

**SB TITCK 28.09.2023 METOTREKSAT İÇEREN ÜRÜNLERİN ROMATOLOJİK VE DERMATOLOJİK
ENDİKASYON VE POZOLOJİLERİ HAKKINDA_EN**

Turkish Ministry of Health Turkish Medicines and Medical Devices Agency

Number: E-24931227-000-1239366 28.09.2023 Subject: Rheumatologic and Dermatologic Indications and Posologies of Methotrexate-Containing Products

FILE Reference: a) Announcement to associations and unions, dated 17.12.2018 with reference number E.219564 b) Announcement to associations and unions, dated 05.12.2019 with reference number E.206228 c) Announcement to associations and unions, dated 17.04.2023 with reference number E- 62820468-000-1081834

The “Clinical Assessment Committee for Human Medicinal Products” of our Agency has reconsidered the aspects related to the use of methotrexate-containing products for rheumatologic and dermatologic indications, and the previous announcements, reference (a), (b) and (c) above, have been withdrawn. Because the announcement (a) dated 17.12.2018 with reference number E.219564 concerned pharmaceutical form and route of administration without specifying a methotrexate dose, the withdrawal of the announcement will be without prejudice to validity of the wording therein “Products presented in a 50 mg vial without a preservative are also approved for intratracheal use. The specific corrections must be also incorporated in the local package leaflet.” Methotrexate-containing products may be only administered by the subcutaneous or oral route at doses of 30 mg or less for rheumatologic indications and dermatologic indications. The indication and posology for rheumatologic conditions should be removed from [the product information of products administered at doses higher than the foregoing dose by the aforesaid routes of administration. The rheumatologic indications (i.e. rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis) and posology sections should be revised as follows for all doses at or below 30 mg for methotrexate-containing products administered by subcutaneous injection, and for products administered orally at a dose of 2.5 mg.

4.1 Therapeutic indications Rheumatologic indications: Indicated for the treatment of: - active rheumatoid arthritis in adult patients, - polyarthritic forms of active juvenile idiopathic arthritis (JIA) where adequate response to non-steroidal antiinflammatory drugs (NSAIDs) cannot be achieved, - active psoriatic arthritis.

4.2 Posology and method of administration Dosage in adult patients with rheumatoid arthritis The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously or orally. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week, without exceeding a weekly dose of 30 mg. However, doses exceeding 20 mg/week can be associated with significant increase in toxicity, specifically bone marrow suppression. Response to treatment may be expected after approximately 4 to 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in patients aged younger than 16 years with polyarthritic forms of juvenile idiopathic arthritis: The recommended dose is 10 – 15 mg/m² body surface area (BSA) once weekly. In the absence of response to treatment, the dose may be increased to 20 mg/m² BSA once weekly.

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However, an increased monitoring frequency is indicated, as doses exceeding 20 mg/week are associated with significant increase in toxicity, specifically bone marrow suppression, and the total weekly dose must not exceed 25 mg. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose. Pediatric or adolescent patients with juvenile idiopathic arthritis must in all cases be referred to a pediatric rheumatologist. Safety and efficacy has not been evaluated in children aged younger than 3 years.

The announcement to associations and unions, reference (b) above, dated 05.12.2019 with reference number E.206228 has been withdrawn, as methotrexate was specified among conventional treatments for dermatologic conditions. The dermatologic indications and posology sections should be revised as follows for all doses at or below 30 mg for methotrexate-containing products administered by subcutaneous injection, and for products administered orally at a dose of 2.5 mg. Dermatologic indications: 4.1 Therapeutic indications "Indicated for the treatment of moderate to severe psoriasis." It is recommended that a test dose of 5 – 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously. The dose may be increased gradually, but the weekly dose should not exceed 25 mg/week generally. However, doses exceeding 20 mg/week are associated with significant increase in toxicity, specifically bone marrow suppression. Response to treatment may be expected after 2 – 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose. The announcement (c) dated 17.04.2023 with reference number E-62820468-000-1081834 has been withdrawn, and copies of local SmPC/PL for the products concerned, incorporating the changes described above, must be submitted to the Pharmacologic Assessment Unit within one month after the issuing date of this announcement to associations and unions. Submissions related to products pending marketing authorization should be made to the Marketing Authorization Unit, and new applications for marketing authorization should align with this announcement. Such submissions must not be made to the Clinical Assessment Unit. For your information and appropriate action.

Dr. Asım Hocaoglu Agency President

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Turkish Ministry of Health Turkish Medicines and Medical Devices Agency

Number: E-62820468-000-1081834 17.04.2023 Subject: Methotrexate-containing products

FILE [WITHDRAWN]

Reference: a) Communication to associations dated 17.12.2018 with reference number E.219564 b) Communication to associations dated 05.12.2019 with reference number E.206228

Our letters, reference (a) and (b) above, concerning methotrexate-containing products, have been withdrawn upon by a decision of our Agency's "Clinical Assessment Committee for Human Medicinal Products." Methotrexate-containing products are administered only orally or subcutaneously at doses of 30 mg or lower for the treatment of rheumatologic conditions. The therapeutic indications and posology sections for all strengths of subcutaneous injection forms and 2.5 mg oral forms should be revised as described below for rheumatologic conditions; for products with strengths and posologies other than the foregoing, the therapeutic indication and posology sections for rheumatologic conditions must be removed.

4.1 Therapeutic indications Indicated for the treatment of: - active rheumatoid arthritis in adults, - polyarthritic forms of active juvenile idiopathic arthritis (JIA) with inadequate response to non-steroid antiinflammatory drugs (NSAIDs), or - active psoriatic arthritis.

4.2 Posology and method of administration Dosing in adults with rheumatoid arthritis: The recommended initial dose is 7.5 mg of subcutaneous or oral methotrexate, once weekly. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week, up to no more than a weekly dose of 30 mg. It should be noted that doses exceeding 20 mg/week are associated with a significant increase in toxicity, including in particular bone marrow suppression. Response to treatment may be expected after approximately 4 to 8 weeks. After the desired therapeutic outcome has been achieved, the dose should be reduced gradually to the lowest effective maintenance dose.

Dosing in children aged younger than 16 years with polyarthritic forms of juvenile idiopathic arthritis: The recommended dose is 10-15 mg/m² body surface area (BSA), once weekly by the oral or subcutaneous route. If response to treatment cannot be achieved, the dosage may be increased to 20 mg/m² (BSA) once a week. However, considering that doses exceeding 20 mg/week are associated with a significant increase in toxicity, including in particular bone marrow suppression, frequency of monitoring should be increased and the total weekly dose must not exceed 25 mg. Pediatric/juvenile patients with juvenile idiopathic arthritis should be always referred to a rheumatologist for treatment. Safety and efficacy have not been evaluated in children aged younger than 3 years.

Dosing in patients with psoriasis or psoriatic arthritis: It is recommended that a test dose of 5-10 mg be administered parenterally one week before initiating therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of subcutaneous or oral methotrexate, given once weekly. The dose may be gradually increased, but should not exceed a weekly dose of 30 mg.

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It should be noted that doses exceeding 20 mg/week are associated with a significant increase in toxicity, including in particular bone marrow suppression. Response to treatment may be expected after approximately 2 to 6 weeks. After the desired therapeutic outcome has been achieved, the dose should be reduced gradually to the lowest effective maintenance dose.

Please forward any opinions, suggestions or contributions concerning the decision above to the Clinical Assessment Unit within 10 (ten) days after the issuing date of this communication to associations, and abstain from submitting any applications to the Pharmacological Assessment Unit or the Registration Unit concerning "Methotrexate-Containing Products" in the meantime. For your information and appropriate action.

For the Agency President F. Handan Öztunca, M.Sc., Pharm. Department Head

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Turkish Ministry of Health Turkish Medicines and Medical Devices Agency [WITHDRAWN]
NORMAL Number: 62820468-000-E.206228 05.12.2019 Subject: Methotrexate-containing products for dermatologic indications

FILE

The therapeutic indications section for products in tablet or injectable forms containing “methotrexate” used for dermatologic indications at doses not exceeding 30 mg must be revised to read “Indicated for the treatment of moderate to severe psoriasis not responding to conventional therapies.” Examples of local SmPC/PL for the aforesaid products, incorporating the change described above, must be submitted to the Pharmacologic Assessment Unit for review by 13.01.2020. For your information and appropriate action.

Eray Kaplan Acting President of Agency

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Turkish Ministry of Health Turkish Medicines and Medical Devices Agency [WITHDRAWN]
NORMAL Number: 77893119-000-E.219564 17.12.2018 Subject: Methotrexate-containing products

FILE

Reference: Our announcement to associations and unions dated 02.11.2017 with reference number E.218411

The announcement to associations and unions on “methotrexate-containing products” has been withdrawn. Accordingly, the method of administration for products containing methotrexate active substances in prefilled syringe should be revised to subcutaneous administration, and for those in vial, to intravenous, intramuscular and intraarterial, in the relevant sections of the summary of products characteristics. Moreover, products presented in a 50 mg vial without a preservative are also approved for intratracheal use. The specific corrections must be also incorporated in the local package leaflet. Examples of local SmPC/PL for the aforesaid products, incorporating the changes described above, must be submitted to the Pharmacologic Assessment Unit for review by 11.01.2019. For your information and appropriate action.

Dr Hakkı Gürsöz President of Agency

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