



Summary of investigation results

Cyclophosphamide hydrate

March 24, 2015

Non-proprietary name

Cyclophosphamide hydrate

Brand name (Marketing authorization holder)

- a. Endoxan Injections 100 mg and 500 mg (Shionogi & Co., Ltd)
- b. Endoxan Tablets 50 mg and Endoxan Powder for oral use 100 mg (Shionogi & Co., Ltd)

Indications

- a. Endoxan Injections 100 mg and 500 mg
- Remission of signs and symptoms of the following diseases:
Multiple myeloma, malignant lymphoma (Hodgkin's disease, lymphosarcoma, and reticulosarcoma), lung cancer, breast cancer, acute leukaemia, polycythaemia vera, uterine cervical cancer, endometrial cancer, ovarian cancer, nervous system tumour (neuroblastoma and retinoblastoma), and bone tumour

It should be noted that this drug should be used concurrently with other antineoplastics for the following diseases:

- Chronic lymphocytic leukaemia, chronic myeloid leukaemia, pharyngeal cancer, gastric cancer, pancreatic carcinoma, hepatic cancer, colon cancer, testicular tumour, trophoblastic diseases (choriocarcinoma, destructive hydatidiform mole, and hydatidiform mole), rhabdomyosarcoma, and malignant melanoma
- Concomitant therapy with other antineoplastics for the following cancers:
Breast cancer (neoadjuvant or adjuvant chemotherapy in operable patients)
 - Pheochromocytoma
 - Pretreatment for hematopoietic stem cell transplantation for the following diseases:
Acute leukaemia, chronic myeloid leukaemia, myelodysplastic syndrome, severe aplastic anaemia, malignant lymphoma, genetic diseases (immunodeficiency, congenital metabolic disorders, and congenital blood diseases [Fanconi's anaemia, Wiskott–Aldrich syndrome, Hunter's syndrome, etc.])
 - The following treatment-resistant rheumatic diseases:
Systemic lupus erythematosus, systemic vasculitis (microscopic polyangiitis, Wegener's granulomatosis, polyarteritis nodosa, Churg–Strauss syndrome, aortitis syndrome, etc.),

polymyositis/dermatomyositis, scleroderma, mixed connective tissue disease, and refractory rheumatic diseases with vasculitis

b. Endoxan Tablets 50 mg and Endoxan Powder for oral use 100 mg

● Remission of signs and symptoms of the following diseases:

Multiple myeloma, malignant lymphoma (Hodgkin's disease, lymphosarcoma, and reticulosarcoma), breast cancer

Acute leukaemia, polycythaemia vera, lung cancer, nervous system tumour (neuroblastoma and retinoblastoma), and bone tumour

It should be noted that this drug should be used concurrently with other antineoplastics for the following diseases:

Chronic lymphocytic leukaemia, chronic myeloid leukaemia, pharyngeal cancer, gastric cancer, pancreatic carcinoma, hepatic cancer, colon cancer, uterine cervical cancer, endometrial cancer, ovarian cancer, testicular tumour, trophoblastic diseases (choriocarcinoma, destructive hydatidiform mole, and hydatidiform mole), rhabdomyosarcoma, and malignant melanoma

● The following treatment-resistant rheumatic diseases:

Systemic lupus erythematosus, systemic vasculitis (microscopic polyangiitis, Wegener's granulomatosis, polyarteritis nodosa, Churg–Strauss syndrome, aortitis syndrome, etc.), polymyositis/dermatomyositis, scleroderma, mixed connective tissue disease, and refractory rheumatic diseases with vasculitis

● Nephrotic syndrome (in patients who are not sufficiently responsive to appropriate treatment with corticosteroids)

Summary of revision

‘Rhabdomyolysis’ should be added in the Clinically significant adverse reactions section.

Background of the revision and investigation results

Cases of adverse events suggestive of rhabdomyolysis have been reported in patients treated with cyclophosphamide hydrate injections in Japan. Following an investigation based on the opinions of expert advisors and available evidence, the MHLW/PMDA concluded that revision of the package insert was necessary.

Although there are no domestic cases of adverse events suggestive of rhabdomyolysis in which causality to cyclophosphamide hydrate tablets could not be ruled out, rhabdomyolysis may occur in patients treated with cyclophosphamide hydrate tablets. Following an investigation



This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

based on the opinions of expert advisors and available evidence, the MHLW/PMDA concluded that revision of the package insert was necessary.

The number of reported adverse reactions and fatal cases in the last 3 fiscal years in Japan

a. Endoxan Injections 100 mg and 500 mg

A case of an adverse event suggestive of rhabdomyolysis has been reported. Causality could not be ruled out in this case. No fatalities have been reported.

b. Endoxan Tablets 50 mg and Endoxan Powder for oral use 100 mg

No adverse event suggestive of rhabdomyolysis has been reported.