PMDA Alert for Proper Use of Drugs
Pharmaceuticals and Medical Devices Agency
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Dependence Associated with Benzodiazepine Receptor Agonists

[To Patients]
This document is for healthcare professionals.
If you are taking these drugs, please consult with your physicians or pharmacists.
Please don't reduce the dosage or stop taking the drugs on self-judgment.

Precautions regarding dependence associated with benzodiazepine receptor agonists have been added to the electronic package inserts. In addition, "PMDA Alert for Proper Use of Drugs" No.11 was issued in March 2017, and it has been disseminated to healthcare professionals. However, cases have been continuously reported in which dependence associated with benzodiazepine receptor agonists is suspected.

Physical dependence may be caused by the long-term use with chronic administration of benzodiazepine receptor agonists even within an approved dose range. In such cases, various withdrawal symptoms may occur at the time of dose reduction or discontinuation.

<Major withdrawal symptoms> insomnia, anxiety, feeling irritated, headache, queasy/vomiting, delirium, tremor, seizure, etc.

Please pay careful attention to the following

when using benzodiazepine receptor agonists as hypnotics-sedatives and anxiolytics.

◎ **Healthcare professionals should avoid long-term use with chronic administration.**
- **Dependence may occur with long-term use even within an approved dose range.**
- **Therapeutic necessity should be carefully considered when continuing administration of the drug.**

◎ **Healthcare professionals should adhere to the dosage and confirm that there are no multiple prescriptions of similar drugs.**
- **Long-term administration, high-dose administration, or multiple medications increase the risk of developing dependence.**
- **Healthcare professionals should confirm that similar drugs are not prescribed by other medical institutions.**

◎ **Healthcare professionals should reduce or discontinue the drug carefully by gradual dose reduction, alternate-day administration, etc. when discontinuing the administration.**
- **Serious withdrawal symptoms will occur in addition to the aggravation of primary diseases when the drug is suddenly discontinued.**
- **Reduce or discontinue the drug gradually by alternate-day administration, etc. depending on an individual patient basis.**
- **Instruct patients not to discontinue the drug on self-judgment.**

Typical case reports

Case 1 A male patient in his 30s; primary disease: social anxiety disorder
The patient started taking 1 mg/day of etizolam and 50 mg/day of sulpiride for the treatment of social anxiety disorder. The dose of etizolam was increased to 2 mg/day due to worsening of symptoms approximately 1 year and 8 months after the initiation of administration. The prescription was further continued for approximately 1 year and 6 months because the patient reported feeling much better. Tonic-clonic seizure (loss of consciousness, convulsion, and twilight state) and queasy/vomiting developed when etizolam was discontinued for 2 to 3 days. The patient had no medical history of epileptic seizure.

Case 2 A female patient in her 40s; primary diseases: insomnia and ulcerative colitis; complications: anxiety and numbness
After administration of 7.5 mg/day of zopiclone for approximately 4 months, the patient started taking 5 mg/day of zolpidem tartrate for the treatment of insomnia, followed by addition of 5 mg/day of zolpidem as needed, 1 mg/day of lormetazepam, and 2 mg/day of diazepam. She took these 3 medications for approximately 2 weeks. Although oral administration of these hypnotics improved her insomnia, she discontinued administration on self-judgment because she wished not to rely on and to stop hypnotics. After 1 week, worsened insomnia, headache, photophobia, and symptoms of discomfort occurred, and administration of the drugs that she was taking before discontinuation (1 to 2 mg/day of lormetazepam and 2 mg/day of diazepam) was resumed. Due to inadequate response, 10 mg/day of zolpidem tartrate was resumed. 0.5 mg of etizolam, 2 mg of diazepam, and 0.25 mg of triazolam were added as needed. She increased their doses to the amount of higher than instructed by her doctor on self-judgment. She was diagnosed with hypnotic dependence based on tolerance, withdrawal symptoms, unsuccessful discontinuation and limitation of hypnotic use. The doses of the hypnotics were gradually reduced with a concomitant use of 12.5 mg/day of chlorpromazine hydrochloride. Hypnotic dependence remitted after approximately 3 months.

●Reports of cases

Even after 2017 when “PMDA Alert for Proper Use of Drugs” No.11 was issued, cases have been continuously reported in which dependence on benzodiazepine receptor agonists is suspected.

Fiscal Year	2016	2017	2018	2019	2020	2021	2022	2023
Number of reports of adverse drug reactions related to dependence, withdrawal symptoms, etc.	57	72	118	60	103	89	55	43

*Tabulated using the reports on adverse drug reactions reported to the PMDA by the marketing authorization holders or healthcare professionals between April 1, 2016 and November 30, 2023 (as of February 2, 2024)

● Benzodiazepine receptor agonists approved in Japan* (as of April 2024)

Nonproprietary Name	Brand Name
Alprazolam	Constan, Solanax, and the others
Eszopiclone	Lunesta and the others
Estazolam	Eurodin and the others
Etizolam	Depas and the others
Oxazolam	Serenal
Quazepam	Doral and the others
Cloxazolam	Sepazon
Clotiazepam	Rize and the others
Clorazepate dipotassium	Mendon
Chlordiazepoxide	Contol and the others
Diazepam	Cercine, Horizon, Diapp, and the others
Zopiclone	Amoban and the others
Zolpidem tartrate	Myslee and the others
Triazolam	Halcion and the others
Haloxazolam	Somelin
Fludiazepam	Erispan
Flutazolam	Coreminal

Nonproprietary Name	Brand Name
Flunitrazepam	Silece and the others
Flurazepam hydrochloride	Dalmate
Brotizolam	Lendormin and the others
Bromazepam	Lexotan and the others
Mexazolam	Melex
Medazepam	Resmit and the others
Rilmazafone hydrochloride hydrate	Rhythmy
Ethyl loflazepate	Meilax and the others
Lorazepam	Wypax and the others
Lormetazepam	Evamyl and Loramet
Clonazepam	Rivotril and Landsen
Clobazam	Mystan
Midazolam	Midafresa
Nitrazepam	Nelbon, Benzalin, and the others

*Among hypnotics-sedatives (indicated for either insomnia or sleep disorder), antianxietics, and antiepileptics, drugs for which adverse drug reactions of “dependency,” “drug dependence,” or “withdrawal symptoms” are included in the electronic package inserts are listed.

About this information
- PMDA Alert for Proper Use of Drugs communicates to healthcare providers with clear information from the perspective of promoting the proper use of drugs. The information presented here includes such cases where the reporting frequencies of similar reports have not decreased despite relevant alerts provided in electronic package inserts, among Adverse Drug Reaction/infection cases reported in accordance with the PMD Act.
- We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future
- This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibility on them, but is provided to promote the proper use of the drugs.
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This document is for healthcare professionals. For patients taking these drugs, please consult with your physicians or pharmacists.