SAFETY ALERT

DRAP SAFTEY ALERT NO. 62

Safety Alert of Risk of Intrahepatic Cholestasis of Pregnancy with Thiopurines

Date: 3rd February, 2026

Target Audience.

- Provincial Health Departments/Provincial PV Centres;
- Manufacturers and importers of Thiopurines;
- Healthcare Professionals; and
- Patients

Background.

The MHRA on 15th of May, 2025, through a Drug Safety Update informed that Intrahepatic cholestasis of pregnancy (ICP) has been rarely reported in patients treated with azathioprine products and is believed to be a risk applicable to all drugs in the thiopurine class (azathioprine, mercaptopurine and tioguanine). Cholestasis of pregnancy associated with thiopurines tends to occur earlier in pregnancy than non-drug-induced cholestasis of pregnancy, and elevated bile acid levels may not be reduced with ursodeoxycholic acid.

A risk of developing intrahepatic cholestasis of pregnancy (ICP) has been identified from a small number of case reports in the scientific literature. ICP has been reported in some pregnant patients treated with azathioprine and mercaptopurine, and, due to similar metabolic pathways utilised by thiopurines, this risk is believed to be applicable to all drugs in the thiopurine class (azathioprine, mercaptopurine and tioguanine). For context, the occurrence of thiopurine-induced ICP is thought to occur much less frequently than non-thiopurine-induced ICP, which occurs in roughly 1 in every 150 pregnancies.

Case reports occur mainly in patients being treated for IBD or in transplant recipients. In many cases, ICP associated with thiopurine treatment has developed earlier in pregnancy than typical non-drug-induced ICP, and in some cases, bile acid levels did not reduce with ursodeoxycholic acid. However, in some cases, improvement in bile acid and liver function did occur on stopping thiopurine. Reported cases were often serious, with some resulting in fetal death. However, reporting bias may result in the more serious cases being reported.

Early diagnosis and discontinuation or dose reduction of the thiopurine may minimise adverse effects on the fetus. A thorough assessment of the important benefits of treatment of the underlying disease against the risk of thiopurines to the mother and the effects of ICP on the fetus should be performed if ICP is confirmed. In patients with ICP, measure serum bile acids to identify

pregnancies at particular risk of spontaneous preterm birth (≥40uM) or stillbirth (non-fasting serum bile acids ≥100uM). Patients should be made aware of the signs and symptoms of ICP, which include intense itching without a rash, nausea, and loss of appetite, and advised to seek healthcare professional advice immediately if they experience these symptoms.

The Saudi Food & Drug Authority (SFDA) on 13-06-2025, also through a safety communication, announced that the product information for thiopurines, including azathioprine and mercaptopurine, will be updated to include the potential risk of intrahepatic cholestasis of pregnancy (ICP). ICP, also known as obstetric cholestasis, is a liver disorder that occurs during pregnancy, characterised by intense itching and elevated bile acid levels. It was informed that globally, post-marketing cases of ICP have been reported in women treated with thiopurine drugs for Crohn's disease (CD) or ulcerative colitis (UC) or systemic lupus erythematosus (SLE) during pregnancy, based on which the SFDA took the decision. The SFDA advises healthcare professionals to closely monitor pregnant patients using thiopurines and educate patients to seek medical help if they develop signs and symptoms of ICP, such as itching, dark urine and pale stools.

Action in Pakistan.

The case was discussed in the 6th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) held on 31st of December, 2025 which decided as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 that registration holders are required to include the risk of intrahepatic cholestasis of pregnancy, with a frequency of "not known", in the Adverse Drug Reactions and Warnings and Precautions sections of the SmPC/label of thiopurine-containing medicines registered in Pakistan, in line with the SmPC approved by MHRA.

Therapeutic Good Affected.

Name: The thiopurines include Azathioprine, 6-Mercaptopurine and Thioguanine (also known as tioguanine). Their uses are in anticancer indications, primarily leukaemia, and immunosuppression to treat inflammatory disorders such as inflammatory bowel diseases (IBD) and to increase graft survival following organ transplant.

Advice for Healthcare Professionals.

Healthcare professionals are informed that cholestasis of pregnancy has rarely been reported in association with Azathioprine therapy. This risk is believed to also apply to the other thiopurine drugs, mercaptopurine and thioguanine. It may occur earlier in pregnancy than non-drug-induced cholestasis of pregnancy, and it may not respond to ursodeoxycholic acid. Withdrawal or dose reduction of the thiopurine drug may improve liver function tests. Healthcare professionals are advised to remain vigilant to signs and symptoms of ICP in pregnant patients taking thiopurines and discuss any concerns with clinicians managing the patient's immunosuppressant therapy and

a hepatologist, as necessary. If cholestasis of pregnancy occurs, a case-by-case assessment is required to determine the appropriate course of action. In patients with ICP, measure serum bile acids to identify pregnancies at particular risk of spontaneous preterm birth (≥40uM) or stillbirth (non-fasting serum bile acids ≥100uM).

Advice for patients.

Patients are advised to talk with their doctor or midwife immediately if they experience symptoms of cholestasis of pregnancy, which include intense itching without a rash, nausea, and loss of appetite. Patients are also advised not to stop taking their medication unless advised to do so by their doctor or midwife.

Guidelines for reporting Adverse Drug Reactions (ADRs).

Healthcare professionals and patients are requested to report any adverse drug reaction/ events with Thiopurines (Azathioprine, 6-Mercaptopurine and Thioguanine) and/or any other medicines to the National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP), through the Med Vigilance E-Reporting System (E-forms) available on the DRAP website. Similarly, adverse events and adverse drug reactions can also be reported through the VigiMobile App by scanning the following QR code, which can also be downloaded (add to home screen) in the mobile:

References.

- Minutes of the 6th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC), DRAP.
- MHRA-UK: Drug Safety Update of Thiopurines and intrahepatic cholestasis of pregnancy
- SFDA Safety communication: Potential Risk of Intrahepatic Cholestasis of Pregnancy (ICP) Associated with the Use of Thiopurines