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Summary of Investigation Results

Methotrexate

October 12, 2022

Non-proprietary name

a. Methotrexate (oral dosage form) (preparations indicated for rheumatic disease)
b. Methotrexate (oral dosage form) (preparations indicated for malignant tumor)
c. Methotrexate (intravenous infusions)
d. Methotrexate (parenteral 5 mg preparations)
e. Methotrexate (parenteral 50 mg preparations)

Brand name (Marketing authorization holder)

a. Rheumatrex Capsules 2 mg (Pfizer Japan Inc.), and the others
b. Methotrexate Tablets 2.5 mg (Pfizer Japan Inc.)
c. Methotrexate Injection 200 mg, 1000 mg (Pfizer Japan Inc.)
d. Methotrexate Parenteral 5 mg (Pfizer Japan Inc.)
e. Methotrexate Parenteral 50 mg (Pfizer Japan Inc.)

Indications

See Attachment.

Summary of revisions

“Progressive multifocal leukoencephalopathy” should be added to the Clinically Significant Adverse Reactions section.

Investigation results and background of the revision

Cases involving progressive multifocal leukoencephalopathy reported in Japan and overseas were evaluated. Cases for which a causal relationship between methotrexate and

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progressive multifocal leukoencephalopathy was reasonably possible have been reported in Japan and overseas. As a result of consultation with expert advisors, MHLW/PMDA concluded that revision of Precautions was necessary.

Number of cases and patient mortalities involving progressive multifocal leukoencephalopathy reported in Japan and overseas during the previous 3 fiscal years

A total of 8 cases have been reported in Japan to date (including 6 cases for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported in Japan to date.
A total of 15 cases have been reported overseas to date (including 6 cases for which a causal relationship between the drug and event was reasonably possible).
A total of 12 patient mortalities have been reported overseas to date. (A causal relationship between the drug and deaths subsequent to the event could not be established for any of these cases.)

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

Attachment

	Non-proprietary name	Brand name	Indications
a.	Methotrexate (oral dosage form) (preparations indicated for rheumatic disease)	Rheumatrex Capsules 2 mg, and the others	·Rheumatoid arthritis ·Treatment of psoriasis vulgaris in patients who have had an inadequate response to local therapies ·Psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis ·Juvenile idiopathic arthritis associated with arthritic symptoms
b.	Methotrexate (oral dosage form) (preparations indicated for malignant tumor)	Methotrexate Tablets 2.5 mg	Remission of signs and symptoms of the following diseases: Acute leukaemia Chronic lymphocytic leukaemia, chronic myeloid leukaemia Trophoblastic diseases (choriocarcinoma, destructive hydatidiform mole, and hydatidiform mole)
c.	Methotrexate (intravenous infusions)	Methotrexate Injection 200 mg, 1000 mg	Methotrexate and leucovorin rescue therapy: Sarcomas (bone sarcomas, soft tissue sarcomas, etc.) Remission of leukaemic infiltration of central nervous system or testicles in patients with acute leukaemia Remission of malignant lymphoma infiltration of central nervous system

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	Non-proprietary name	Brand name	Indications
d.	Methotrexate (parenteral 5 mg preparations)	Methotrexate Parenteral 5 mg	<Conventional therapy with methotrexate> Remission of signs and symptoms of the following diseases: ·Acute leukaemia ·Chronic lymphocytic leukaemia ·Chronic myeloid leukaemia ·Trophoblastic disease (choriocarcinoma, destructive hydatidiform mole, and hydatidiform mole) <Cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy> ·Breast cancer <Methotrexate plus vinblastine, doxorubicin, and cisplatin (M-VAC) therapy> ·Urothelial carcinoma
e.	Methotrexate (parenteral 50 mg preparations)	Methotrexate Parenteral 50 mg	<Conventional therapy with methotrexate> Remission of signs and symptoms of the following diseases: ·Acute leukaemia ·Chronic lymphocytic leukaemia ·Chronic myeloid leukaemia

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	Non-proprietary name	Brand name	Indications
			·Trophoblastic diseases (choriocarcinoma, destructive hydatidiform mole, and hydatidiform mole) <CMF chemotherapy> ·Breast cancer <Methotrexate and folinate rescue therapy> ·Sarcomas (bone sarcomas, soft tissue sarcomas, etc.) ·Remission of leukaemic infiltration of central nervous system or testicles in patients with acute leukaemia ·Remission of malignant lymphoma infiltration of central nervous system <Sequential methotrexate and fluorouracil therapy> ·Enhancement of antitumor effect of fluorouracil against gastric cancer <M-VAC therapy> ·Urothelial carcinoma

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