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 taking the drug, please consult with your physicians or pharmacists.
Please don't reduce the dosage or stop taking the drug on self-judgment.

Benzodiazepine receptor agonists have a characteristic of developing physical dependence with long-term use even within an approved dose range, leading to various withdrawal symptoms on 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 is no multiple prescription 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 the dose or discontinue carefully such as by gradual dose reduction or alternate-days administration when discontinuing the administration.**

- **Sudden discontinuation will develop serious withdrawal symptoms in addition to aggravate primary diseases.**
- **Instruct patients not to discontinue 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 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.

Benzodiazepine receptor agonists approved in Japan

Nonproprietary Name	Brand Name
alprazolam	Constan, Solanax, and the others
eszopiclone	Lunesta
estazolam	Eurodin and the others
etizolam	Depas and the others
oxazolam	Serenal and the others
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
nimetazepam	Erimin
haloxazolam	Somelin

Nonproprietary Name	Brand Name
fludiazepam	Erispan
flutazolam	Coreminal
flutoprazepam	Restas
flunitrazepam	Silece, Rohypnol, 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 and the others
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

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 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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