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Report on Investigation Results

June 15, 2018
Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name] Azathioprine
[Branded name] a. Imuran Tablets 50 mg, b. Azanin Tablets 50 mg
[Approval holder] a. Aspen Japan K.K., b. Mitsubishi Tanabe Pharma Corporation
[Indications] See Appendix
[Dosage and administration] See Appendix
[Remarks] Nothing noteworthy
[Investigating office] Office of Safety II

II. Investigation background

Azathioprine has been shown to be teratogenic in reproductive toxicity studies using rabbits, rats, and mice. Administration to “pregnant women or women who may be pregnant” is contraindicated in the current package insert of the drug.

In May 2018, the Information Provision Working Group Committee at the Japan Drug Information Institute in Pregnancy (the Working Group), which was established as a project by the Ministry of Health, Labour and Welfare (MHLW) for the purpose of reflecting the latest knowledge with respect to pregnancy and other related issues in pharmaceutical product package inserts, concluded that administration of preparations containing azathioprine to “pregnant women or women who may be pregnant” should be removed from the Contraindications section of the package insert and should be replaced with a precaution stating that such women “should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks” as an appropriate revision of the package insert.

In response to a report prepared by the Working Group, on May 29, 2018, the Pharmaceutical Safety Division of the Pharmaceutical Safety and Environmental Health Bureau at MHLW requested an investigation of the revision of precautions regarding preparations containing azathioprine proposed by the Working Group based on its report to be conducted by the Pharmaceuticals and Medical Devices Agency (PMDA). PMDA accordingly evaluated the proposed revision of the azathioprine package insert.

PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion 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).

III. PMDA Investigation

The Working Group, taking into account the latest knowledge and the current medical environment, concluded in its report that revision of the package insert is appropriate for

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preparations containing azathioprine, as follows:

1. Contraindication of the administration to “pregnant women or women who may be pregnant” in the current package insert

A precaution stating that such women “should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks” should be included in the 6. Use during Pregnancy, Delivery, or Breastfeeding section and language of "pregnant women or women who may be pregnant” should be removed from the Contraindications section.

2. Addition of risk information related to pregnancy

The current version states, in the 6. Use during Pregnancy, Delivery, or Breastfeeding section, that “azathioprine has been shown to be teratogenic in non-clinical studies and that chromosomal anomalies in lymphocytes in neonates, premature birth cases or low birth weight baby, and miscarriage have been observed in clinical practice.” In addition to such statements, it is appropriate to add, considering the clinical reports evaluated by the Working Group together with statements of the overseas package inserts, language concerning the reports on placental transfer in humans, decrease in blood cell count or immunocompetent cell counts observed in the neonate.

3. Revision of precaution regarding contraception

Language concerning contraception in the 2. Important Precautions section should be removed and a precaution that women should be instructed to avoid pregnancy whenever possible during treatment, women with reproductive potential, or men having partners with reproductive potential should be informed of the risks associated with this drug.

PMDA concluded, based on the report of the Working Group and its own investigation, the proposed revision as the result of discussion in the Group may be properly adopted with some modifications of language.

The above conclusion reached by PMDA was supported by its expert advisors.

VI. Overall Evaluation

PMDA concluded that precautions in the package insert should be appropriately revised as follows:

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[Proposed revision] Azathioprine

Revised language is underlined

Current version	Proposed revision
[Contraindications] (This drug should not be administered to the following patients) (1)-(3) (snip) (4) Pregnant women or women who may be pregnant (Refer to the Use during Pregnancy, Delivery, or Breastfeeding section.)	[Contraindications] (This drug should not be administered to the following patients) (1)-(3) (snip) (deleted)
[Precautions] 2. Important Precautions (1)-(5) (snip) (6) Cases of neonates born with chromosomal anomalies in lymphocytes to women who received azathioprine during pregnancy have been reported. Teratogenic effects have been reported in animal studies (rabbits, rats, mice) [1) – 3)]. Both men and women receiving this drug should be instructed to use contraception (Refer to the Use during Pregnancy, Delivery, or Breastfeeding section.) (7), (8) (snip) 6. Use during Pregnancy, Delivery, or Breastfeeding (1) This drug should not be administered to pregnant women or women who may be pregnant (Cases of neonates born with	[Precautions] 2. Important Precautions (1)-(5) (snip) (deleted) (6), (7) (snip) 6. Use during Pregnancy, Delivery, or Breastfeeding (1) Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are

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chromosomal anomalies in lymphocytes have been reported. Cases of premature birth and low birth weight baby have been reported in women who received this drug during pregnancy [particularly in women who concomitantly received adrenocorticosteroids] Miscarriage subsequent to administration of this drug to either parent has also been reported. Teratogenic effects have been reported as a result of animal studies [rabbits, rats, mice] 1)–3).)	considered to outweigh the potential risks. Women with reproductive potential should be informed of the risks associated with this drug. Women should be counseled to avoid pregnancy whenever possible while receiving this drug. [Placental transfer in humans has been reported1). Cases of neonates born with chromosomal anomalies in lymphocytes, and congenital anomalies, decrease in blood cell count or immunocompetent cell counts observed in the neonates have been reported1)–4). Cases of premature birth or low birth weight baby have been reported in women who received this drug during pregnancy (particularly in women who concomitantly received adrenocorticosteroids.) Miscarriage subsequent to administration of this drug to either parent has also been reported. Teratogenicity has been reported as a result of animal studies (rabbits, rats, mice) 5)-7).]
(newly added)	(2) Men having partners with reproductive potential should be informed of the risks associated with this drug if they are to be administered this drug and should be counseled to avoid pregnancy of their partners whenever possible while they are receiving this drug. [Genotoxicity has been reported in bacterial reverse mutation studies and micronucleus studies in mice and rats 8)–10).]
(2) Women should be instructed to stop breastfeeding if they are to be administered this drug. [Safety in breast-feeding women has not been established]	(3) Women should be instructed to stop breastfeeding if they are to be administered this drug. [Safety in breast-feeding women has not been established]
(References)	(References)

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(newly added) 1)-3) (snip) (newly added) 4)-29) (snip)	1) Jharap B, et al. :Gut, 63, 451-457 (2014) 2) Cleary BJ, et al. : Birth Defects Res A Clin Mol Teratol, 85, 647-654 (2009) 3) DeWitte DB, et al. :J Pediatr, 105, 625-628 (1984) 4) Ono E, et al.:Am J Transplant, 15, 1654-1665 (2015) 5)-7) (snip) 8) Speck WT, et al. :Cancer Res, 36, 108-109 (1976) 9) Henderson L, et al. :Mutat Res, 291, 79-85 (1993) 10) van Went GF. :Mutat Res, 68, 153-162 (1979) 11)-36) (snip)

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Appendix

List of drugs investigated

As of June 2018

Branded name	Marketing authorization holder	Indications	Dosage and administration
a. Imuran Tablets 50 mg b. Azanin Tablets 50 mg	a. Aspen Japan K.K b. Mitsubishi Tanabe Pharma Corporation	a., b. 1. Prophylaxis of organ rejection in kidney, liver, heart, and lung transplants 2. Remission induction or remission maintenance therapy for steroid-dependent Crohn’s disease and remission maintenance therapy for steroid-dependent ulcerative colitis 3. Treatment-resistant cases of the following rheumatic diseases: systemic vasculitis (microscopic polyangiitis, Wegener's granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome, and aortitis syndrome etc.), systemic lupus erythematosus (SLE), polymyositis, dermatomyositis, scleroderma, mixed connective tissue disease, and refractory rheumatic diseases	a., b. 1. Transplantation The usual daily dose for adults and children administered orally is as mentioned below. The dose should be carefully adjusted in order to obtain the optimal therapeutic effects, since the tolerable dosage and effective dosage of azathioprine can vary with individual patients. (1) Kidney transplantation The initial dose is 2-3 mg/kg of azathioprine. The maintenance dose is 0.5-1 mg/kg of azathioprine. (2) Liver, heart, and lung transplantation The initial dose is 2-3 mg/kg of azathioprine. The maintenance dose is 1-2 mg/kg of azathioprine. 2. Remission induction or remission maintenance therapy for steroid-dependent Crohn’s disease and remission maintenance therapy for steroid-dependent ulcerative colitis The usual daily dose for adults and children is 1-2 mg/kg of azathioprine administered orally (usually for adults, 50 - 100 mg). 3. Systemic vasculitis (microscopic polyangiitis, Wegener's granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome, and aortitis syndrome etc.), systemic lupus

Branded name	Marketing authorization holder	Indications	Dosage and administration
			erythematosus (SLE), polymyositis, dermatomyositis, scleroderma, mixed connective tissue disease, and refractory rheumatic diseases The usual daily dose for adults and children is 1-2 mg/kg administered orally. The dose may be adjusted depending on the symptoms of the patients. The daily dose should not exceed 3 mg/kg.