Heberon® alfa R (interferon alfa-2b) for patients with Coronavirus Disease 2019 (COVID-19). Clinical use protocol

Rationality

Due to its known mechanism of action, it is common to use interferon (IFN) against viral infections for which specific therapies are not available. IFN alfa-2b is one of the drugs of greatest attention used as experimental biotherapy for patients affected by COVID-19 [1,2]. Its use is based and justified by the antiviral properties of the interferon molecule, a member of the first line of antiviral defense with activation of the innate immune response against the virus and the mechanism of inhibition of viral replication, mediated by the inducer genes of IFN.

SARS-CoV (coronavirus associated with the 2002 epidemic) has been reported to reduce IFN expression and prevent IFN-inducing STAT1 and MyD88 genes from activating, as well as antiviral defense mechanisms detect the presence of the virus. On the other hand, IFN induction has been shown to protect against infection by MERS-CoV (coronavirus associated with the 2012 epidemic) [3]. There are current reports of clinical use of nebulized IFN in pediatric and pregnant populations affected by COVID-19 [4,5].

Due to the urgency of COVID-19 pandemic, not only IFN, but various drugs are being used as therapeutic tools, even though their efficacy has not been demonstrated for the treatment of SARSCOV-2. These previous evidences and studies suggest the possible usefulness of IFN as a preventive measure in vulnerable populations and in early stages of infection, in addition to the fact that its use continues to be published in the current pandemic and appears recommended in patient treatment protocols by different countries and organizations.

There are guideline issued by Expert Committees of WHO, Singapore, South Korea and US Institutions who recommend the clinical use of IFN for the treatment and prevention of COVID-19 [6-10]. China and Spain have incorporated this drug into their national protocols and clinical guidelines for the care of this type of patient [11,12]. For example, the combined use of nebulized Lopinavir / ritonavir + interferon alfa-2b is the recommended treatment in China for the treatment of patients with COVID-19 pneumonia. Similarly, several clinical trials for COVID-19 are being carried out in China, including treatment of mild infections with lopinavir / ritonavir as monotherapy (ChiCTR2000029387, ChiCTR2000029539) and in combination with interferon alfa2b (ChiCTR2000029308) [13].

(COVID-19): respiratory illness caused by a novel (new) coronavirus designated SARS-CoV-2. Protocol for clinical use of Heberon® Alfa R (interferon alfa-2b).

Drug (active ingredient)

Heberon® Alfa R (Recombinant Human Interferon alfa-2b)

Commercial presentation

Liquid injectable solution with 3 or 5 million international units (MIU) of recombinant human interferon alfa-2b, presented in hermetically sealed vial.

Active ingredient

Recombinant human interferon alpha-2b, produced in *Escherichia coli* at the Center for Genetic Engineering and Biotechnology, Havana, Cuba.

Other Ingredients

Benzyl alcohol, sodium chloride, polysorbate 80, disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrated and water for injection.

Pharmacological action

Antiviral

Therapeutic indication

Coronavirus disease (COVID-19) patients

Administration route

Nebulization by vaporization through the respiratory tract

Posology

5 MUI or 6 MUI of Heberon® Alfa R diluted in 2 mL of water for injection or in saline solution (physiological serum).

Schedule (frequency and duration) of treatment

Twice a day for 5 to 10 days

Nebulization solution preparation method

1. Extract the total content of Heberon® Alfa R solution to be used into a nebulizer container, consisting of one 5 MUI bulb or two 3 MUI bulbs, depending on the drug presentation.
2. Add 2 mL of water for injection or saline solution in the nebulizer container (in this step the solution to be nebulized will be ready)
3. Administer in nebulization way.

The Heberon® Alfa R solution is designed for immediate use after the bulb has been opened, therefore, the described steps must occur immediately. At the end of step 3 the used Heberon® Alfa R bulbs and any remaining volume of solution in the nebulizer device should be discarded. To prepare the solution to be nebulized in the next dose, new Heberon® Alfa R bulbs must be used.

Cautions

Heberon® Alfa R must be administered under the supervision of a specialist physician. Should be administered cautiously in patients with pre-existing heart disease.

Contraindications

The use of Heberon® Alfa R is contraindicated in patients with hemoglobinopathies, autoimmune diseases, severe liver failure or decompensated liver cirrhosis. It should also not be used in patients with hypersensitivity to interferon alfa or to any of the salts present in the preparation.

Heberon® Alfa R is contraindicated in children less than three years of age, especially in premature newborns, because it uses benzyl alcohol as a preservative in its formulation.

Main side effects

Most of the adverse events associated with the use of Heberon® Alfa R occur with mild intensity; however, it can cause adverse reactions of moderate or severe intensity that require reducing the dose, temporarily withdrawing the treatment or discontinuing it permanently.

The main adverse events that may occur are anorexia, depression, insomnia, anxiety, emotional lability, dizziness, headache, nausea, vomiting, diarrhea, abdominal pain, alopecia, rash, myalgia, arthralgia, musculoskeletal pain, fatigue, stiffness, pyrexia, flu-like symptoms, malaise, and irritability.

Storage conditions

Heberon® Alfa R vials must be kept, until the moment of their use, inside pharmaceutical refrigerators with permanently temperatures between 2 and 8 degrees Celsius and located in rooms with controlled temperature and humidity conditions.

Heberon® Alfa R must not be frozen.

Estimated required product

In the proposed dosage, each patient requires two daily doses of 5 MIU or 6 MIU of Heberon® Alfa R.

In case of prescribing 5 MUI dose, each individual will require the use of a Heberon® Alfa R 5 MUI vial in each administration; therefore two vials will be used for daily treatment. Up to TEN days, would require 20 vials per patient.

In case of prescribing 6 MUI dose, each individual will require the use of two vials of Heberon® Alfa R 3 MIU in each administration; therefore four units will be used for daily treatment and, up to TEN days, would require 40 vials per patient.

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