

Drugs	Notes
Rifampicin (a potential inducer of the CYP3A4 enzyme)	causes a large decrease in lopinavir levels, which significantly reduces the therapeutic effect
	not recommended unless the benefits outweigh the risk of systemic corticosteroid effects including chusing syndrome and adrenal suppression
sildenafil, tadalafil, vardenafil or avanafil (erectile dysfunction drugs)	increase the levels of these drugs, to increase the incidence of side effects, such as hypotension and longer erections
lovastatin, simvastatin, atorvastatin (HMG-CoA reductase inhibitors)	increase in plasma concentration
tipranavir	reduce lopinavir levels
zidovudin and abakavir	reduce plasma levels of zidovudin and abakavir
tenofovir	related to the occurrence of side effects
evafirenz and nevirapin	reduce the plasma concentration of

Drugs	Notes
	lopinavir / ritonavir
delavirdine	increase plasma lopinavir levels
amprenavir, indinavir, nelfinavir, and saquinavir	thought to increase levels of these drugs
fosamprenavir	reduce plasma lopinavir levels
amiodarone, bepridil, systemic lidocaine and quinidine (antiarrhythmics)	increase levels of antiarrhythmic
digoxin	increase digoxin levels
warfarin	affect warfarin levels
ritonavir with trazodone	increase the concentration of trazodone and the possibility of side effects (nausea, dizziness, hypotension, and fainting)
phenobarbital, phenytoin, and carbamazepine (anticonvulsants)	induces CYP3A4 and decreases lopinavir concentration
ketoconazole and itraconazole	increase serum levels of ketoconazole and itraconazole
voriconazole	need to consider the risk-benefit factor because it can reduce steady levels of voriconazole

Drugs	Notes
clarithromycin	increase clarithromycin levels
atovaquone	reduce levels of atovaquone
Felodipine, Nifedipine, and Nicardipine (calcium pump inhibitors)	increase serum levels of calcium pump inhibitors
cyclosporine, tacrolimus, and sirolimus (immunosuppressants)	increase immunosuppressant levels
methadone	reduce plasma methadone levels
ethinylestradiol	decrease ethinylestradiol levels
colchicine	increase levels of colchicine in blood plasma. Reportedly there was a patient's condition being fatal
corticosteroid	increases the plasma level of the drug, thereby increasing and prolonging the therapeutic effect and side effects
St. John's Wort (Hypericum perforatum)	reduce levels of protease inhibitors such as lopinavir and ritonavir, thereby eliminating the therapeutic effect and causing the

Drugs	Notes
	development of resistance to lopinavir or other protease inhibitors

## 2. AZITHROMYCIN

Drugs	Notes
Theophylline	● Antibacterial: azithromycin and isoniazid increase the concentration of theophylline in plasma
Ritonavir	● Antibacterial: ritonavir can increase the concentration of azithromycin and erythromycin in plasma; ritonavir increases concentration

## 3. MIDAZOLAM

Drugs	Notes
Verapamil	Verapamil inhibits midazolam metabolism (increasing plasma concentration and increasing sedation);
Thelithromycin	Thelithromycin inhibits midazolam metabolism (increases the effect of sedation due to increased concentration in plasma)
Saquinavir	Saquinavir increases the plasma concentration of midazolam (long-term sedation risk)

Drugs	Notes
Ritonavir	Ritonavir can increase plasma concentrations of midazolam (risk of severe sedation and respiratory depression - avoid concurrent use)
Posaconazole	Posaconazole increases the plasma concentration of midazolam (risk of extended sedation)
Nelfinavir	The effects of sedation can be prolonged when nelfinavir is given with midazolam - avoiding concurrent use
Clarithromycin	Clarithromycin inhibits midazolam metabolism (increasing plasma concentration also increases sedation)
Erythromycin	Erythromycin inhibits midazolam metabolism (increasing plasma concentration also increases sedation)
Kuiniipristin	Quiniipristin inhibits midazolam metabolism (increasing plasma concentration also increases sedation)
Dalfopristin	Dalfopristin inhibits midazolam metabolism (increasing plasma concentration also increases sedation)
Fluconazole	Fluconazole increases the plasma concentration of midazolam (risk of extended sedation)
Itraconazole	Itraconazole increases the plasma concentration of midazolam (risk of extended sedation)
Ketoconazole	Ketoconazole increases the plasma concentration of midazolam (risk of extended sedation)

<b>Drugs</b>	<b>Notes</b>
Amprenavir	Amprenavir increases the risk of extended sedation and respiratory depression if midazolam is given together
Efavirenz	Efavirenz increases the risk of extended sedation if midazolam is given together
Indinavir	Indinavir increases the risk of extended sedation if midazolam is given together
Lercanidipin	Midazolam increases absorption of Lercanidipine
Diltiazem	Diltiazem inhibits midazolam metabolism (increasing plasma concentration also increases sedation)
Verapamil	Verapamil inhibits midazolam metabolism (increasing plasma concentration also increases sedation)