SAFETY ALERT

DRAP SAFTEY ALERT NO. 26

Risk of Reduced Vitamin B12 Level with Metformin and Metformin-Containing Medicines

Date: 23rd of November, 2022

Target Audience:

- Manufacturers and importers of metformin and metformin-containing medicines;
- Healthcare Professionals; and
- Patients, consumers or caregivers.

Background:

The Medicine and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom on 20th June, 2022 through a drug safety update informed that decreased vitamin B12 levels, or vitamin B12 deficiency, is now considered a common side effect in patients on metformin treatment, especially in those receiving a higher dose or longer treatment duration and in those with existing risk factors. It was informed that the known adverse drug reaction of vitamin B12 deficiency was recently reviewed for the brand leader Glucophage (Metformin) within Europe with input from the MHRA. After this review, the MHRA agreed that the product information for patients and healthcare professionals for medicines containing metformin should be updated to state that vitamin B12 deficiency is a common adverse drug reaction, and may affect up to 1 in 10 people who take it. The product information for other medicines containing metformin will also be updated including fixed-dose combination products containing metformin.

The product information has also been updated to note that the risk of this adverse reaction occurring increases with increasing metformin dose and treatment duration and in patients with risk factors known to cause vitamin B12 deficiency such as:

i. baseline vitamin B12 levels at the lower end of the normal range;
ii. conditions associated with reduced vitamin B12 absorption (such as elderly people and those with gastrointestinal disorders such as total or partial gastrectomy, Crohn's disease and other bowel inflammatory disorders, or autoimmune conditions);
iii. diets with reduced sources of vitamin B12 (such as strict vegan and some vegetarian diets);
iv. concomitant medications that are known to impair vitamin B12 absorption (including proton pump inhibitors or colchicine); and
v. genetic predisposition to vitamin B12 deficiency, such as intrinsic factor receptor deficiency (Imerslund-Gräsbeck syndrome) and transcobalamin II deficiency.

Action in Pakistan:-

Accordingly, the case of the risk of reduced vitamin B12 level with metformin and metformin-containing medicines was discussed in the 1st meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the National Pharmacovigilance Centre (NPC), Division of Pharmacy Services, Drug Regulatory Authority of Pakistan (DRAP). The PRAEC after discussion decided as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 (reliance mechanism) to update prescribing information of Metformin and other medicines containing Metformin to state that vitamin B12 deficiency is an adverse drug reaction with Metformin use and the risk of this adverse reaction occurrence increases with increasing metformin dose and treatment duration and in patients with risk factors known to cause vitamin B12 deficiency.

Therapeutic Goods Affected:-

Name: **Metformin and metformin-containing medicines**

Metformin is a medicine authorized to treat type 2 diabetes mellitus and to help prevent type 2 diabetes in patients at high risk of developing it.

Advice for patients:-

Patients who have low vitamin B12 levels or elderly patients and those with gastrointestinal disorders such as total or partial gastrectomy, Crohn's disease and other bowel inflammatory disorders, or autoimmune conditions or those patients who have a genetic predisposition to vitamin B12 deficiency are advised to talk to their healthcare professionals during the treatment with metformin and metformin containing medicines.

Advice for healthcare professionals:-

Healthcare professionals are informed that metformin can commonly reduce vitamin B12 levels in patients, which may lead to vitamin B12 deficiency. The risk of low vitamin B12 levels increases with higher metformin doses, longer treatment duration, and in patients with risk factors for vitamin B12 deficiency. Healthcare professionals are advised to test vitamin B12 serum levels if deficiency is suspected and also consider periodic vitamin B12 monitoring in patients with risk factors of vitamin B12 deficiency.

Guidelines for reporting of Adverse Drug Reactions (ADRs):-

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with metformin and metformin-containing medicines to the National Pharmacovigilance Centre**,** Drug Regulatory Authority of Pakistan through Med Vigilance E-Reporting system available on the DRAP website.

Similarly, ADRs can also be reported through Med Safety App which is available for download from App Store (for iOS devices) and Google Play (for Android devices).

References:

1. Minutes of 1st meeting of Pharmacovigilance Risk Assessment Expert Committee of the DRAP.
2. MHRA update on Metformin and reduced vitamin B12 levels: new advice for monitoring patients at risk.