KAMADA
High Quality Pharmaceuticals

יוני 2020

רופא/ה, רוקח/ת נכבד/ה,

חברת קמהדע מבקשת להודיע על עידכון עלון כמפורט להלן, עבור התכשיר:

Hepatect CP; הפטקט CP

Solution for infusion, IV

מרכיבים פעילים בהתאם לרישיון:

PROTEIN IMMUNOGLOBULIN 50 MG/ML

המאושר להתויה:

Prophylaxis against hepatitis B in adults and children over 2 years of age who have not been vaccinated against hepatitis B (including persons whose vaccination is incomplete or missing) who are at risk of infection with hepatitis B by accidental contact with Hepatitis B virus containing material following:
- percutaneous exposure (e.g. accidental needle stick).
- direct mucous membrane contact.

When the administration of an intramuscular hepatitis B immunoglobulin is not possible.
The immunoglobulin should be administered in association with hepatitis B vaccine.
Prophylaxis against re-infection of a transplanted liver in patients who carry the surface antigen of the hepatitis B virus.
Immunoprophylaxis of hepatitis B in the newborn of a hepatitis B virus carrier mother.

מהות השינוי: עידכון עלון לרופא. בהודעה זו מצוינים השינויים המהווים החמרה (הודגשו בצהוב). בעלון שינויים נוספים שאינם החמרה.

4.2 Posology and method of administration

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Method of administration

Intravenous use.
Hepatect CP should be infused intravenously at an initial rate of 0.1 ml/kg/hr for 10 minutes. See section 4.4. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated, the rate of administration may gradually be increased to a maximum of 1 ml/kg/hr.

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4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to human immunoglobulin.
- Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

4.4 Special warnings and precautions for use

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Precautions for use

Monitoring of anti-HBs antibody level:

Patients should be monitored for serum anti-HBs antibody levels regularly. The dosage shall be adjusted to maintain the therapeutic antibody levels and to avoid underdosing (see section 4.2).

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human immunoglobulins by initially injecting Hepatect CP slowly (0.1 ml/kg/hr).
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human immunoglobulin products, patients switched from other immunoglobulins or when there has been a long interval since the previous infusion. These patients should be monitored at the hospital during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

Especially if applied at higher doses, intravenous human immunoglobulin administration requires:

- adequate hydration prior to the initiation of the infusion of human immunoglobulins
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics (see section 4.5).

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

Infusion reaction

Certain ~~severe~~ adverse ~~drug~~ reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea and hypotension) may be related to the rate of infusion. The recommended infusion rate given under section 4.2 “Method of administration“ must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Adverse reactions may occur more frequently

- in case of high rate of infusion,
- in patients with hypo- or agammaglobulinemia with or without IgA deficiency,
- in patients who receive human immunoglobulins for the first time or, in rare cases, when the human immunoglobulin product is switched or when there has been a long interval since the previous infusion,
- in patients with an untreated infection or underlying chronic inflammation.

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The following adverse reactions have been associated with the use of human normal immunoglobulin for intravenous administration (IVIg):

Head Office 2 Holtzman St., Science Park, P.O. Box 4081, Rehovot, 7670402, Israel | Tel. +972-8-9406472 | Fax. +972-89406473

Plant Kibbutz Beit Kama, M.P Negev 8532500, Israel | Tel. +972-8-9913111 | Fax. +972-8-9912083

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses, which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolaemic patients, patients with diseases which increase blood viscosity).

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Acute renal failure

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered.

While reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number.

In patients at risk, the use of human immunoglobulin products that do not contain these excipients may be considered. Hepatect CP does not contain sucrose, maltose or glucose.

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl.

AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment. Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

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Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Haemolytic anaemia

IVIg products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. (See section 4.8.).

Neutropenia/Leukopenia

A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIgs. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion related acute lung injury (TRALI)

In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema TRALI. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

4.5 Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines

Immunoglobulin administration may ~~interfere with the development of an immune response to~~ impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as rubella, mumps, measles and varicella ~~for a period of up to 3 months~~. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines.

In case of measles vaccination, this impairment may persist for up to 1 year. Therefore, patients receiving measles vaccine should have their antibody status checked.

~~Human hepatitis B immunoglobulin should be administrated three to four weeks after vaccination with such a live attenuated vaccine; in case administration of human hepatitis B immunoglobulin is essential within three to four weeks after vaccination, then revaccination should be performed three months after the administration of human hepatitis B immunoglobulin.~~

Loop diuretics

Avoidance of concomitant use of loop diuretics.

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Paediatric population

The listed interactions apply to adults and children.

4.8 Undesirable effects

Summary of the safety profile

~~Most adverse drug reactions (ADRs) were mild to moderate in nature. In isolated cases human normal immunoglobulins may cause an anaphylactic shock.~~

Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass (see also section 4.4): ~~Adverse reactions observed with other human immunoglobulin preparations:~~

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- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)

…….

- cases of Transfusion Related Acute Lung Injury (TRALI)

Skin and subcutaneous tissue disorders	Skin reaction, ~~erythema, itching~~rash, pruritus

…….

Paediatric population

Adverse reactions in children are expected to be the same as in adults.

4.9 Overdose

~~Consequences of an overdose are not known~~

Overdose of immunoglobulins may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment (see section 4.4).

6.2 Incompatibilities

~~In the absence of compatibility studies, this~~ This medicinal product must not be mixed with other medicinal products, nor with any other IVIg products.

No other preparations may be added to the Hepatect CP solution as any change in the electrolyte concentration or the pH may result in precipitation or denaturisation of the proteins.

העלון לרופא המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס ע"י פניה לבעל הרישום, חברת קמהדע בע"מ (טל' 08-9406472).

להלן הקישור למאגר התרופות:

https://data.health.gov.il/drugs/index.html#/byDrug

בברכה,

צוות רישום קמהדע בע"מ