This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Summary of Investigation Results

Zolpidem tartrate, zopiclone, eszopiclone, triazolam

July 20, 2022

Non-proprietary name

a. Zolpidem tartrate
b. Zopiclone
c. Eszopiclone
d. Triazolam

Brand name (Marketing authorization holder)

a. Myslee Tablets 5 mg, 10 mg (Astellas Pharma Inc.), and the others
b. Amoban Tablet 7.5, 10 (Sanofi K.K.), and the others
c. Lunesta Tablets 1 mg, 2 mg, 3 mg, (Eisai Co., Ltd.) and the others
d. Halcion Tablets 0.125 mg, 0.25 mg (Pfizer Japan Inc.), and the others

Indications

a. Insomnia (except for insomnia associated with schizophrenia and manic depressive)

b., d. · Insomnia
· Anaesthetic premedication

c. Insomnia

Summary of revisions

a.

1. “Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug” should be added in the CONTRAINDICATIONS section.

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2. A statement should be added to the Clinically Significant Adverse Reactions section that there have been reports of serious self/other-injuries, accidents, etc. including death.

b., d.

1. “Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug” should be added in the CONTRAINDICATIONS section.

c.

1. “Patients who have experienced abnormal behavior as parasomnia (somnambulism, etc.) with administration of this drug” should be added in the Careful Administration section.

Investigation results and background of the revision

The U.S. FDA has taken the following measures with regard to non-benzodiazepine drugs:

(1) To contraindicate their use in patients with a history of complex sleep behavior, and

(2) To alert patients to the risk of serious self/other-injuries, including death, due to complex sleep behaviors.

In response to the decision, the necessity of revision of Precautions was discussed. Considering overseas measures and adverse drug reactions reported in Japan, ultrashort-acting benzodiazepine receptor agonists indicated for insomnia were subjected to the investigation.

(1)

Based on the published literature on the pharmacological mechanisms of parasomnia and cases involving parasomnia reported in Japan, as well as consultation with expert advisors, MHLW/PMDA concluded that revision of the CONTRAINDICATIONS section for the Precautions of zolpidem tartrate, zopiclone, and triazolam was necessary taking into account the following points:

・In patients with a history of drug-induced parasomnia, the risk of recurrence cannot be excluded, and it is difficult to predict serious self/other-injuries or accidents that may occur secondary to adverse drug reactions. In addition, patients are considered to be unconscious and will not exercise intentional control when adverse drug reactions occur.

・There is no certainty in reducing the dose of the drugs or controlling adverse drug reactions when they occur. Discontinuation of the suspected drugs is currently considered

the best way to avoid the recurrence of parasomnia.

・Cases involving parasomnia have been reported in Japan.

・It has been reported that parasomnia tends to occur due to their pharmacological properties such as half-life.

Regarding eszopiclone, MHLW/PMDA in consultation with expert advisors concluded that revision of the Careful Administration section was appropriate at this time, considering that no cases involving parasomnia have been reported in Japan to date, as well as its pharmacological properties.

(2)

Cases in which parasomnia developed and resulted in secondary serious self/other-injuries or accidents (hereinafter referred to as “secondary events”) reported in Japan and overseas were evaluated. Cases for which a causal relationship between zolpidem tartrate and secondary events associated with parasomnia was reasonably possible have been reported in Japan and overseas. As a result of consultation with expert advisors, MHLW/PMDA concluded that revision of the Clinically Significant Adverse Reactions section was necessary for the Precautions of zolpidem tartrate. Of note, regarding zopiclone, eszopiclone and triazolam, no cases for which a causal relationship between the drugs andevents was reasonably possible have been reported. Therefore, MHLW/PMDA concluded that revision of the Clinically Significant Adverse Reactions section was not necessary.

Number of cases and patient mortalities of parasomnia reported in Japan during the previous 3 fiscal years*

a. A total of 2 cases have been reported to date.
   No patient mortalities have been reported to date.
b. No cases have been reported to date.
c. No cases have been reported to date.
d. 1 case has been reported to date.
   No patient mortalities have been reported to date.

Number of cases and patient mortalities of secondary events associated with

parasomnia reported in Japan and overseas during the previous 3 fiscal years

a. No cases have been reported in Japan to date.
b. No cases have been reported in Japan to date.
c. No cases have been reported in Japan to date.
d. No cases have been reported in Japan to date.

a. 1 case† has been reported overseas to date. (A causal relationship between the drug and event could not be established for this case.)
   No patient mortalities have been reported to date.
b. No cases have been reported overseas to date.
c. No cases have been reported overseas to date.
d. No cases have been reported overseas to date.

*The possibility of a causal relationship between the drugs and events was not evaluated.
†The possibility of a causal relationship between the drugs and events was evaluated for cases with no risk factors for parasomnia and a clear date of onset of the adverse drug reactions.

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

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