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MINISTRY OF HEALTH OF THE REPUBLIC OF TURKEY Medicines and Medical Devices Agency of Turkey

Number : E-24931227-000-420657 Subject : Intravenous Products Containing Immunoglobulin NORMAL

29.04.2021 DOSSIER

Ref: Our association announcement dated 27.04.2018, with No. E.79754.

Our association decision dated 27.04.2018, with No. E.79754, regarding intravenous products containing immunoglobulin has been updated. The relevant sections of the Summary of Product Characteristics and Package Leaflet of intravenous products containing Immunoglobulin shall be amended as follows. This announcement does not cover products containing immunoglobulin which are administered subcutaneously.

Therapeutic indications: 1. It is administered for replacement therapy in case of immunodeficiency: a) In primary (Congenital) immunodeficiencies with disrupted antibody production, b) In secondary immunodeficiencies (SID) in patients with severe or recurrent infections, with a proven specific antibody deficiency (SAD)* or with serum IgG level of <4 g/L, in whom antimicrobial treatment falls short. *Proven SAD: Failure to achieve at least 2-fold increase in the IgG antibody titer for pneumococcal polysaccharide and polypeptide antigen vaccines.

2. For an immunomodulatory effect: a) In immune thrombocytopenia (ITP) subjects with high hemorrhagic risk or in whom the platelet count needs to be increased before surgical intervention, b) In Guillain-Barré syndrome, c) In Kawasaki disease, d) In multifocal motor neuropathy disease, e) In the treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), f) In the treatment of Myasthenia Gravis with bulbar involvement.

Posology and mode of administration: The replacement therapy should be initiated and monitored under the supervision of a physician experienced in immunodeficiencies. The posology and frequency of administration vary depending on the indication. In replacement therapy, it may be necessary to adjust the dose individually depending on the pharmacokinetic and clinical response of the patient.

Replacement therapy in primary immunodeficiencies The dose should be adjusted to enable the serum IgG level measured before the next infusion to be consistently maintained at the level of minimum 500-600 mg/dL. This is required for 3-6 months as of the onset of treatment in order to achieve this balance. The recommended initial dose is minimum 0.2 g/kg administered once every 3-4 weeks following the infusion of 0.4-0.8 g/kg applied once. The average dose required for fixing the serum immunoglobulin level at 500-600 mg/dL is 0.2-0.8 g/kg. The dose interval changes in 3-4 weeks after achieving a steady serum level. The steady serum levels should be measured and evaluated together with the clinical response of the patient. Dose and/or dose interval adjustment may be considered for achieving a higher steady serum level in relation to the clinical response (e.g., frequency of infections).

Replacement therapy in secondary immunodeficiencies The recommended dose for secondary immunodeficiency is 0.2-0.4 g/kg administered once every 3-4 weeks.

Primary immune thrombocytopenia There are two alternative dosing schemes: • On the first day, a dose of 0.8-1 g/kg should be used; the dose may be repeated once within 3 days. • A dose of 0.4 g/kg/day should be used for a period of 2-5 days. The treatment may be repeated in case of relapse.

Guillain Barré Syndrome A dose of 0.4 g/kg/day should be administered for a period of 5 days.

Kawasaki Disease A single dose of 2 g/kg should be administered for 8-12 hours in combination with acetylsalicylic acid.

Multifocal Motor Neuropathy (MMN) disease Initial dose: a total of 2 g/kg in divided doses for a period of 2-5 days Maintenance dose: 1-2 g/kg once every 2-6 weeks

Chronic inflammatory demyelinating polyneuropathy (CIDP): The recommended initial dose should be a total dose of 2 g/kg in divided doses to be administered in 2-5 consequent days. In case of no response, a total dose of 1 g/kg should be administered for 1-2 days once every 3 weeks and the treatment should be discontinued in case no response is obtained at the end of 2 months. Maintenance dose: It should be administered at a total dose of 0.4-1 g/kg for 1-2 days once every 3 weeks if a response is obtained in the initial treatment. The dose providing the maximum benefit is recommended and the dose should be determined by the physician. The dose should be reduced until the lowest effective maintenance dose is identified, and the frequency of administration should be adjusted.

Myasthenia Gravis A dose of 0.4 g/kg/day for a period of 5 days in the critical phase where no response is obtained to other special treatments.

Pediatric population The posology for each indication in children and adolescents (0-18 years) does not differ from that of adults and should be adjusted according to the clinical endpoints in cases described above.

Mode of Administration: It should be administered intravenously.

Maximum infusion rate should be determined according to clinical study protocols for each product.

Additional Information on Special Populations Renal/Liver impairment: Acute renal impairment cases were reported in patients who received IVIG treatment. IVIG preparations should be administered in the lowest applicable infusion speed and dose in patients with risk of renal impairment (see Section 4.4). No additional information is provided in patients with liver impairment.

Pediatric population: As the posology is administered according to body weight and clinical response in each case mentioned above, the posology will not change in children and adolescents (0-18 years).

Geriatric population: Acute renal impairment cases were reported in patients who received IVIG treatment. It was reported there were certain risk factors in most of these cases including the fact that the patients were above the age of 65. Furthermore, there is clinical evidence demonstrating the connection between the administration of IVIG and thromboembolic events in highly risky patients. Therefore, attention should be paid when prescribing IVIG and administering the infusion in patients with risk factors for thrombotic events including advanced age and the lowest applicable infusion speed and dose should be used (see Section 4.4).

The SPC/PL applications related to the products in which abovementioned changes are made should be submitted to the Pharmacological Evaluation Unit within 1 month as of the date of publication of this association decision, the applications related to the products with ongoing registration process should be submitted to the Registration Unit, and this announcement should be taken into account for products for which registration application will be made. I hereby submit for your information and kindly request that the referred applications are not submitted to the Clinical Evaluation Unit.

Assoc. Prof. Dr. Tolga KARAKAN Deputy President of the Agency

Distribution: Association of Research-Based Pharmaceutical Companies Pharmaceutical Manufacturers Association of Turkey Turkish Pharmaceutical Industry Association Association of Innovator Pharmaceutical Companies Self-Care Products Association Turkish Foundation on Pharmaceuticals, Pharmacy, Health Sciences and Technologies

MINISTRY OF HEALTH OF THE REPUBLIC OF TURKEY Medicines and Medical Devices Agency of Turkey

Revoked.

Number : 77893119-000-E.79754 Subject : Intravenous preparations containing immunoglobulin NORMAL

27.04.2018 DOSSIER

In line with the decision adopted by the “Commission for the Evaluation of Medicinal Products for Human Use” at our Agency regarding intravenous products containing Immunoglobulin, the decision dated 22.03.2017, with No. E.65249, addressed at associations, has been updated. The relevant sections of the Summary of Product Characteristics and Package Leaflet of intravenous products containing Immunoglobulin should be arranged as follows.

Therapeutic indications: 3. It is administered for replacement therapy in case of immunodeficiency; c) In primary (congenital) immunodeficiencies with disrupted antibody production, d) In subjects diagnosed with Chronic Lymphocytic Leukemia, with hypogammaglobulinemia, in whom prophylactic antibiotics fall short and who develop recurrent bacterial infections, e) In subjects diagnosed with Multiple Myeloma, who have hypogammaglobulinemia, in whom pneumococcal immunization is insufficient and who develop recurrent bacterial infections, f) In children and adolescents with congenital AIDS and recurring infections, g) In subjects in whom hypogammaglobulinemia develops following allogenic hematopoietic stem cell transplantation. 2) For achieving an immunomodulatory effect; g) In immune thrombocytopenia (ITP) subjects with high hemorrhagic risk or in whom the platelet count needs to be increased before a surgical intervention, h) In Guillain-Barré syndrome, i) In Kawasaki disease, j) In multifocal motor neuropathy disease, k) In the acute treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), l) In the treatment of Myasthenia Gravis with bulbar involvement.

Posology and mode of administration: The replacement therapy should be initiated and monitored under the supervision of a physician experienced in immunodeficiencies.

Posology/frequency and duration of administration: The posology and frequency of administration varies depending on the indication.

In the replacement therapy, it may be necessary to adjust the dose individually depending on the pharmacokinetic and clinical response of the patient. The following dosing schemes are provided for guidance.

Replacement therapy in primary immunodeficiencies The dose should be adjusted to enable the serum IgG level measured before the next infusion to be consistently maintained at the level of minimum 500-600 mg/dL. This is required for 3-6 months as of the onset of treatment in order to achieve this balance. The recommended initial dose is minimum 0.2 g/kg administered once every 3-4 weeks following the infusion of 0.4-0.8 g/kg applied once. The average dose required for fixing the serum immunoglobulin level at 500-600 mg/dL is 0.2-0.8 g/kg. The dose interval changes in 3-4 weeks after achieving a steady serum level. The steady serum levels should be measured and evaluated together with the clinical response of the patient. Dose and/dose interval adjustment may be considered for achieving a higher steady serum level in relation with the clinical response (e.g., frequency of infections).

The recommended dose for the following cases is 0.2-0.4 g/kg administered once every 3-4 weeks:

In subjects diagnosed with Chronic Lymphocytic Leukemia, with hypogammaglobulinemia, in whom prophylactic antibiotics are insufficient and who develop recurrent bacterial infections,

In subjects diagnosed with Multiple Myeloma, who have hypogammaglobulinemia (IgG<500 mg/dL), in whom pneumococcal immunization is insufficient and who develop recurrent bacterial infections

In children and adolescents with congenital AIDS and recurring infections.

The recommended dose for the following cases is 0.2-0.4 g/kg administered once every 3-4 weeks. The steady serum levels should be kept above 500 mg/dL:

Patients with bacteremia following allogenic stem cell transplantation and recurring sinopulmonary infections, with an IgG level of <400 mg/dL.

Primary immune thrombocytopenia

There are two alternative dosing schemes: • On the first day, a dose of 0.8 g/kg should be used; the dose may be repeated once within 3 days. • A dose of 0.4 g/kg/day should be used for a

period of 2-5 days. The treatment may be repeated in case of relapse.

Guillain Barré Syndrome A dose of 0.4 g/kg/day should be administered for a period of 5 days.

Kawasaki Disease A single dose of 2 g/kg should be administered for 8-12 hours in combination with acetyl salicylic acid.

Multifocal Motor Neuropathy (MMN) disease

Initial dose: a total of 2 g/kg in divided doses for a period of 2-5 days Maintenance dose: 1-2 g/kg once every 2-6 weeks

Chronic inflammatory demyelinating polyneuropathy (CIDP)

The recommended initial dose should be a total dose of 2 g/kg in divided doses in 2-5 consequent days. In case of no response, a total dose of 1 g/kg should be administered for 1-2 days once every 3 weeks and the treatment should be discontinued in case no response is obtained at the end of 2 months. The maintenance dose should be a total dose of 0.4-1 g/kg for 1-2 days once every 3 weeks if no response is obtained to the initial treatment. The dose providing the maximum benefit is recommended and the dose should be determined by the physician. The dose should be reduced until the lowest effective maintenance dose is identified, and the frequency of administration should be adjusted.

Myasthenia Gravis A dose of 0.4 g/kg/day for a period of 5 days in the critical phase where no response is obtained to other special treatments.

Pediatric population The posology for each indication in children and adolescents (0-18 years) does not differ from that of adults and should be adjusted according to the clinical endpoints in cases described above. If this is tolerated well by the patient, the speed of administration should be increased gradually to maximum 4.8 mL/kg (see Section 4.4). The clinical data obtained on a limited number of patients demonstrated that primary immunodeficiency (PID) patients who could tolerate well the infusion speed of 4.8 mL/kg/hour in adults, could tolerate an infusion speed of 7.2 mL/kg/hour. See Section 4.4 for detailed information on use.

Mode of Administration: It should be administered intravenously. Human normal immunoglobulin should be administered intravenously at a rate of 0.3 mL/kg/hour within the first 30 minutes. If this is tolerated well by the patient, the administration speed may be gradually increased up to a maximum rate of 4.8 mL/kg (see Section 4.4). The clinical data obtained on a limited number of patients demonstrated that primary immunodeficiency (PID) patients who could tolerate well the infusion speed of 4.8 mL/kg/hour in adults, could tolerate an infusion speed of 7.2 mL/kg/hour. See Section 4.4 for detailed information on use. In case of need for dilution prior to infusion, IVIG may be diluted with a 5% glucose solution until reaching the final concentration (5% immunoglobulin) of 50 mg/mL. See Section 6.6 for detailed information on dilution. In case of occurrence of side effects associated with infusion, the infusion speed should be reduced or stopped.

Additional Information on Special Populations

Renal/Liver impairment: Acute renal impairment cases were reported in patients who received IVIG treatment. IVIG preparations should be administered in the lowest applicable infusion speed and dose in patients with risk of renal impairment (see Section 4.4). No additional information is provided in patients with liver impairment.

Pediatric population: As the posology is administered according to body weight and clinical response in each case mentioned above, the posology will not change in children and adolescents (0-18 years).

Geriatric population: Acute renal impairment cases were reported in patients who received IVIG treatment. It was reported there were certain risk factors in most of these cases including the fact that the patients were above the age of 65.

Furthermore, there is clinical evidence demonstrating the connection between the administration of IVIG and thromboembolic events in highly risky patients. Therefore, attention should be paid when prescribing IVIG and administering the infusion in patients with risk factors

for thrombotic events including advanced age and the lowest applicable infusion speed and dose should be used (see Section 4.4).

I hereby submit for your information and kindly request that relevant information is provided to the member companies of your Association on abovementioned topics in the registration, and SPC/PL applications submitted/to be submitted to us and that the companies holding the registration of “Parenteral products containing immunoglobulin” should apply to the “Clinical Evaluation Unit” with the SPC-PL samples in which abovementioned requirements regarding this topic are faithfully fulfilled until 01.06.2018.

Dr. Hakkı GÜRSÖZ President of the Agency

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