30/09/2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

הנדון: **FLEBOGAMMA 5% DIF**
Solution for Infusion

חברת מדיצ'י מדיקל בע"מ מבקשת להודיע על עדכון העלון לרופא של Flebogamma 5% DIF

Therapeutic indications

Replacement therapy in:

- Primary immunodeficiency syndromes such as:
- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- Wiskott Aldrich syndrome
- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.
- Children with congenital AIDS and recurrent infections.

Immunomodulation :

- Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome
- Kawasaki disease.
- Allogeneic bone marrow transplantation

Qualitative and Quantitative Composition

Human normal immunoglobulin (IVIg) One ml contains:

Human normal immunoglobulin..... 50 mg (purity of at least 97% of IgG)

Each vial of 10 ml contains: 0.5 g of human normal immunoglobulin
Each vial of 50 ml contains: 2.5 g of human normal immunoglobulin
Each vial of 100 ml contains: 5 g of human normal immunoglobulin
Each vial of 200 ml contains: 10 g of human normal immunoglobulin
Each vial of 400 ml contains: 20 g of human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):
IgG_1 66.6%
IgG_2 28.5%
IgG_3 2.7%
IgG_4 2.2%

The maximum IgA content is 50 micrograms/ml. Produced from the plasma of human donors.

Excipient with known effect: One ml contains 50 mg of sorbitol.

For the full list of excipients, see section 6.1.

להלן עדכוני הבטיחות העיקריים: (מסומנים ברקע צהוב):

[…]

4.3 Contraindications

[…]

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 special precautions for use

[…]

Infusion reaction

Certain adverse 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 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 patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal 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

[…]

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.

[…]

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 mm^3, 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.

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

[…]

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 [Transfusion Related Acute Lung Injury (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.

[…]

Paediatric population

It is recommended to monitor vital signs when administering Flebogamma DIF to paediatric patients.

[…]

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass (see also section 4.4):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

For safety information with respect to transmissible agents, see section 4.4.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention:

- very common (≥1/10)
- common (≥1/100 to <1/10)
- uncommon (≥1/1,000 to <1/100)
- rare (≥1/10,000 to <1/1,000)
- very rare (<1/10,000)
- not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Source of the safety database from clinical trials and post-authorisation safety studies in a total of 128 patients exposed to Flebogamma 5% DIF (with a total of 1318 infusions)

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency per patient	Frequency per infusion
Infections and infestations	Nasopharyngitis	Uncommon	Uncommon
Immune system disorders	Hypersensitivity	Uncommon	Rare
Psychiatric disorders	Abnormal behaviour	Uncommon	Rare
	Headache	Very Common	Common

Nervous system disorders	Dizziness	Common	Uncommon
	Migraine	Uncommon	Rare
Cardiac disorders	Tachycardia	Common	Common
	Cardiovascular disorder	Uncommon	Rare
Vascular disorders	Diastolic hypotension, Hypotension	Common	Common
	Diastolic hypertension, Hypertension		Uncommon
	Systolic hypertension	Uncommon	
	Blood pressure fluctuation, Flushing		Rare
Respiratory, thoracic and mediastinal disorders	Bronchitis, Wheezing	Common	Uncommon
	Productive cough	Uncommon	Uncommon
	Asthma, Cough, Dyspnoea, Epistaxis, Nasal discomfort, Laryngeal pain		Rare
Gastrointestinal disorders	Abdominal pain upper, Abdominal pain, Diarrhoea, Nausea, Vomiting	Common	Uncommon
Skin and subcutaneous tissue disorders	Urticaria	Common	Uncommon
	Pruritus, Rash pruritic	Uncommon	
	Dermatitis contact, Hyperhidrosis, Rash		Rare
Musculoskeletal and connective tissue disorders	Back pain, Arthralgia, Myalgia	Common	Uncommon
	Muscle spasms, Neck pain, Pain in extremity	Uncommon	Rare
Renal and urinary disorders	Urinary retention	Uncommon	Rare
General disorders and administration site conditions	Pyrexia	Very Common	Common
	Chills, Injection site reaction, Pain, Rigors	Common	Uncommon
	Asthenia, Chest pain, Infusion site erythema, Infusion site extravasation, Infusion site inflammation, Infusion site pain, Injection site oedema, Injection site pain, Injection site pruritus, Injection site swelling, Oedema peripheral	Uncommon	Rare
Investigations	Blood pressure systolic increased, Body temperature increased, Coombs test positive	Common	Uncommon
	Blood pressure systolic decreased	Uncommon	Uncommon
	Alanine aminotransferase increased, Blood pressure increased		Rare
Injury, poisoning and procedural complications	Infusion related reaction	Uncommon	Uncommon
Product issues	Device dislocation	Uncommon	Rare

Description of selected adverse reactions

The most reported post-marketing ADRs received since the product was authorised for both concentrations were chest pain, flushing, blood pressure increased and decreased, malaise, dyspnoea, nausea, vomiting, pyrexia, back pain, headache and chills.

[…]

העלון מכיל עדכונים נוספים. למידע נוסף יש לעיין בעלון לרופא המעודכן.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://data.health.gov.il/drugs/index.html#!/medDetails/160%2019%2035153%2000 וניתן לקבלו מודפס על ידי פניה לחברת מדיצ'י מדיקל בע"מ, רח' המחשב 3 נתניה, בטלפון 09-7446170.

בברכה,

האלה ביאדסה - רוקחת ממונה