HOSPITAL PHARMACY PROCEDURES FOR THE MANAGEMENT OF ANTIVIRAL TREATMENT IN THE NEW CORONAVIRUS SARS-CoV-2 DISEASE COVID-19

Recommendations of the Spanish Society of Hospital Pharmacy

March 19, 2020

Given the current situation caused by SARS-CoV-2 coronavirus (COVID-19) infection, the hospital pharmacy is an essential link in the health system. In order to contribute in the best possible way to the management of antiviral treatment, the Spanish Society of Hospital Pharmacy gives the following recommendations.

TREATMENT

The protocol for the treatment of COVID-19 recommended by de Ministry of Health is available and constantly updated in:

https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos.htm

The specific antiviral treatment includes the following drugs (informed consent required):

Lopinavir/ritonavir (oral)

> Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol. 2020 Feb 27. doi: 10.1002/jmv.25729.
>
> B. Cao, Y. Wang, D. Wen, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. NEJM 2020; This article was published on March 18, 2020, at NEJM.org. DOI: 10.1056/NEJMoa2001282

Lopinavir/ritonavir (oral) + interferon beta-1B (subcutaneous)

Lopinavir/ritonavir (oral) +interferon alfa- 2B (nebulized)

Remdesivir (intravenous)

AVAILABLE ANTIVIRALS

LOPINAVIR/RITONAVIR:	LOPINAVIR/RITONAVIR 200/50 mg film-coated tablets KALETRA 200/50 mg film-coated tablets KALETRA 80/20 mg oral solution 60 ml
INTERFERON BETA-1B:	BETAFERON 250 mcg/ml powder and solvent for solution for injection. EXTAVIA 250 mcg/ml powder and solvent for solution for injection.
INTERFERON ALFA-2B	INTRONA 10 million IU solution for injection or infusion.
REMDESIVIR:	Remdesivir 150 mg lyophilized formulation for injection.

Remdesivir 100 mg lyophilized formulation for injection.

DOSAGE

Adult dosage

- LOPINAVIR/RITONAVIR: 400/100 mg/12 hours oral x 14 days
- IFN BETA-1b 250 mcg/48 hours sc x 14 days
- IFN ALFA-2B: There is no commercialized presentation for inhalation in Spain. The solution for infusion could be used for inhalation: 5 million IU/ml adding 2 ml of sterile saline solution.

  Nebulization with interferon-α2b 100,000–200,000 IU / kg for mild cases, and 200,000–400,000 IU / kg for severe cases, twice/day for 5–7 days.
- REMDESIVIR: 200 mg as a loading dose on day 1 followed by 100mg/iv once daily for a total duration of 10 days.

Pediatric dosage

- LOPINAVIR/RITONAVIR: 7 days of therapy (maximum 14 days). Dosage is based on patient body weight (mg/kg) or body surface area (mg/m2); recommendations are based on the lopinavir component, but treatment will always be done with the co-formulated lopinavir/ritonavir.

  Recomendaciones de tratamiento específico en caso de infección específico en casos de infección respiratoria por SARS-CoV2 en pacientes pediátricos con enfermedades crónica de alto riesgo y en paciente hospitalizados. Asociación Española de Pediatría. 18 de marzo de 2020.

Pediatric dosing guidelines based on body weight (> 6 months to 18 years)		
Body weight (Kg)	**Twice daily oral solution dose** **(dose in mg/kg)**	**Volume of oral solution twice daily taken with food (80 mg lopinavir/20 mg ritonavir per ml)*** Non-polyurethane feeding tube should be used (silicone and polyvinyl chloride feeding tubes) in order to administer oral solution. After administration, the tubes must be washed with milk.
7 to 15 kg 7 to 10 kg > 10 kg < 15 kg	12/3 mg/kg	 1,25 ml 1,75 ml
15-40 kg 15-20 kg >20 -25 kg >25 -30 kg >30 –35 kg > 35-40 kg	10/2,5 mg/kg	 2,25 ml 2,75 ml 3,50 ml 4 ml 4,75 ml
> 40 kg	Adult dosage	**400 mg/100 mg twice daily**

* the volume (ml) of oral solution represents the average dose for the weight range.

Pediatric dosing guidelines (>2 weeks to 6 months)		
Weight-directed dosing (mg/kg)	**BSA-directed dosing:(mg/m^2)**	**Twice daily administered with meals.**
16/4 mg/kg (corresponds to 0,2ml/kg)	300/75 mg/m^2 (corresponds to 3,75 ml/m^2).	Twice daily administered with meals.

*The body surface area (BSA) can be calculated with the following equation: √ Height (cm) x weight (kg) / 3600

Precautions:

The oral solution contains large amounts of ethanol (42.4%) and propylene glycol (15.3%). Monitor patients with renal impairment or with decreased ability to metabolize propylene glycol for propylene glycol toxicity.

Do not use oral solution in neonates if the patient is either postnatal age <14 days old or postmenstrual age<42 weeks because of an increased risk of toxicity by propylene glycol.

- INTERFERON ALFA-2B (INTRONA®):

Nebulization of 100,000-200,000 IU / kg for mild cases; 200,000-400,000 IU / kg in severe cases, twice / day for 5-7 days

- INTERFERON BETA-1B

  - **< 12 years of age:** There is no information on the use of Betaferon in children under 12 years of age.
  - **12-16 years of age:** 250 mcg (8.0 million IU) of Interferon beta 1B sc / 48h x 14 days.

The summary of product characteristics says dose titration is recommended at the start of treatment. Patients should be started at 62.5 microgram (0.25 ml) subcutaneously every other day and increased slowly to a dose of 250 microgram (1.0 ml) every other day.

- REMDESIVIR:

Proposed doses for the pediatric population are:

- ≥ 40 kg of weight, same dose as in adults: IV 200 mg as a single dose on day 1, followed by 100 mg once daily for a total duration of 10 days.
- <40 kg of weight: IV 5 mg/kg as a single dose on day 1, followed by 2,5 mg/kg once daily for a total duration of 10 days.

SPECIFIC CONSIDERATIONS OF SOME OF THE DRUGS USED

Lopinavir/ritonavir tablets

Requested through the Spanish Agency of Medicines and Medical Devices.

Method of administration:

> Lopinavir/ritonavir tablets cannot be broken or crushed because it leads to a decreased AUC of lopinavir and ritonavir by approximately 45% and 47% respectively (Best el al. JAIDS 2011; 58: 385-91).
>
> Tablets are administered orally and must be swallowed whole and not chewed, broken or crushed.
>
> Film-coated tablets are formulated by Meltrex (Melt Extrusion Technology) in order to improve the solubility of lopinavir and ritonavir by dissolving the drug in a polymer (Klein et al. JAIDS 2007; 44: 401-410).

Lopinavir/ritonavir oral solution

Requested through the Spanish Agency of Medicines and Medical Devices.

Each 1 ml of oral solution contains 80 mg of lopinavir co-formulated with 20 mg of ritonavir, and the recommended dosage is 5 ml of oral solution (400/100 mg) twice daily taken with food.

One 60 ml bottle provides 6 days of treatment. If necessary, it could be assessed in 5mL oral syringes, which do not contain polyurethane, with a maximum expiration date of 14 days.

The oral solution will be saved for ICU intubated patients.

Method of administration:

> Because lopinavir/ritonavir oral solution contains alcohol, it is not recommended for use with polyurethane feeding tubes due to potential incompatibility. Silicone or polyvinyl feeding tubes should be used.

Remdesivir

Requested through the Spanish Agency of Medicines and Medical Devices.

It must be accessed using the keys of each center. Once inside the application, look for "remdesivir" in the "Info Medicamentos" tab and the necessary information is updated.

In case there is any problem on the website of the Spanish Agency Of Medicines And Medical Devices, you can contact medicamentosespeciales@aemps.es. The last recommendations are available on the website. The

request must be sent also to Gilead. Once the medicine request is processed, it takes between 48-72h to arrive.

Preparation and administration:

Remdesivir 150 mg vial. Each vial must be reconstituted with 29 ml of sterile water for injection in order to obtain a 5 mg/ml solution. The corresponding dose must be diluted with 100-250 ml of saline solution and must be administered in 30 minutes.

Remdesivir 100mg vial. Each vial must be reconstituted with 19 ml of sterile water for injection in order to obtein a 5 mg/ml solution. The corresponding dose must be diluted with 100-250 ml of saline solution and must be administered in 30 minutes.

Stability of diluted solution is 4 hours at room temperature and 24 hours in the refrigerator.

OTHER DRUGS

Other medications are being used, with very limited evidence and outside the technical specifications, such as hydroxychloroquine, chloroquine, darunavir/cobicistat and tocilizumab.

Hydroxychloroquine

- Evidence for the recommendations is drawn from the following studies

Cortegiani A. et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. Disponible en: https://doi.org/10.1016/j.jcrc.2020.03.005

Xueting Yao et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2.Cli Infect Dis. 2020 Mar 9. Oii: ciaa237. Doi: 10.1093/cid/ciaa237

https://reec.aemps.es/reec/public/web.html. Código EC 2020-001031-2. Protocolo CQ4COV19

Wang M. et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020 Mar;30(3):269-271)

Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020 Feb 19. doi: 10.5582/bst.2020.01047)

Cortegiani A.et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. https://doi.org/10.1016/j.jcrc.2020.03.005

- Dosage:

Adults: 400 mg/12h on day 1, followed by 200 mg/12h x 4 days (oral)

Yao X, Ye F, Zhang M, Cui C, Huang B, Niu Pet al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9. pii: ciaa237. doi: 10.1093/cid/ciaa237. [Epub ahead of print]

Pediatrics: Initially treat for 5 days (maximum duration 14 days). If it is maintained more than 5 days, lower the dose by half.

- <6 years: hydroxychloroquine sulfate 6.5 mg / kg / day divided every 2 times/day (max 400 mg / day).
- > 6 years: hydroxychloroquine sulfate 10 mg / kg / day divided every 2 times/day (max 400 mg / day).

** NOTE: 200 mg of hydroxychloroquine sulfate is equivalent to 155 mg of hydroxychloroquine base.

For dose adjustment, it may be necessary to develop solid oral formulations - hard capsules that can be opened for easy administration - or oral suspension of hydroxychloroquine at a concentration of 25 mg/ml, with good published stability data.

McHenry AR, Wempe MF, Rice PJ. Stability of Extemporaneously Prepared Hydroxychloroquine Sulfate 25-mg/mL Suspensions in Plastic Bottles and Syringes. Int J Pharm Compd. 2017 May-Jun;21(3):251-254.

Tocilizumab

- Evidence for the recommendations is drawn from the following studies

Xiaoling Xu et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. Available at: https://www.ser.es/wp-content/uploads/2020/03/TCZ-and-COVID-19.pdf)

- Dosage

Based on the clinical experience of using tocilizumab in patients with COVID-19, the Spanish Agency of Medicines and Medical Devices recommends to reserve it to the patients with the following criteria:

Inclusion criteria	**Exclusion criteria**
Intesticial pneumonia with severe respiratory failure (score=2)	AST/ALT with values higher than 5 times normal levels.
Fast respiratory worsening requiring non-invasive or invasive ventilation (COVID respiratory severity scale ≥3)	Neutrophils< 500 cell/mmc
Presence of extrapulmonary organic failure (Shock or SOFA≥3 scale)	Platelets<50.000 cell/mmc
Critical Systemic Inflammatory Response Criteria	Documented sepsis by other pathogens other than COVID-19
Adults: High levels of IL-6 (40>pg/ml) (alternatively high levels of D-dimer (> 1500) or increasing D-dimer).	Presence of comorbidity that can lead, according to clinical judgment, to poor prognosis.

Pediatrics: High levels of IL-6 (3.5> pg / ml) (alternatively high levels of D-dimer (> 400) or increasing D-dimer).	Complicated diverticulitis or intestinal perforation
	Ongoing skin infection (e.g. pyodermitis)
	Anti-rejection immunosuppressive therapy

Dosage for adults:

- Patients weighing ≥80 kg: An initial dose of 600 mg followed by a second infusion of 600 mg with an interval of 12 hours between both doses. (6 vials of 10ml or 15 of 4ml must be requested).
- Patients weighing <80 kg: An initial dose of 600 mg followed by a second infusion of 400 mg with an interval of 12 hours between both doses (5 vials of 10 ml or 13 of 4 ml must be requested).

Exceptionally, if there is a partial or incomplete clinical response, a third infusion of 400 mg will be evaluated 16-24 hours after the second infusion. It will be requested independently and must meet the following criteria: persistence of fever and worsening of analytical parameters such as PCR, IL-6 or D-dimer.

Pediatric dosage:

It is under investigation and has been considered as a possible treatment in seriously ill patients. There are no data in children under 2 years. Treatment requires IL-6 determination before and after 24 hours from the last administration.
It was considered in severe patients admitted to the PICU and with IL-6 elevation above the reference laboratory values (generally > 40 pg / mL) and / or D-dimer (> 400 ng / mL or in a progressive increase). The doses used in CAR T-CELLS cytokine release syndrome are:

- <30 kg: 12 mg / kg IV (dilute up to 50 ml with saline solution and administer in 1 hour)
- ≥30 kg: 8 mg / kg IV (dilute up to 100 ml with saline solution and administer in 1 hour). Maximum dose 800 mg per infusion.

If partial or incomplete response, administer third infusion at 16-24 hours after the second.

Preparation and administration:

Tocilizumab should be diluted to a final volume of 100 mL with sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection and administered IV in 1 hour.

Diluted Tocilizumab is stable 24h at room temperature (30ºC).

It is important to remember that, according to the note of the Spanish Agency of Medicines and Medical Devices "Information to health professionals on the distribution of drugs related to the treatment of COVID-19" the evidence that would support the use of other drugs is partial and preliminary. That's why the Agency recommends that any general use should be considered in the context of clinical studies that can potentially provide evidence of its usefulness.

The Spanish Society of Hospital Pharmacy recommends monitoring the clinical results related to these drugs, since the analysis of the information derived from their use may be relevant in the next weeks.

TOPICAL HYDROALCOHOLIC SOLUTION

In the absence of hydroalcoholic disinfectant, its preparation will be evaluated in the Pharmacy Service following the applicable protocols and regulations.

The Spanish Society of Hospital Pharmacy recommends following the Guide to Local Production: WHO-recommended Handrub Formulations.

https://www.who.int/gpsc/5may/Guide_to_Local_Production.pdf .

STOCK CONTROL AND CUSTODY

- Anticoronavirus antivirals should be properly stored and under direct supervision, with strict stock control and frequent counts.

PRESCRIPTION ASSISTANCE

- When prescribing an antiviral treatment for coronavirus, there must be a system of validation, management and urgent dispensation throughout the day.
- Prescription protocols must be available in the electronic prescription systems and dosage and treatment duration must be documented.
- If lopinavir/ritonavir is prescribed, tablets should be used whenever possible. Oral lopinavir/ritonavir solution will be reserved for intubated ICU patients.
- It is recommended to visit http://www.covid19-druginteractions.org/ or any other source of verified information for the validation of possible interactions or adjustment of the prescription of patients with any prescribed treatment.

INTERACTIONS

Check interactions in:
https://www.hiv-druginteractions.org/checker
http:/www.covid19-druginteractions.org/

DISPENSING

Dispensing Anti-Coronavirus antivirals for COVID-19

Unitary dose drug dispensation is recommended.

Lopinavir/ritonavir dispensing restriction in HIV patients

It is recommended to restrict dispensation of lopinavir/ritonavir tablets for one month for HIV patient's treatment.

It is recommended to restrict theuse of lopinavir/ritonavir solution for COVID-19 patients. HIV patients will be transferred to tablets if possible.

In those patients with current antiretroviral treatment which includes lopinavir/ritonavir, it is recommended the evaluation by a multidisciplinary team in order to, as far as possible, modify their treatment to other options currently available, following the recommendations of GESIDA (GESIDA 2020 http://gesida-seimc.org/category/guias-clinicas/).

Dispensing and returning medications of hospitalized COVID-19 patients

Unitary dose drug dispensation is recommended. Medications returned to the Pharmacy Department will be discarded.

For those hours in which there is no physical presence of a hospital pharmacist, it is recommended to guarantee the availability of treatments in the Intensive Care Unit and in the Pharmacy Department.

Ambulatory Care Pharmacy

Special measures must be taken in order to prevent COVID-19 infections in Ambulatory Care Pharmacy.

Considering that COVID-19 has a high transmission capacity, the following measures are recommended to minimize exposure and the risk of contagion:

1. Patient targeted measures

- The presence of patients in the Ambulatory Care Pharmacy will be limited, with a maximum of patients that allows maintaining at least one meter between them.
- A hydroalcoholic gel dispenser will be available for patients to disinfect their hands.
- Patients will be encouraged to make the appointment by phone or e-mail instead of remaining in the appointment queue. It would be advisable that if these patients don't require medication dispensing, they should be attended through a non-face-to-face consultation (telephone, telemedicine, etc.).
- It is recommended to limit the accompaniment of patients in the Ambulatory Care Pharmacy to a maximum of one person.

2. Health care professional targeted measures

- Health care professionals will avoid touching patient documents with their hands as much as possible. Therefore, the patient's documentation and identification (ID card or health card) will be visually checked, avoiding passing cards through the readers.
- An hydroalcoholic gel dispenser shall be available on each table/dispenser and shall be used at least every time patient documents have been touched.
- An hydroalcoholic gel dispenser will be available at the appointment desk for administrative officer and for patients who want to disinfect their hands.
- A minimum distance of one meter shall be maintained between professionals and patients.
- It is recommended to review the patient's medical history prior to the consultation to minimize the time of contact/exposure with the patient.
- Disinfect the dispensing table, computer, keyboard, and other objects on the table surface with ethanol 70% periodically (and specifically after professional care for a patient with respiratory symptoms).
- The access doors to the unit and/or office should be kept open whenever possible and if confidentiality is required, the handle should be disinfected after each consultation.
- Medication will be dispensed, whenever it is possible, until the next medical appointment, with a maximum quantity that minimizes patient movements and contacts with the hospital.
- Visiting hours will be extended in order to avoid contacts between patients.
- Patients with respiratory pathology or immunosuppressive medication should avoid going to the pharmacy, recommending a family member or authorized persons to pick up the medication.

Exceptionally, for those patients who are self-isolate at home or those who are interviewed by telephone to avoid exposure, and who do not have any authorized person available to collect the medication in the Ambulatory Care Pharmacy, the possibility of home delivery through the procedures established in the center should be considered.

General organization of the Pharmacy Department

The availability of interchangeable and impervious work equipment is generally recommended for healthcare areas, which do not maintain contact with each other and can be replaced if temporary isolation is required, so that the healthcare activity can continue.

It is advisable to limit the number of clinical sessions in order to avoid contact of the entire team, as well as meetings in which a distance of 1.5 m cannot be maintained between the attendees.

It is recommended to incorporate the use of telework in order to favor flexibility of hours, in accordance with the instructions of the centers.

Evolution and updating of recommendations

Given the exceptional nature of the situation, it will be necessary to update this document and incorporate all those recommendations and guidelines stipulated by the organizations with competence in the health field.

It is recommended to constant review all those information sources that allow updating this document.

The measures proposed in this document must be accompanied by all those considered locally at each center.