

RESTRICTED

Turkish Ministry of Health Turkish Medicines and Medical Devices Agency
Number: E-62820468-000-1546143 30.07.2024 Subject: Intravenous Products Containing Immunoglobulin

FILE

Reference: Union/association announcement regarding intravenous products containing immunoglobulin, dated 29.04.2021 and numbered E-24931227-000-420657.

The referenced union/association announcement regarding "Intravenous products containing immunoglobulin." has been updated. According to the decision taken; The relevant sections of the SmPC/PIL documents for intravenous products containing immunoglobulin should be revised as follows. This announcement does not cover products containing immunoglobulin administered subcutaneously.

SmPC 4.1. Therapeutic indications 1. For replacement therapy in cases of immunodeficiency: a) In primary (Congenital) immunodeficiencies where antibody production is impaired, b) In secondary immunodeficiencies (SIDs) with proven specific antibody deficiency (SAE) or serum IgG level <4 g/L and severe or recurrent infections in which antimicrobial therapy is inadequate Proven SAE: Failure to achieve at least a 2-fold increase in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

2. For immunomodulatory effect: a) In cases of immune thrombocytopenia (ITP) with a high risk of bleeding or in which the platelet count must be increased rapidly 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 Polyradiculoneuropathy (CIDP), f) In the treatment of myasthenic crisis

SmPC 4.2. Posology and method of administration (Note: For each product, information on special populations and other issues to be considered in administration should be determined according to the clinical study protocols or literature data of the product.) Replacement therapy should be initiated and monitored under the supervision of a specialist physician experienced in immunodeficiencies.

Posology/frequency and duration of administrations Posology and frequency of administrations vary according to indications.

In replacement therapy, the dose may need to be individually adjusted depending on the patient's pharmacokinetics and clinical response.

Replacement therapy in primary immunodeficiencies: The dose should be adjusted to ensure that the measured serum IgG level is maintained at a stable level of at least 600 mg/dL before the next infusion. In order to achieve this level, 3-6 months must pass from the beginning of the treatment. The recommended starting dose should be administered at least 0.2 g/kg every 3-4 weeks, following the initial infusion of 0.4-0.8 g/kg. The average dose required to keep the serum immunoglobulin level stable at 600 mg/dL is 0.2- 0.8 g/kg. Once a stable serum level is achieved, the dose interval varies between 3 and 4 weeks. Stable serum levels should be measured and evaluated along with the patient's clinical response. Depending on clinical response (e.g., frequency of infection), adjustment of dose and/or dosing interval may be considered to achieve higher stable serum levels.

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

In primary immune thrombocytopenia: There are two alternative dosage schemes: • It is administered at a dose of 0.8-1 g/kg on the first day, the same dose can be repeated once again within 3 days, or • It is administered at a dose of 0.4 g/kg/day for 2-5 days. In case of relapse, treatment may be repeated.

Guillain–Barré Syndrome: It is administered at a dose of 0.4 g/kg/day for 5 days.

Kawasaki Disease: 2 g/kg administered as a single dose for 8-12 hours and given in combination with acetyl salicylic acid.

In Multifocal Motor Neuropathy (MMN) disease: Starting dose: 2 g/kg total in divided doses for 2-5 days Maintenance dose: 1-2 g/kg every 2-6 weeks

Chronic inflammatory demyelinating polyneuropathy (CIDP): Starting dose: 2 g/kg total in divided doses over 2-5 consecutive days. In case of no response, a total dose of 1 g/kg over 1-2 days is given every 3 weeks, and if no response is obtained after 2 months, the treatment is discontinued. Maintenance dose: If a response to the initial treatment has been achieved, a total dose of 0.4- 1 g/kg is administered over 1-2 days every 3 weeks. The dose that provides maximum benefit is recommended and the dose should be determined by the physician. The dose is reduced and the frequency of administration adjusted until the lowest effective maintenance dose is determined.

Myasthenia Gravis: In cases of myasthenic crisis, it is administered at a dose of 0.4 g/kg/day for 5 days.

Paediatric population The posology in children and adolescents (0-18 years) does not differ from adults for any of the indications and is adjusted according to body weight.

Method of application: It is administered intravenously. (The maximum infusion rate should be determined for each product according to the clinical study protocols of the product and added under this heading.)

Additional information on special populations

Renal/Hepatic failure: Cases of acute renal failure have been reported in patients receiving IVIG therapy. In patients at risk of renal failure, IVIG preparations should be used at the lowest applicable infusion rate and dose (See Section 4.4). There is no additional information regarding patients with hepatic failure.

Paediatric population:

Since the posology in the indications reported above is given according to body weight and clinical response, the posology in children and adolescents (0-18 years) is not different from that in adults.

Gaeriatric population: Cases of acute renal failure have been reported in patients receiving IVIG therapy. Many of these cases were reported to have certain risk factors, including the person being over 65 years of age. There is also clinical evidence showing a link between IVIG administration and thromboembolic events in high-risk patients. Therefore, caution should be exercised when prescribing and infusing IVIG in patients with risk factors for thrombotic events, including advanced age, and it should be used at the lowest applicable infusion rate and dose.

PIL 1 What ... is and what is it used for ... belongs to a group of medicines called immunoglobulins. These medicines contain human antibodies that are also found in your blood. Antibodies help your body fight microbial diseases (infections). This group of medicines is used for replacement (completing what is missing) therapy in patients who do not have enough antibodies in their blood and are more frequently infected. It can also be used in patients who need more antibodies to treat certain inflammatory conditions (autoimmune diseases) that the immune system mistakenly develops against its own tissues. ... is used in the following cases: 1. For replacement therapy in cases where the immune system is inadequate (immunodeficiency); a) In patients who, by birth, are not able to produce antibodies or who produce little (primary congenital immunodeficiencies),

b) This medicine is used if the antibodies in your body are missing (IgG <4 g/L) or if you do not have an adequate immune response to some vaccines and antimicrobial treatment is inadequate and severe or recurrent infections develop. 2. For its immune regulating effect; a) In cases of immune thrombocytopenia (ITP) with a high risk of bleeding or in which the platelet count must be increased rapidly before surgical intervention, b) In Guillain-Barré syndrome seen in the peripheral nervous system, c) In case of a vascular inflammation disease (Kawasaki disease), which often occurs in children under five years of age and is characterized by fever, skin rash,

strawberry-like tongue, red and cracked lips, redness in the eyes, enlargement of the lymph node in the neck and can affect the coronary arteries in the heart, d) In a rare disease characterized by slow and progressive, non-symmetrical weakness in the legs without any sensory deficit (Multifocal Motor Neuropathy), e) In the acute treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), a chronic disease characterised by inflammation of the peripheral nerves causing progressive muscle weakness and/or numbness in the legs and arms, f) In worsening, known as crisis, of Myasthenia Gravis, which is a disease characterized by weakness of body muscles (especially eye muscles).

PIL 3. How to use...? section should be revised in line with the information in SmPC Posology and method of administration.

Please be informed and take necessary actions to submit your opinions, suggestions and contributions, if any, regarding the decision taken to the Clinical Evaluation Unit within 15 (fifteen) days as of the publication date of this union/association announcement, and not to submit any applications regarding “intravenous products containing immunoglobulin” to the Pharmacological Evaluation Unit and Licensing Unit during this period.

For the Agency President F. Handan ÖZTUNCA, Spec. Pharm. Head of Department

Distribution: Association of Research-Based Pharmaceutical Companies Pharmaceutical Manufacturers’ Association of Türkiye Turkish Pharmaceutical Industry Association Developmental Pharmaceutical Companies Association Health Products Association Pharmaceuticals, Pharmacy, Health Science and Technologies Foundation

This document has been signed with a secure electronic signature.

Document Verification Code: ZW56akIUQ3NRZlAxZW56ZW56ZlAxM0Fy Document Tracking Address: <https://www.turkiye.gov.tr/saglik-titck-ebys>

Turkish Ministry of Health Turkish Medicines and Medical Devices Agency

NORMAL Number: E-24931227-000-420657 29.04.2021 Subject: Intravenous Products Containing Immunoglobulin

FILE

Reference: Our union/association announcement dated 27.04.2018 and numbered E.79754.

The union/association decision numbered E.79754 dated 27.04.2018 regarding intravenous products containing immunoglobulin has been updated. The relevant sections of the Summary of Product Characteristics and Patient Information Leaflet documents of intravenous products containing immunoglobulin should be revised as follows. This announcement does not cover products containing immunoglobulin administered subcutaneously.

Therapeutic indications: 1. For replacement therapy in cases of immunodeficiency: a) In primary (Congenital) immunodeficiencies where antibody production is impaired, b) In secondary immune deficiencies (SIDs) in patients who develop severe or recurrent infections, in whom antimicrobial treatment is insufficient and in patients with proven specific antibody deficiency (SAE) or serum IgG level <4 g/L. Proven SAE: Failure to achieve at least a 2-fold increase in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

2. For immunomodulatory effect; a) In cases of immune thrombocytopenia (ITP) with a high risk of bleeding or in which the platelet count must be increased rapidly 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 Polyradiculoneuropathy (CIDP), f) In the treatment of Myasthenia Gravis with bulbar involvement.

Posology and method of application:

Replacement therapy should be initiated and monitored under the supervision of a specialist physician experienced in immunodeficiencies. Posology and frequency of administrations vary according to indications. In replacement therapy, the dose may need to be individually adjusted depending on the patient’s pharmacokinetics and clinical response.

Replacement therapy in primary immunodeficiencies: The dose should be adjusted to ensure that the measured serum IgG level is maintained at a stable level of at least 500-600 mg/ dL before the next infusion. In order to achieve this balance, 3-6 months must pass from the beginning of the treatment. CANCELLED

The recommended starting dose is a single infusion of 0.4-0.8 g/kg followed by at least 0.2 g/kg administered every 3-4 weeks. The average dose required to keep the serum immunoglobulin level stable at 500-600 mg/dL is 0.2-0.8 g/kg. Once a stable serum level is achieved, the dose interval varies between 3 and 4 weeks. Stable serum levels should be measured and evaluated along with the patient's clinical response. Depending on clinical response (e.g., frequency of infection), adjustment of dose and/or dosing interval may be considered to achieve higher stable serum levels.

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

In primary immune thrombocytopenia: There are two alternative dosage schemes: • It is administered at a dose of 0.8-1 g/kg on the first day, the dose can be repeated once in 3 days, or • It is administered at a dose of 0.4 g/kg/day for 2-5 days. In case of relapse, treatment may be repeated.

Guillain Barre Syndrome: It is administered at a dose of 0.4 g/kg/day for 5 days.

Kawasaki Disease: 2 g/kg administered as a single dose for 8-12 hours and given in combination with acetyl salicylic acid.

In Multifocal Motor Neuropathy (MMN) disease: Starting dose: 2 g/kg total in divided doses for 2-5 days Maintenance dose: 1-2 g/kg every 2-6 weeks

Chronic inflammatory demyelinating polyneuropathy (CIDP): Recommended starting dose: 2 g/kg total in divided doses over 2-5 consecutive days. In case of no response, a total dose of 1 g/kg is given over 1-2 days every 3 weeks, and if no response is obtained after 2 months, the treatment is discontinued. Maintenance dose: If a response to the initial treatment has been achieved, a total dose of 0.4-1 g/kg is administered over 1-2 days every 3 weeks. The dose that provides maximum benefit is recommended and the dose should be determined by the physician. The dose is reduced and the frequency of administration adjusted until the lowest effective maintenance dose is determined.

Myasthenia Gravis: It is administered at a dose of 0.4 g/kg/day for 5 days in the critical phase that does not respond to other specific treatments.

Paediatric population The posology in children and adolescents (0-18 years) does not differ from that in adults for any of the indications and is adjusted according to clinical outcomes in the above-mentioned situations.

Method of Application:

It is administered intravenously.

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

Additional Information on Special Populations: Renal/Hepatic failure: Cases of acute renal failure have been reported in patients receiving IVIG therapy. In patients at risk of renal failure, IVIG preparations should be used at the lowest applicable infusion rate and dose (See Section 4.4). There is no additional information regarding patients with hepatic failure.

Paediatric population: Since in all cases mentioned above the posology is given according to body weight and clinical response, the posology is unchanged in children and adolescents (0- 18 years).

Gaeriatric population: Cases of acute renal failure have been reported in patients receiving IVIG therapy. Many of these cases were reported to have certain risk factors, including the person being over 65 years of age. There is also clinical evidence showing a link between IVIG administration and thromboembolic events in high-risk patients. Therefore, caution should be

exercised when prescribing and infusing IVIG in patients with risk factors for thrombotic events, including advanced age, and it should be used at the lowest applicable infusion rate and dose (See Section 4.4).

The SPC/KT applications for the products that reflect the changes mentioned above should be submitted to the Pharmacological Evaluation Unit within 1 month as of the publication date of this union/association decision for review, the applications for the products whose registration process is ongoing should be submitted to the Licensing Unit, and this announcement should be considered for the products for which a registration application will be made. Please be informed and take necessary actions not to submit the said applications to the Clinical Evaluation Unit.

Assoc. Dr. Tolga KARAKAN Deputy President of the Institution

Distribution: Association of Research-Based Pharmaceutical Companies Pharmaceutical Manufacturers' Association of Türkiye Turkish Pharmaceutical Industry Association Developmental Pharmaceutical Companies Association Health Products Association Pharmaceuticals, Pharmacy, Health Science and Technologies Foundation

This document has been signed with a secure electronic signature.

Document Verification Code: ZW56akIUQ3NRZlAxZW56ZW56ZlAxM0Fy Document Tracking Address: <https://www.turkiye.gov.tr/saglik-titck-ebys>