in less than 20 % of patients treated. Most of these events were reported with mild intensity, while none of the moderate or severe were irreversible or had consequences that affected or endangered the integrity of the patient.

DOSAGE AND METHOD OF ADMINISTRATION

The therapeutic regimen should be established by a physician experienced in treating patients with hepatitis B or C. When **PEG-Heberon®** is used in combination with ribavirin, professional information on ribavirin should also be consulted.

• *Chronic hepatitis C*: 180 µg of **PEG-Heberon®** is recommended once a week, subcutaneously in combination with oral ribavirin, or as monotherapy in cases where ribavirin is contraindicated. In patients with genotypes 1 or 4, the standard daily doses of ribavirin will be administered depending on body weight: 1200 mg for those over 75 kg and 1000 mg for those under 75 kg. In patients with genotypes 2 or 3, 800 mg are administered daily. The data available for patients infected with genotypes 5 or 6 are limited; therefore, it is recommended that they be treated with a schedule similar to that used for genotypes 1 or 4. The duration of combined treatment with ribavirin depends on the viral genotype and the reduction in baseline viral load at weeks 12 and 24 of treatment (see the leaflet or the summary of the characteristics of the product, published by CECMED). Regardless of the viral genotype and the viral load existing at week 12 of treatment, all patients with detectable viral particles at week 24 of treatment must permanently discontinue treatment.

• *Patients co-infected with hepatitis C virus and human immunodeficiency virus (HIV):* the recommended dose of **PEG-Heberon®** alone or in combination with 800 mg of ribavirin is 180 µg in a weekly subcutaneous injection, regardless of genotype viral.

• *Prediction of sustained virological response:* early virological response at week 12 of treatment, defined by a decrease in viral load ≥ 2 log or undetectable levels of hepatitis C virus RNA, is an important predictive value of the response. Sustained virologic (SVR) six months after the end of the treatment. The chronic hepatitis C treatment consensus recognizes that there is a 98 % negative predictive value of SVR in patients with less than 2 log reduction in baseline viral load at week 12 of treatment.

• *Chronic hepatitis B:* the recommended dosage, both for those with positive or negative HBsAg, is 180 µg subcutaneously, once a week for 48 weeks.

DOSE ADJUSTMENT DURING ADVERSE REACTIONS

In the event of adverse effects of moderate or severe intensity, mainly on hematological parameters, it is recommended to reduce the dose of **PEG-Heberon®** to 135 µg. Sometimes it is necessary to reduce to 90 µg or 45 µg or temporarily interrupt treatment. Once the adverse reactions disappear, consideration should be given to increasing the dose until the initial 180 µg is recovered.

INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTION

In HIV-coinfected patients, cases of anemia exacerbation due to ribavirin have been reported when zidovudine is part of treatment, although the exact mechanism has not yet been determined. The combination of ribavirin with zidovudine is not recommended due to the increased risk of anemia. Zidovudine substitution should be considered in combination antiretroviral therapy if this has been previously established. This is especially important in patients with a history of zidovudine-induced anemia. There is no other evidence that indicates that treatment with **PEG-Heberon®** alters and/or modifies the metabolism of other drugs.

USE IN PREGNANCY AND LACTATION

There are no studies on the use of **PEG-Heberon®** in pregnant women or during breastfeeding. Therefore, there are no elements that prevent or establish its safe use during pregnancy. Its use should only be under medical prescription and respond to a risk-benefit analysis of the doctor. Breastfeeding should be stopped before starting treatment.

EFFECTS ON THE DRIVING OF VEHICLES / MACHINERY

The influence of **PEG-Heberon®** on the ability to drive and use machines is small or moderate. If the patient is dizzy, confused, sleepy, or fatigued, she should be advised that she should avoid driving vehicles or using machines.

OVERDOSE

Cases of overdose with similar products have been described, after the administration of 2 injections on consecutive days (instead of weekly doses), up to daily injections for a week (that is, 1,260 µg per week). None of these patients experienced unusual, severe, or treatment-limiting reactions. In clinical studies with similar products, weekly doses reaching 540 µg and 630 µg were administered to patients with renal cell carcinoma and chronic myeloid leukemia, respectively. Dose-limiting toxic reactions, such as fatigue, elevated liver enzymes, neutropenia, and thrombocytopenia, are characteristic effects of interferon therapy.

Center for Genetic Engineering and Biotechnology

Distinctive company of Cuban biotechnology which develops, produces, markets and exports innovative products, for key areas of the biomedical, veterinary, agricultural, aquaculture and industrial sectors, for one health. It has a portfolio of research and development (R&D) projects and products, protected by patents. Its more than 30 products marketed in more than 35 countries, include first and only drugs of its kind, to treat diseases that do not have other effective therapeutic solutions. Several of its medicines are inserted into national programs to offer comprehensive health care. We work with social responsibility and in harmony with the environment.

CIGB CENTRO DE INGENIERÍA GENÉTICA Y BIOTECNOLOGÍA

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PEG-Heberon®

RECOMBINANT HUMAN INTERFERON ALPHA 2B CONJUGATED TO POLYETHYLENE GLYCOL FOR THE TREATMENT OF CHRONIC HEPATITIS B AND C

EVERY DOSE COUNTS

PEG-Heberon ®

Recombinant human interferon alpha 2b conjugated to polyethylene glycol for the treatment of chronic hepatitis B and C

EVERY DOSE COUNTS

• THE USE OF **PEG-HEBERON®** IN COMBINATION WITH RIBAVIRIN FOR THE TREATMENT OF CHRONIC HEPATITIS C ACHIEVES UP TO 40 % SUSTAINED VIROLOGICAL RESPONSE IN PATIENTS WITH GENOTYPE 1 WITHOUT PRIOR TREATMENT.

• AFTER SIX MONTHS OF TREATMENT WITH **PEG-HEBERON®** VIRAL REPLICATION REMAINS UNDETECTABLE.

• WITH **PEG-HEBERON®**, DISEASE CONTROL INCREASES BY 27% COMPARED TO CONVENTIONAL ALPHA-INTERFERON MONOTHERAPY.

PHARMACEUTICAL FORM

Solution for subcutaneous injection.

STRENGTH

0.18 mg/mL of human recombinant alpha 2b interferon conjugated with polyethylene glycol.

PRESENTATION

- Single case
- Multiple cases for 10 cases with 10 vials
- Case with 10 vials

COMPOSITION

Each 1 mL contains 0.18 mg polyethylene glycol conjugated recombinant human interferon alpha 2b; polysorbate 80; EDTA; sodium chloride; disodium hydrogen phosphate (Na_2HPO_4); sodium dihydrogen phosphate dihydrate ($NaH_2PO_4 \times 2H_2O$); water for injection.

INDICATIONS

• *Chronic hepatitis B*: **PEG-Heberon®** is indicated as monotherapy in adult patients with compensated liver disease, with positive or negative HBsAg, with evidence of viral replication, with high levels of alanine aminotransferase and proven necroinflammatory activity with or without fibrosis.

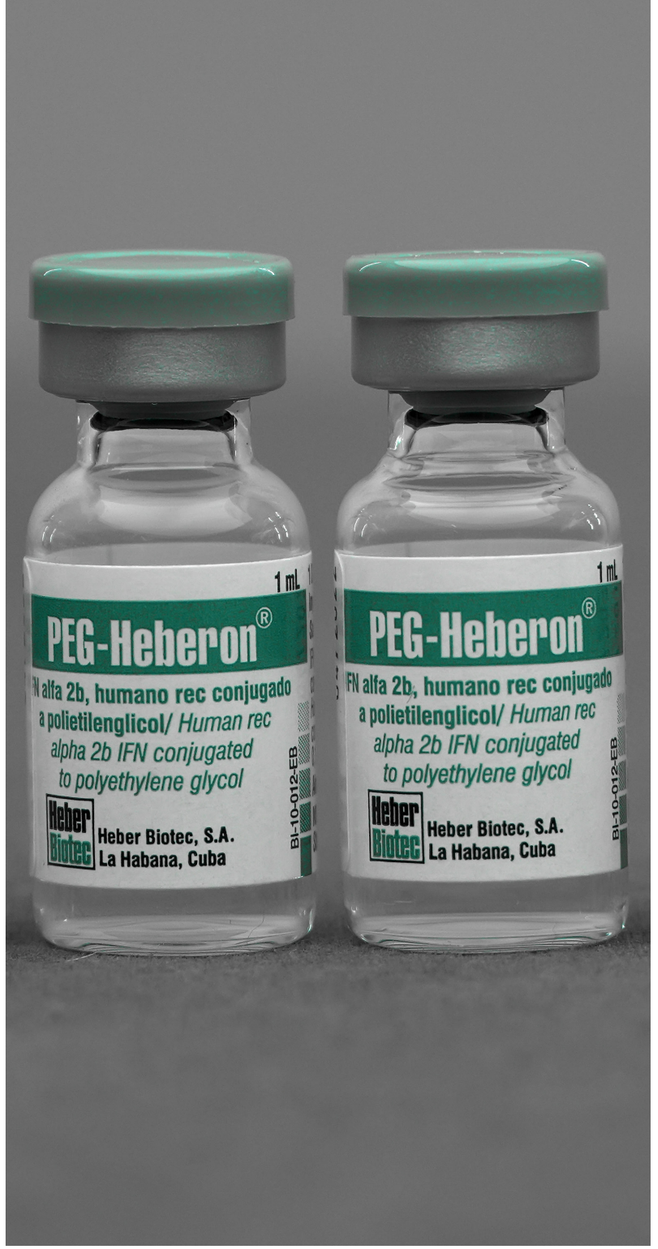
• *Chronic hepatitis C*: **PEG-Heberon®** is indicated in adults with liver cirrhosis or not, with compensated liver disease, at risk of complications associated with liver cirrhosis or hepatocellular carcinoma; also in individuals who have not received conventional interferon alpha monotherapy or its combination with ribavirin, and in those who have received this treatment but have not shown a response or who have relapsed; also in patients coinfected with the human immunodeficiency virus (HIV) or with the hepatitis B virus (HBV); and in those who have received a liver transplant. The highest SVR percentages are achieved by combining **PEG-Heberon®** with ribavirin. The duration and dosing schedule of the combination of **PEG-Heberon®** and ribavirin can be individualized per patient based on genotype, baseline viral load, and virologic response at week 12 of treatment. Monotherapy with **PEG-Heberon®** is indicated when there is intolerance to ribavirin or when it is contraindicated.

CONTRAINDICATIONS

PEG-Heberon® is contraindicated in people with hypersensitivity to interferon alpha, to products derived from Escherichia coli, to polyethylene glycol (macrogol) or to any of the salts present in the pharmaceutical preparation. It is also contraindicated in autoimmune hepatitis, severe liver failure and decompensated cirrhosis; people with a history of severe heart disease, unstable or uncontrolled heart disease in the past 6 months; patients with hemoglobinopathies; and during breastfeeding. Its efficacy and toxicity in children under 18 years of age have not been proven. In associated administration with ribavirin, professional information on ribavirin should also be consulted.

PRECAUTIONS

PEG-Heberon® should be administered with caution, and maintain periodic monitoring or interrupt treatment in patients with heart disease, myelosuppression, compromised kidney function, psychiatric disorders, thyroid diseases, allergic or autoimmune diseases, eye changes, pulmonary, dental and periodontal disorders. In patients with hepatitis C who have received liver transplantation, **PEG-Heberon®** with ribavirin can be used after appropriate individualized diagnosis and a risk-benefit analysis by the medical team responsible for the patient. **PEG-Heberon®** with ribavirin is contraindicated in pregnant patients. Extreme caution should be exercised in female patients and in female partners of male patients treated with **PEG-Heberon®** in combination with ribavirin, in order to avoid pregnancy. Patients and their sexual partners must use effective contraception during treatment and for 6 months after treatment. It is recommended to consult professional information on ribavirin.



SPECIAL WARNINGS AND PRECAUTIONS FOR USE

PEG-Heberon® in monotherapy or with ribavirin should be administered under the supervision of a specialist physician. Treatment may cause adverse reactions of moderate or severe intensity that require a dose reduction, temporary interruption or discontinuation of treatment.

UNDESIRABLE EFFECTS

Adverse reactions are mild to moderate in intensity, dose dependent, and reversible. The prophylactic use of antipyretics or analgesics reduces the number and intensity of adverse events. The most common reactions are burning at the injection site, leukopenia, fever, thrombocytopenia, increased liver enzymes, and asthenia.

It has been reported that the use of **PEG-Heberon®** in combination with ribavirin in patients with chronic hepatitis C can cause a decrease in leukocyte and hemoglobin levels as the most frequent hematological events (48 and 44 % respectively). Clinically, the most common adverse events have been asthenia (48 %, headache (26 %), and burning at the injection site (25 %) at the time of administration. Fever, arthralgias, and myalgias were reported