SAFETY ALERT

DRAP SAFTEY ALERT NO. 32

# Safety Alert of Potential Risk of Abuse, Dependence and Withdrawal with Benzodiazepines

**Date: 10th of April, 2023.**

## Target Audience:

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

## Background:

The Medsafe of Newzealand in June 2022 reminded prescribers about the update to the product information for benzodiazepines regarding the potential risks of abuse, dependence and withdrawal, even when taken at recommended dosages. As per information, the dispensing data of New Zealand showed that diazepam and lorazepam are the most dispensed benzodiazepines. The total amount of these medicines that were dispensed for all indications increased in the period between 2016 and 2020 which suggested frequent and/or long-term use. As per data shared, between August 1969 and March 2022, the Centre for Adverse Reactions Monitoring (CARM) received 23 case reports of withdrawal and/or dependence with the use of benzodiazepines. Clonazepam (nine cases) was the most frequently reported benzodiazepine, followed by lorazepam (five), diazepam (three) and triazolam (three). Therefore, Medsafe advised healthcare professionals to counsel patients about the risks of benzodiazepines when initiating treatment, regularly review the ongoing need for treatment, and gradually taper benzodiazepines following continuous or high-dose use to reduce the risk of withdrawal reactions.

Back in September 2020 and also through Podcast in January 2022, the United States Food and

Drug Administration (US-FDA) through a Drug Safety Communication informed that the agency is requiring Boxed warnings of all benzodiazepines drugs to include information about the risk of abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioid pain relievers, alcohol, or illicit drugs. Physical dependence can occur when benzodiazepines are taken steadily for several days to weeks, even as prescribed. Stopping these medicines abruptly or reducing the dosage too quickly can result in withdrawal reactions, including seizures, which can be life-threatening. The boxed warning also states that concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Therefore, these medicines may be reserved concomitant prescribing for use in patients for whom alternative treatment options are inadequate.

## Action in Pakistan:

Accordingly, the case of the potential risk of abuse, dependence and withdrawal with benzodiazepines was discussed in the 2nd 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) which after detailed deliberation and discussion decided as per Rule 10 (1) (h) (iv) & (vi) of Pharmacovigilance Rules, 2022 to update the prescribing information/safety specification of benzodiazepines containing medicines by including information related to abuse, misuse, addiction and withdrawal in the warning and precaution section and to create a boxed warning as per FDA format.

## Therapeutic Goods Affected.

Name: **Benzodiazepines such as Diazepam, Alprazolam, Clonazepam, Lorazepam, Bromazepam etc.**

Benzodiazepines are indicated to treat generalized anxiety disorders, insomnia, seizures, social phobia and panic disorders.

## Advice for patients.

Patients are advised to inform healthcare professionals about all the prescription and over-the-counter (OTC) medicines that the patient are taking or any other substances the patient is using, including alcohol. Benzodiazepines should be taken exactly as prescribed by healthcare professionals. If there is a need to discontinue the medicines, discuss a plan for slowly decreasing the dose and frequency of benzodiazepine(s) with your healthcare professional. A healthcare professional should be immediately contacted if any withdrawal symptoms are experienced.

## Advice for healthcare professionals.

Healthcare professionals are advised to assess each patient's risk for abuse, misuse, and addiction before prescribing and throughout treatment. Likewise, caution should be taken when prescribing benzodiazepines to patients with a history of alcohol or drug abuse. When prescribing a benzodiazepine for anxiety or insomnia, it must be ensured that the patient understands that these medicines are intended for short-term use (2-4 weeks). Ongoing use of benzodiazepines may lead to dependence that increases with the dose and duration of treatment and in patients with a history of alcohol or drug abuse or a marked personality disorder. Therefore, healthcare professionals should regularly review the ongoing need for treatment, particularly if the patient is at high risk of dependence. Abrupt discontinuation or rapid dosage reduction of benzodiazepines after continued use may lead to withdrawal reactions. The likelihood and degree of severity of withdrawal depend on the duration of treatment, dose and degree of dependency. Sudden cessation of benzodiazepines that have been used continually and/or at high doses is associated with serious withdrawal reactions, such as convulsions, delirium or psychosis. Therefore, healthcare professionals should inform patients of these risks and advise them to consult their doctor before decreasing the dose or abruptly stopping the medicine. Patients should also be advised that stopping treatment requires an individualized tapering schedule which is supervised by their doctor.

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## Guidelines for reporting Adverse Drug Reactions (ADRs):

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with benzodiazepine medicines to the National Pharmacovigilance Centre, Drug Regulatory Authority of Pakistan through the 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 the App Store (for iOS devices) and Google Play (for Android devices).

## References:


1. Minutes of 2nd meeting of Pharmacovigilance Risk Assessment Expert Committee.



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