

Summary of Investigation Results

Azathioprine

Non-proprietary name Brand name	Non-proprietary name	Brand name (marketing authorization holder)
	Azathioprine	a. AZANIN Tablets (Fuji Pharma Co.,Ltd.) b. Imuran Tablets 50mg (Sandoz Pharma K.K.)
Japanese market launch	a. August 1978 b. October 1969	
Indications	a., b. ☐ Prophylaxis of organ rejection in kidney, liver, heart, and lung transplants ☐ Remission induction or remission maintenance therapy for steroid-dependent Crohn's disease and remission maintenance therapy for steroid-dependent ulcerative colitis ☐ 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 ☐ Autoimmune hepatitis	
Summary of revisions	“Posterior reversible encephalopathy syndrome” and “Sinusoidal obstruction syndrome (SOS) /Veno-occlusive disease (VOD)” should be added to the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS.	
Investigation results and background of the revision	Cases involving posterior reversible encephalopathy syndrome and sinusoidal obstruction syndrome (SOS) /veno-occlusive disease (VOD) were evaluated. Cases in which a causal relationship between Azathioprine and posterior reversible encephalopathy syndrome and sinusoidal obstruction syndrome (SOS) /veno-occlusive disease (VOD) was reasonably possible have been reported. As a result of consultation with expert advisors regarding the causality assessment of the cases and the necessity of revision of PRECAUTIONS, the MHLW/PMDA concluded that revision of PRECAUTIONS was necessary	
Reference:	Japan	Overseas

Number of cases* involving posterior reversible encephalopathy syndrome and sinusoidal obstruction syndrome (SOS) /veno-occlusive disease (VOD) reported in Japan and overseas	< Posterior reversible encephalopathy syndrome >※¹ A total of 13 cases have been reported to date (including 7 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. <Sinusoidal obstruction syndrome (SOS) /veno-occlusive disease (VOD) >※² A total of 1 case have been reported to date (including 1 case in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date.	< Posterior reversible encephalopathy syndrome > — <Sinusoidal obstruction syndrome (SOS) /veno-occlusive disease (VOD) >※² A total of 12 cases have been reported to date (including 10 cases in which a causal relationship between the drug and the event was reasonably possible). A total of 2 deaths have been reported to date (including 1 case in which a causal relationship between the drug and the death following the event was reasonably possible).
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※¹: Cases collected in PMDA's safety database for drugs. Among cases reported to the regulatory authority with MedDRA SMQ (narrow) "Noninfectious encephalopathy/delirium", cases suspected to be attributable to alternative causes of encephalopathy (e.g., hepatic encephalopathy or influenza encephalopathy) were excluded.

※²: Cases collected in PMDA's safety database for drugs. Among cases reported to the regulatory authority with MedDRA PTs "Hepatic vein embolism," "Hepatic vein stenosis," "Hepatic vein thrombosis," "Hepatic vein occlusion," "Portal hypertension," "Portal vein embolism," "Portal vein stenosis," "Portal vein thrombosis," "Portal vein occlusion," "Porto-sinusoidal vascular disorder," "Venocclusive liver disease," "Non-cirrhotic portal hypertension", cases meeting the Probable or higher according to European Society for Blood and Marrow Transplantation (EBMT)※³ diagnostic criteria for SOS/VOD were retrieved.

※³: Mohty M, Malard F, Alaskar AS, et al., Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a refined classification from the European society for blood and marrow transplantation (EBMT), Bone Marrow Transplant., 58, 749-754, 2023, Springer Nature

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).