September 26, 2022
Eisai Co., Ltd.
nippon medac Co., Ltd.

METOJECT® SUBCUTANEOUS INJECTION SYRINGE (METHOTREXATE) APPROVED IN JAPAN FOR RHEUMATOID ARTHRITIS

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and nippon medac Co., Ltd. (Headquarters: Tokyo, CEO: Hirohisa Iriyama, "nippon medac"), a subsidiary of medac Gesellschaft für klinische Spezialpräparate mbH (Headquarters: Germany) announced today that they have obtained manufacturing and marketing approval from the Japanese Ministry of Health, Labour and Welfare for the indication of the anti-rheumatic agent "Metoject® Subcutaneous Injection 7.5mg syringe 0.15mL, 10mg syringe 0.20mL, 12.5mg syringe 0.25mL and 15mg syringe 0.30mL" (methotrexate, "MTX") for the treatment of rheumatoid arthritis. Metoject will be the first self-administrable MTX subcutaneous injection formulation for rheumatoid arthritis in Japan. Based on the license agreement signed by Eisai and medac GmbH in May 2019, nippon medac will hold the marketing authorization of Metoject, while Eisai will be responsible for product distribution of Metoject in Japan.

The approval is based on the results of a Phase III clinical trial (MC-MTX.17/RA) conducted in Japan by nippon medac to compare the efficacy and safety of Metoject with that of oral MTX, which consisted of a double-blind phase and an extension phase. In the double-blind phase of this trial, 102 rheumatoid arthritis patients who had not been treated with MTX received either 7.5 mg/week of Metoject or 8 mg/week of oral MTX for 12 weeks in repeated doses. The primary endpoint of ACR20 response* at 12 weeks was 59.6% in the Metoject group versus 51.0% in the oral MTX group, indicating comparable efficacy. The adverse drug reaction incidence rates in this trial were 25.0% in the Metoject group and 34.0% in the oral MTX group. In the double-blind phase, the most common adverse drug reactions (incidence 5% and higher) were stomatitis (5.8%) in the Metoject group, and nausea (12.0%) and stomatitis (6.0%) in the oral MTX group.

It is reported that there are approximately 700,000 - 800,000 rheumatoid arthritis patients in Japan[1]. MTX is used as the first-line option for the treatment of rheumatic arthritis, but only the oral formulation is available in Japan. Eisai and nippon medac will provide a self-administrable subcutaneous injection as a new treatment option for rheumatoid arthritis patients in Japan as soon as possible, and will make further contributions to address the diversified needs of, and increase the benefits provided to, rheumatoid arthritis patients.

* ACR20 is a criterion developed by the American College of Rheumatology that measures improvement in clinical symptoms of rheumatoid arthritis. It expresses the percentage of patients who demonstrated a 20% or greater improvement in tender and swollen joint counts and at least three of the following five disease activity variables: patient assessment of pain; patient assessment of global disease activity; physician assessment of global disease activity; patient assessment of physical function; and chronic response protein or erythrocyte sedimentation rate concentrations.

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[Notes to editors]

1. About Metoject® Subcutaneous Injection Syringe (methotrexate)

Methotrexate (MTX) is positioned as the anchor drug for rheumatoid arthritis treatment.[2] For rheumatoid arthritis, it is believed that MTX regulates cell growth by inhibiting folate metabolism in lymphocytes and other cells, and also has an anti-inflammatory mechanism through the promotion of adenosine synthesis in vascular endothelial cells and other cells in synovial membranes. Metoject will be the first self-administrable MTX subcutaneous injection formulation for rheumatoid arthritis in Japan. It is approved in approximately 50 countries, primarily in Europe.

2. About the Phase III Clinical Trial (MC-MTX.17/RA)

In the double-blind phase of the domestic Phase III clinical trial (MC-MTX.17/RA), 102 patients with rheumatoid arthritis who had not been treated with MTX, were administered 7.5 mg/week of Metoject or 8 mg/week of oral MTX repeatedly for 12 weeks. The primary endpoint of ACR20 response at 12 weeks was 59.6% (31/52 patients) in the Metoject group versus 51.0% (25/49 patients) in the oral MTX group, indicating comparable efficacy. The adverse drug reaction incidence rates in the double-blind phase of this trial were 25.0% (13/52 patients) in the Metoject group and 34.0% (17/50 patients) in the oral MTX group. The most common adverse drug reactions (incidence 5% and higher) were stomatitis at 5.8% (3/52 patients) in the Metoject group, and nausea at 12.0% (6/50 patients) and stomatitis at 6.0% (3/50 patients) in the oral MTX group.

In the extension phase, a dose escalation clinical trial of Metoject at a maximum dose of 15 mg was conducted in a total of 109 patients, including 98 patients who were transferred from the double-blind phase (50 patients from the Metoject group and 48 patients from the oral group) and 11 additional patients previously treated with 8 mg of oral MTX. The maximum doses of 7.5 mg, 10 mg and 12.5 mg, and 15 mg were used in 7.3%, 12.8%, 12.8% and 67.0% of patients, respectively. In patients who were in the Metoject group during the double-blind phase, ACR20, ACR50 and ACR70 response at 64 weeks was 59.6% (31/52 patients), 51.9% (27/52 patients), and 42.3% (22/52 patients), respectively. The adverse drug reaction incidence rate in the extension phase was 54.1% (59/109 patients). The most common adverse drug reactions (incidence 5% and higher) were nausea at 13.8% (15/109 patients), stomatitis at 11.9% (13/109 patients), increased alanine aminotransferase at 9.2% (10/109 patients), and decreased white blood cell count and abnormal liver function both at 8.3% (9/109 patients).

3. About Eisai

Eisai's Corporate Concept is "to give first thought to patients and people in the daily living domain, and to increase the benefits that health care provides." Under this Concept (also known as our *human health care* (*hhc*) Concept), we aim to effectively achieve social good in the form of relieving anxiety over health and reducing health disparities. With a global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to create and deliver innovative products to target diseases with high unmet medical needs, with a particular focus in our strategic areas of Neurology and Oncology.

In addition, our continued commitment to the elimination of neglected tropical diseases (NTDs), which is a target (3.3) of the United Nations Sustainable Development Goals (SDGs), is demonstrated by our work on various activities together with global partners.
For more information about Eisai, please visit www.eisai.com (for global headquarters: Eisai Co., Ltd.), and connect with us on Twitter @Eisai_SDGs

4. About nippon medac

nippon medac Co., Ltd. was established in April 2016 as the Japanese subsidiary of medac GmbH. We are working to develop new drugs that can expand treatment options for diseases for which medical needs have not yet been fully met. We will work diligently to deliver quality drugs as quickly as possible to improve the quality of life of patients and their families in areas with high medical needs.

[1] Report from Study Committee on Rheumatoid Arthritis and Allergy
http://www.mhlw.go.jp/stf/houdou/2r9852000001nfao-att/2r9852000001nfdx.pdf

[2] Japan College of Rheumatology, Clinical practice guideline of methotrexate for patients with rheumatoid arthritis: 2016 update version