



Report on the Investigation Results

February 28, 2017

Pharmaceuticals and Medical Devices Agency

I. Overview of Product

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|-----------------------------|---------------------|
| [Non-proprietary name] | See Attachment 1 |
| [Brand name] | See Attachment 1 |
| [Approval holder] | See Attachment 1 |
| [Indications] | See Attachment 1 |
| [Dosage and administration] | See Attachment 1 |
| [Investigating office] | Office of Safety II |

II. Background of the investigation

1. Status in Japan

Hypnotics and anxiolytics are prescribed by various specialties and widely used in clinical practice. In particular, benzodiazepine (BZ) receptor agonists, which act on BZ receptors, bind to gamma-aminobutyric acid (GABA)_A-BZ receptor complex and enhance the function of GABA_A receptors. This promotes neurotransmission of inhibitory systems and demonstrates hypnotic/sedative effects, anxiolytic effects, muscle relaxant effects, and antispasmodic effects. Since the approval of chlordiazepoxide in March 1961, many BZ receptor agonists have been approved as hypnotics and anxiolytics.

Currently, hypnotics and anxiolytics are causative agents of drug-related disorders such as drug dependence in Japanese clinical practice. Hypnotics and anxiolytics that rank high in causative agents are BZ receptor agonists for which high frequencies of high doses and multidrug prescriptions have been reported (Japanese Journal of Clinical Psychopharmacology 2013; 16(6): 803-812, Modern Physician 2014; 34(6): 653-656, etc.). In addition, the International Narcotics Control Board (INCB), one of the organizations of the United Nations, indicated in their 2010 “Special Report: Availability of Internationally Controlled Drugs: Ensuring Adequate Access for Medical and Scientific Purpose” that Japan has a high consumption level of BZ drugs compared to other Asian countries and that the high consumption levels may reflect the large elderly population as well as inappropriate prescription patterns and associated abuse (Report of International Narcotics Control Board for 2010. suppl.1, 2010, 40).

Based on these circumstances, the Ministry of Health, Labour and Welfare (MHLW) has implemented a demerit point system in medical fees when administering 3 or more drugs etc., in the FY 2012 and FY 2014 revisions of health insurance medical fees in order to enforce proper prescription of hypnotics and anxiolytics. Furthermore, given that risk of abuse was confirmed for zopiclone and etizolam, the MHLW revised the “Cabinet Order specifying narcotics, narcotic plants, psychotropics, and narcotics/psychotropics raw materials,” and issued a ministerial announcement stating that the maximum duration of treatment would be 30 days (MHLW Ministerial Announcement No. 365 dated October 13, 2016) in addition to newly specifying these drugs as psychotropics (third-class psychotropics) (Cabinet Order No. 306 dated September 14, 2016).

Precautions in the package insert are mostly related to dependence in connection with high doses and continuous administration stated in the Precautions section. Dependence on BZ receptor agonists has been frequently reported overseas since the beginning of the 1960s. A majority of such reports are on the onset of withdrawal symptoms during large doses and long-term use. The idea is that dependence sets in only when administering a large dose over a long period of time to patients who are predisposed to become dependent (The Journal of Practical Pharmacy 2015; 66(12): 2949-2954). The Japanese precautions are thought to be based on this idea. However, perception toward dependence on BZ receptor agonists changed in the 1980s, and it has been gradually accepted that dependence due to medical use, rather than abuse or non-medical use, is the core problem (The Journal of Practical Pharmacy 2015; 66(12): 2949-2954).

Given these circumstances, on January 26, 2017, the Safety Division of the Pharmaceutical Safety and Environmental Health Bureau at MHLW requested the Pharmaceuticals and Medical Devices Agency (PMDA) to conduct investigations on safety issues such as dependence for hypnotics/sedatives (drugs indicated for either “insomnia” or “sleep disorder”), anxiolytics, and antiepileptics, which include “dependence,” “drug dependence,” or “withdrawal symptoms” (excluding transplacental) as adverse drug reactions (ADRs) in the precautions of the package inserts. Based on this request, PMDA conducted investigations on the safety regarding dependence of the drugs subject to investigation and considered whether there was a need to revise their package inserts.

Moreover, PMDA has held an Expert Discussion as part of the investigations. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the drugs subject to investigation, and in accordance with the “Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

2. Status overseas

In order to deliberate precautions for proper use related to dependence associated with medical use, limitations, or recommendations on the duration of prescription imposed by regulatory agencies overseas were confirmed.

The United Kingdom has been concerned about the risks of drug dependence and withdrawal symptoms due to long-term use of BZ since the 1980s. The committee on the safety of medicines, Medicines and Healthcare products Regulatory Agency (MHRA), limited the use of BZ to short-term relief (2–4 weeks only) of severe anxiety in 1988¹. In July 2011, MHRA issued reminders to healthcare professionals that the maximum duration of treatment should be 4 weeks including the dose-tapering phase².

In France, L'Agence nationale de sécurité du médicament et des produits de santé (ANSM: The National Agency for the Safety of Medicines and Health Products) announced action plans in September 2012 to decrease misuse of BZ. The plan limits continued the use of BZ to a maximum of 4 weeks for insomnia treatment and 12 weeks for anxiety treatment³.

In Canada, Health Canada published a book on the use of BZ in 1982. The book recommends that the duration of treatment be 1 to 2 weeks as the anxiolytic effects of BZ cannot be expected when administration exceeds 2 to 4 weeks. On the other hand, based on various study results regarding dependence on BZ, dependence on diazepam is estimated to occur anywhere from 2 weeks to 4 months after initial use⁴.

In Denmark, the National Health Board announced guidance on the prescription of addictive drugs that recommends that BZ be prescribed for 1 to 2 weeks for insomnia treatment and 4 weeks for anxiety treatment⁵.

III. Investigation by PMDA

1. Accumulated adverse drug reaction reports in Japan

¹ MHRA HP: Current Problems in Pharmacovigilance: Number 21 (pages 1-4) January 1988

² MHRA HP: Addiction to benzodiazepines and codeine

³ ANSM HP: Plan d'actions de l'ANSM visant à réduire le mésusage des benzodiazépines - Point d'information

⁴ Authority of The Minister of National Health and Welfare, The Effects of Tranquillization: Benzodiazepine Use in Canada, 1982

⁵ Danish Health HP: Vejledning om ordination af afhængighedsskabende lægemidler og om substitutionsbehandling af personer med opioidafhængighed

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

The number of reported serious and non-serious ADRs in Japan related to dependence and withdrawal symptoms, etc.⁶(hereinafter referred to as dependence-related events) obtained by the marketing authorization holders (MAH) of each investigated drug since launch to June 30, 2016, is as noted in Attachment 2.

Of the drugs subject to investigation, ingredients for which 50 or more dependence-related events were reported include etizolam with 720 events in 695 cases, alprazolam with 179 events in 171 cases, triazolam with 163 events in 158 cases, zolpidem tartrate with 129 events in 126 cases, clonazepam with 121 events in 118 cases, and ethyl loflazepate with 74 events in 64 cases, all of which are BZ receptor agonists. Reports of dependence-related events were limited for barbiturates (BA) and non-BA drugs, and even the most frequently reported ingredient, pentobarbital calcium, only had 17 events in 15 cases.

Since regulatory agencies overseas have established recommended durations for treatment based on the efficacy and risk of developing dependence (refer to “2. Status overseas” section), the ADR reports in Japan were compared for treatment duration within 14 days and for longer than 14 days. Of the 473 cases administered the approved daily dose of the drugs subject to investigation (excluding cases for which the daily dose was unknown) in total, 116 cases had a clear treatment duration. Of these, 15 cases had a treatment duration within 14 days, whereas the remaining 101 cases had a treatment duration of longer than 14 days.

On the other hand, of the 442 cases administered a higher-than-approved daily dose (excluding cases for which the daily dose was unknown) in total, 54 cases had a clear treatment duration. Of these, 41 cases had a treatment duration within 14 days, and the remaining 13 cases had a treatment duration for longer than 14 days. Furthermore, of the 442 cases administered a higher-than-approved dose, 369 cases included PT “intentional overdose” and “intentional product misuse.”

⁶ Of the events related to “dependence” and “withdrawal syndrome” in the “drug abuse, dependence and withdrawal (narrow spectrum)” and preferred term (PT) of the standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) of MedDRA, events excluding cases in which route of administration was “transplacental”

2. Reviews and Japanese Guidelines on Dependence and Withdrawal Symptoms, etc.

2.1 Reviews

Reviews describe dependence and withdrawal symptoms, etc., as follows.

Japanese Journal of Psychiatric Treatment 2013; 28: 232-236⁷

Therapeutic dose dependence with the use of BZ receptor agonists is described as “a clinical condition where the primary disease has improved but the patient has difficulty in stopping the drug as rebound phenomena or withdrawal symptoms occur when administration is discontinued.” The most important factor in the development of dependence is long-term use. When these drugs are used in the long term, dependence develops, and when dependence develops, withdrawal symptoms occur when the drug is decreased or discontinued. Withdrawal symptoms make discontinuation difficult, leading to longer-term use. Factors for long-term use include the use of high doses and combination therapy with multiple drugs. Combination therapy with multiple drugs inevitably leads to high doses, and given that discontinuation of high doses tends to cause withdrawal symptoms, it is likely to be used long-term. Withdrawal symptoms of BZ receptor agonists that are widely recognized include insomnia, anxiety, dysphoria, irritability, tremor, headache, and nausea/vomiting. These are the symptoms that require the use of BZ receptor agonists to treat as well, and it is difficult to distinguish between withdrawal symptoms and relapse of the primary disease.

The Journal of Practical Pharmacy 2015; 66(12): 3003-3007⁸

Withdrawal symptoms of BZ receptor agonists occur at high frequencies in the long-term use if very mild ones are included. On the other hand, withdrawal associated with 2 or more symptoms only occurs in approximately 20% of patients administered BZ receptor agonists. Furthermore, withdrawal symptoms are not detected in short-term clinical trials for a 2-week period. In clinical research, withdrawal symptoms of BZ receptor agonists tend to be evaluated using self-completion assessment scales such as Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ). Research using these scales may have failed to detect very mild withdrawal symptoms.

⁷ Ken Inada, Treatment of therapeutic dose dependence on benzodiazepine, Japanese Journal of Psychiatric Treatment 2013; 28: 232-236

⁸ Ken Inada, Points determining BzRAs dependence, The Journal of Practical Pharmacy 2015; 66(12): 3003-3007

Japanese Journal of Geriatric Psychiatry 2013; 24(8): 763-771⁹

BZ receptor agonists bind to the GABA_A receptor α 1 subunit of GABA interneuron, which suppresses dopaminergic neurons in the ventral tegmental area and thereby decreases GABA release, which leads to activation as a result of disinhibition and dopaminergic neurons projected to the nucleus accumbens causing dependence on BZ receptor agonists.

The Journal of Practical Pharmacy 2015; 66(12): 2949-2954¹⁰

The drug safety committee of MHRA in the United Kingdom clearly stated in 1988 that “there is no epidemiological evidence demonstrating a closer link to development of dependence or occurrence of withdrawal symptoms for specific BZ receptor agonists than other BZ receptor agonists” and that there is a comparable possibility of dependence developing with all types of BZ receptor agonists. The agency has also released statements regarding their proper use such as “use of BZ receptor agonists must be limited to short-term relief” and “dosage of BZ receptor agonists should be gradually decreased.”

Progress in Medicine 2007; 27(10): 131-140¹¹

Tofisopam has nitrogen atoms in the 2nd and 3rd loci of the diazepine ring, whereas BZ anxiolytics represented by diazepam have nitrogen atoms in the 1st and 4th loci. These differences in molecular structure are thought to cause a difference in the pharmacological effect/clinical efficacy between BZ anxiolytics and tofisopam.

Dependence-related acute central nervous system effect, as seen when BA or many BZ anxiolytics are administered, is not found when large doses of tofisopam are administered to rhesus monkeys. Occurrence of withdrawal symptoms after long-term administration of BZ anxiolytics is thought to be a result of the long-term binding of BZ anxiolytics to BZ receptors, and it is considered that dependence is not found with tofisopam that does not bind to BZ receptors.

⁹ Ryo Fukatsu, et al, Are anxiolytics ineffective for elderly dementia patients, Japanese Journal of Geriatric Psychiatry 2013; 24(8): 763-771

¹⁰ Keiichiro Tsuji, Osamu Tajima, BzRAs past/present/future, The Journal of Practical Pharmacy 2015; 66(12): 2949-2954

¹¹ Sueharu Tsutsui, The basics and clinical use of autonomic modulator Tofisopam (tofisopam, GrandaxinTM), Progress in Medicine 2007; 27(10): 131-140

Japanese Journal of Clinical Medicine 2009; 67(8): 1585-1589¹²

BA hypnotics have a narrow window between therapeutic dose and addictive dose (i.e., therapeutic window), and tolerance develops in a relatively short time requiring increased doses to gain the same hypnotic effects. Development of tolerance further narrows the therapeutic window and increases the risk. In addition, BA hypnotics are associated with both psychological and physical dependence. Psychological dependence develops at a relatively early stage and causes abuse or overdose. As a result of overdose, neurological symptoms occur, such as gait disturbance, dyslalia, nystagmus, coordination impairment, muscular weakness, hyporeflexia, flapping tremor-like involuntary movements, and disturbed consciousness as well as psychological symptoms such as emotional instability, irritability, aggression, hallucination/delusion, and a confusional state. Moreover, overdose could cause respiratory depression or shock, which results in death eventually. Withdrawal symptoms occur if the drug is rapidly withdrawn when physical dependence has developed.

NEW Pharmacology; 6: 348-350¹³

Tolerance (tolerance develops with prolonged use and patients are unable to sleep unless administered a higher dose compared with the initial dose. There are metabolic tolerance caused by the acceleration of metabolic degradation induced by liver drug metabolizing enzymes and functional tolerance caused by a decrease in the sensitivity of neurons), and dependence (not only patients require a high dose of the drug during the night, they become anxious to take the drug during the day as well. Physical dependence as well as psychological dependence develop, causing withdrawal symptoms when prolonged use is suddenly discontinued) are adverse reactions of BA hypnotics.

The Japanese Journal of Clinical and Experimental Medicine 2005; 82(5): 771-774¹⁴

BA drugs demonstrate efficacy in suppressing the thalamus, ascending brainstem reticular formation, and central nervous system and demonstrate superior hypnotic efficacy; however, their safety is limited and there are issues such as the tendency to

¹²Atsuomi Baba, Barbiturates, Japanese Journal of Clinical Medicine 2009; 67(8): 1585-1589

¹³ NEW Pharmacology; 6: 348-350

¹⁴Katsuyuki Fukudome, Chiharu Kubo, Pharmacological Treatment for Sleep Disorders, The Japanese Journal of Clinical and Experimental Medicine 2005; 82(5): 771-774

develop tolerance or dependence. They are therefore drugs that require sufficient knowledge when being used. The drugs should only be used for insomnia that is acute and expected to improve over a short period of time and should only be prescribed as hypnotics by healthcare professionals who are experts in sleep disorders.

Non-BA drugs all have strong ADRs and a narrow safety window. Therefore, they are rarely used as hypnotics currently and are used to induce sleep when performing tests such as electroencephalogram (ECG). Bromvalerylurea, chloral hydrate, and triclofos have dependence.

2.2 Japanese Guidelines

Japanese guidelines state the following with regard to dependence and withdrawal symptoms, etc., as well as administration methods such as treatment duration etc., related to these ADRs. They are explained by intended use.

2.2.1 Sleep Disorders

Clinical Guidelines for Proper Use and Withdrawal of Hypnotics¹⁵

Forty clinical questions representative of what is encountered in each treatment stage are established. Of these questions, Q1, Q25, Q34, Q38, and Q39 that address the relationship between dependence or withdrawal symptoms and administration methods are answered as follows:

- A1 There is no significant difference in short-term efficacy between BZ and non-BZ hypnotics. BA and non-BA hypnotics have many serious ADRs and are currently rarely used.
- A25 There is no evidence that combination therapy of multiple hypnotics is more effective when efficacy is insufficient with the usual dose of hypnotics. In order to reduce the risk of ADR, combination therapy with multiple drugs should be avoided as much as possible. In particular, combination use of 3 or more types of BZ and non-BZ hypnotics must be avoided.
- A34 While risk of developing dependence with short-term use of hypnotics is limited, high dose use/long-term administration of these drugs increases such risk and

¹⁵ MHLW Comprehensive Research Project on Scientific Research/Countermeasures Concerning Persons with disabilities "Study group on clinical guidelines for proper use and dosage decrease/discontinuation of hypnotics" and The Japanese Society of Sleep Research/Working group for formulating guidelines on hypnotics use version, Clinical Guidelines for Proper Use and Withdrawal of Hypnotics, 2013

should be avoided. If symptoms of insomnia improve, methods such as as-needed use, tapering, or rest periods can be adopted depending on the condition of the patient. It is desirable to make a treatment plan that corresponds to changes in symptoms.

A38 After remission (recovery from) of insomnia, dosage decrease/withdrawal should be adopted as quickly as possible for hypnotics.

A39 Long-term use, use of high doses, and combination use of multiple drugs are considered to be risk factors for the occurrence of withdrawal symptoms. In order to achieve successful withdrawal of hypnotics, it is important to adopt cautious approaches such as tapering to avoid or minimize withdrawal symptoms.

2.2.2 Anxiety Disorders, Mood Disorders

Treatment Guidelines by Japanese Society of Mood Disorders

I. Bipolar Disorder 2012¹⁶

There is no evidence that long-term administration of BZ has a positive influence on the prolonged course of bipolar disorder. Given that there are issues with therapeutic dose dependence, BZ should not be administered chronically while it may be used temporarily to treat coexisting anxiety disorders.

Treatment Guidelines by Japanese Society of Mood Disorders

II. Depression (DSM-5)/ Major Depressive Disorder 2016¹⁷

Combination therapy with BZ anxiolytics and antidepressants have demonstrated higher efficacy during the early stages of treatment for mild depression compared with monotherapy with antidepressants. However, sufficient caution must be exercised for paradoxical reactions such as disinhibition or excitation, and it is desirable to avoid easy long-term administration by closely monitoring for abuse and the development of dependence. BZ anxiolytics therapy is particularly not recommended for use in patients who currently have or have a history of dependence on substances such as alcohol.

Combination therapy with antidepressants and BZ is useful up until the 4th week of treatment initiation in light of decreasing drop-out rate etc., in moderate/severe

¹⁶ Japanese Society for Mood Disorders Committee for formulating treatment guidelines on mood disorders version, Treatment Guidelines by Japanese Society of Mood Disorders I. Bipolar Disorder 2012, 2012

¹⁷ Japanese Society for Mood Disorders Committee for formulating treatment guidelines on mood disorders version, Treatment Guidelines by Japanese Society of Mood Disorders II. Depression (DSM-5)/Major Depressive Disorder 2016, 2016

depression. BZ is often necessary in moderate or more severe cases to treat anxiety, irritation, and/or insomnia.

Treatment Guidelines for Panic Disorder¹⁸

Pharmacological treatment for panic disorders should be initiated with combination use of antidepressants and BZ. For BZ, a high titer drug should be used and dosage should be gradually decreased once efficacy of antidepressants is observed. Furthermore, if antidepressants cannot be used due to ADRs, etc., patients should be treated with BZ only. In order to prevent withdrawal symptoms, BZ with a long blood concentration half-life is recommended for long-term use.

Treatment Procedures for Generalized Anxiety Disorder¹⁹

While monotherapy should mainly be used for generalized anxiety disorder (GAD), combination therapy should be adopted accordingly based on the symptoms. As a candidate for the combination therapy, BZ is recommended if patients suffer from severe anxiety and it is necessary to resolve anxiety quickly and if patients have symptoms such as autonomic symptoms or muscle tightness; however, the dosage and duration of treatment should be kept to a minimum considering the dependence. The efficacy of BZ should be assessed in 2 weeks and treatment should be maintained if it is efficacious while considering tapering at an early stage given the risk of dependence.

2.2.3 Epilepsy

Treatment Guidelines for Epilepsy 2010²⁰

Acute psychotic symptoms during withdrawal of BZ antiepileptics, depressed state and mental deterioration of phenobarbital, depressed state of clonazepam, and hypomania of clobazam are noted as ADRs of each drug, and it is recommended that these are considered when selecting drugs for patients with psychological symptoms.

¹⁸ MHLW Scientific Research Project on Mental Health Study group on optimizing treatment methods for panic disorders and formulating treatment guidelines version, Treatment Guidelines for Panic Disorder, Igaku-Shoin, 2008

¹⁹ Kazuyuki Nakagome, et al, "Treatment Procedures for GAD" proposed by the GAD Study Group in Japan, Japanese Journal of Clinical Psychopharmacology 2008; 11: 1571-1573

²⁰ Japanese Society of Neurology Committee for formulating treatment guidelines on epilepsy version, Treatment Guidelines for Epilepsy 2010, Igaku-Shoin, 2010

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In addition, when assessing the efficacy of pharmacological treatment, it is stated that dose reduction of antiepileptics can be considered after seizures have stopped for 2 to 5 years or more.

Medication Guidelines for Adult Epilepsy²¹

No related description.

3. Summary of Investigation at PMDA

3.1 Precautions regarding dependence

With regard to ADR reported on dependence-related events in Japan for drugs subject to investigation, many cases have an unknown treatment duration, and while several cases of “intentional overdose” and “intentional product misuse” are included, the number of cases is higher among those prescribed the approved daily dose for a treatment duration of longer than 14 days compared with those prescribed a higher-than-approved daily dose for a treatment duration of longer than 14 days. In addition, for those prescribed a daily dose within the approved range, the number of cases with a treatment duration of longer than 14 days was higher than that with a treatment duration within 14 days (Refer to “1. Accumulated ADR Reports in Japan” section). Of the various drugs subject to investigation, BZ receptor agonist was a common active ingredient for which the number of ADR reports on dependence-related events in Japan was high. In contrast, the number of ADR reports on dependence-related events was limited for BA drugs and non-BA drugs when compared with BZ receptor agonists. For pentobarbital, which had the highest number of reports, all the reports were “intentional overdose” or “intentional product misuse,” and no trends with regard to dosage and treatment duration were seen.

As stated above, while there is a limit to information on ADR reports accumulated in Japan, PMDA has determined that the following revisions 1) to 5) in the package insert of drugs subject to investigation are necessary based on the safety information obtained and the details of “2. Review and Japanese Guidelines on Dependence and Withdrawal Symptoms, etc.”

- 1) For BZ receptor agonists used as hypnotics/sedatives, anxiolytics, and antiepileptics that bind to GABA_A receptor α 1 subunit and could lead to long-term usage or for

²¹ The Japan Epilepsy Society Committee for formulating guidelines version, Pharmacological Treatment Guidelines for Adult Epilepsy, Epilepsy Research 2005; 23(3): 249-253

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which long-term use is expected, precautions about the development of “dependence” should be noted in the Clinically Significant Adverse Reactions section for the following reasons:

- Physical dependence develops with long-term use of BZ receptor agonists even within the approved dose range, and withdrawal symptoms occur when the dosage is decreased or administration is discontinued
- GABA_A receptor α 1 subunits are anticipated to be involved in the mechanism of dependence development

As such, oxazolam, which includes precautions against drug dependence on benzodiazepine drugs in the Clinically Significant Adverse Reactions section, flutazolam, which includes precautions in the Clinically Significant Adverse Reaction (similar drugs) section, and brotizolam, which includes precautions in the “Other Adverse Reaction” section, also require precautions on ADRs for each drug in the Clinically Significant Adverse Reactions section as with other BZ receptor agonists.

Furthermore, similar risks of dependence on BZ receptor agonists cannot be assumed for the autonomic modulator tofisopam, which has the BZ frame as it does not bind to BZ receptors; therefore, PMDA has determined that there is no need to change the current precautions noted in the Other Adverse Reactions section that there have been reports of drug dependence with other BZ drugs.

- 2) Based on 1) above, dependence does not only occur when “large doses are used continuously.” In addition, given that withdrawal symptoms have not been detected as stated in clinical trials so far reported involving short-term use for approximately 2 weeks, dependence is thought to develop due to “prolonged use”. Therefore, precautions regarding “dependence or drug dependence” in the Clinically Significant Adverse Reactions section of BZ receptor agonists should indicate that these occur “due to prolonged use” rather than “due to prolonged use of large doses” as currently stated. In addition, precautions regarding the occurrence of withdrawal symptoms should be revised to “during prolonged use” from “during administration of large doses or during prolonged use” or should add “due to prolonged use” or “during prolonged use” for the occurrence of dependence and withdrawal symptoms.
- 3) Given that dependence on BA drugs may develop with any drug that binds to the BA binding site, precautions regarding the occurrence of “drug dependence” should be added to the Clinically Significant Adverse Reactions section of all BA drugs used as hypnotics/sedatives, anxiolytics, and antiepileptics, including amobarbital and

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primidone, which currently do not have any precautions regarding “drug dependence” in the Clinically Significant Adverse Reactions section of the package insert.

- 4) As non-BA drugs such as chloral drugs or bromvalerylurea are also thought to cause dependence, changing precautions regarding the occurrence of withdrawal symptoms from “during administration of large doses or during prolonged use” to “during prolonged use” as with BA drugs is considered appropriate. However, given the limited number of reviews and guidelines, etc., precautions will be considered upon expert opinion.
- 5) “Caution should be exercised for dosage and treatment duration when administering this drug” should be added to the “dependence or drug dependence” subsection of the Clinically Significant Adverse Reaction” section of the package inserts of BZ receptor agonists and BA drugs for the following reasons:
 - Long-term administration of BZ receptor agonists is the most important risk factor of dependence development, and administration of high doses, etc. is one of the causes of long-term administration
 - BA drugs develop tolerance by prolonged use leading to administration of large doses

3.2 Proper use of products indicated for hypnotics/sedatives and anxiolytics

For the following reasons, PMDA has determined that it is appropriate to add “avoid continuous administration and limit to short-term use” to the Important Precautions section of package inserts for BZ receptor agonists, BA drugs, and non-BA drugs that are indicated for hypnotics/sedatives and anxiolytics and could lead to long-term use in order to avoid development of dependence associated with such long-term use.

- Long-term use is the most important risk factor for the development of dependence in BZ receptor agonists.
- Approaches to the discontinuation of BZ receptor agonists etc. have been established, such as recommendations for replacement with long-acting drugs, switching to alternative drugs, or non-pharmacological treatment
- Japanese guidelines on sleep disorders as well as anxiety disorders/mood disorders note that the use of BZ receptor agonists should not be administered chronically and that long-term administration should be avoided
- BA hypnotics should only be used for acute insomnia expected to improve in a short period of time

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- Non-BA hypnotics should not be used as hypnotics as a general rule since they are associated with severe ADRs and with a limited safety window. These drugs are supposed to be used to induce sleep during tests such as ECG

3.3 Proper use of products indicated for antiepileptics

Products indicated for antiepileptics cannot always be limited to short-term administration given the patient's condition. As control of epilepsy should be emphasized more when deciding whether to continue treatment for epilepsy, it is important to consider that treatment opportunities for patients are not lost by limiting the treatment duration. Because it is necessary to exercise similar caution regarding risks of developing dependence and withdrawal symptoms when discontinuing treatment as with hypnotics/sedatives and anxiolytics, precautions regarding dependence and withdrawal symptoms should be included in the Clinically Significant Adverse Reactions section; however, it is not necessary to include precautions regarding proper use such as treatment duration in the Important Precautions section. Furthermore, since diazepam (injection), nitrazepam, phenobarbital (oral), and phenobarbital sodium (suppository) are products with other indications besides epilepsy and can be used for indications that could lead to long-term administration, it is appropriate to add to "avoid continuous administration and limit to short-term use except when used as an antiepileptic," a precaution similar to 3.2 above in the Important Precautions section.

3.4 Precautions regarding paradoxical reactions

Paradoxical reactions reported to occur using approved doses of BZ receptor agonists are known to occur among patients with notable conflicts related to their environment or human interaction, patients who are hostile or aggressive by nature, patients who have a vulnerable inhibitory mechanism toward the central nervous system (such as those with a history of psychosis, those with structural brain disorder, pediatric patients, and elderly patients), etc (Japanese Journal of Clinical Psychopharmacology 2008; 11(2): 253-259), and may occur in various patients administered these types of drugs. Therefore, PMDA thinks it is desirable to delete "persons with mental disorders such as schizophrenia" noted as a specific patient population in which ADRs corresponding to paradoxical reactions occur. Currently, the population is referred to in the precautions regarding irritable excitation, confusion, etc., which are ADRs corresponding to paradoxical reactions, i.e., "irritable excitation, confusion, etc., may conversely occur due to administration of this drug in persons with mental disorders such as schizophrenia."

In addition, for drugs in which precautions for ADRs corresponding to paradoxical reactions are not noted in the package insert, MAHs should review the need to add such precautions based on the status of ADR reports accumulated in Japan as well as measures being implemented overseas.

PMDA discussed the appropriateness of its conclusion in its Expert Discussion. The conclusion was supported by the expert advisors, i.e., precaution for the development of “Dependence or drug dependence” together with a note added to the effect that “Caution should be exercised for dosage and treatment duration when administering this drug” to the Clinically Significant Adverse Reactions section of the package inserts of BZ receptor agonists and BA drugs, as well as revisions to “due to prolonged use” in the precaution for the development of dependence on BZ receptor agonists and a revision to “during prolonged use” in the precaution for the occurrence of withdrawal symptoms with them.

Regarding the revision to “during prolonged use” from “during administration of large doses or during prolonged use” in the precaution for the occurrence of withdrawal symptoms with non-BA drugs, agreement was reached that precaution for dependence similar to that for BA drugs is necessary despite their low frequency of use or their rarity in prolonged use.

Moreover, regarding the addition of “avoid continuous administration and limit to short-term use” in drugs indicated for hypnotics/sedatives and anxiolytics, there were opinions that such precaution is necessary considering that there are not a few cases of chronic administration, which assist the development of dependence in turn or that avoiding long-term use is just a non-binding goal in clinical practice where patients actually have difficulty in stopping BZs or BAs in the short-term.

Based on these opinions, PMDA concluded that precautions such as “Long-term use by chronic administration should be avoided” and “Therapeutic necessity should be carefully considered when continuing administration of this drug” are appropriate.

Removal of the “persons with mental disorders such as schizophrenia” etc. noted as a specific patient population in which ADRs corresponding to paradoxical reactions occur was supported by the expert advisors.

Expert advisors expressed opinions that alerting healthcare professionals is necessary for confirming whether similar drugs are prescribed in other medical facilities or that PMDA should provide information on issues such as dependence on drugs within approved dosage or risks associated with chronic administration.

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Based on the above, PMDA considers that the core problem of the drugs subject to the investigation that are known to be associated with drug-related disorders such as drug dependence is the dependence caused by the use for treatment purpose that are based on physicians' prescriptions if used long-term, making discontinuation of the drugs difficult, inevitably leading to increased doses. Therefore, PMDA concludes that revision of package inserts to alert prescribing physicians for further precaution against possible development of dependence in the clinical use of the drugs as well.

IV. Overall evaluation

PMDA concludes that the following revisions to the package inserts are appropriate. Revisions for each investigated drug can be found in Attachment 3.

| No. | Non-proprietary name Brand name (name of MAH) | Indications | Dosage and administration |
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| 1 | <p>Alprazolam Constan 0.4 mg Tablets, 0.8 mg Tablets, and the others (Teva Takeda Yakuhin Ltd. and the others)</p> <p>(Teva Takeda Yakuhin Ltd. and the others)</p> <p>Solanax Tablets 0.4 mg, 0.8 mg, and the others (Pfizer Japan Inc.)</p> | <p>Somatic symptoms in psychosomatic disease (gastroduodenal ulcer, irritable bowel syndrome, dysautonomia), and anxiety, tension, depressed mood, sleep disorder</p> | <p>The usual adult dosage of alprazolam is 1.2 mg daily given orally in 3 divided doses.</p> <p>The dose may be adjusted according to the patient's age and symptoms. The dose should be increased gradually, up to a maximum daily dose of 2.4 mg, given orally in 3 to 4 divided doses.</p> <p>In elderly patients, therapy should be initiated at 0.4 mg once to twice daily, and even if increased, should not exceed a daily dose of 1.2 mg.</p> |
| 2 | <p>Eszopiclone Lunesta Tablets 1 mg, 2 mg, 3 mg (Eisai Co., Ltd.)</p> | <p>Insomnia</p> | <p>The usual dosage of eszopiclone is 2 mg for adults and 1 mg for elderly patients, given orally before going to bed. The dose may be adjusted according to the patient's symptoms, but should not exceed 3 mg in adults and 2 mg in elderly patients.</p> |
| 3 | <p>Estazolam Eurodin 1 mg Tablets, 2 mg Tablets, Eurodin Powder 1%, and the others (Teva Takeda Yakuhin Ltd. and the others)</p> | <p>Insomnia, anaesthetic premedication</p> | <p>The dose of this drug may be adjusted according to factors such as the patient's age, symptoms, and disease, but it should generally be administered to adults as follows.</p> <ul style="list-style-type: none"> ○ Insomnia <p>Doses of 1 to 4 mg of estazolam given orally before going to bed</p> <ul style="list-style-type: none"> ○ Anaesthetic premedication <p>Preanesthetic: 2 to 4 mg of estazolam given orally</p> <p>The night before surgery: 1 to 2 mg of estazolam given orally</p> |

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| | | | before going to bed. |
| 4 | <p>Etizolam</p> <p>Depas Tablets 0.25 mg, 0.5 mg, 1 mg, Depas Fine Granules 1%, and the others</p> <p>(Mitsubishi Tanabe Pharma Corporation and the others)</p> | <ul style="list-style-type: none"> • Anxiety, tension, depressed mood, neurasthenia symptoms, sleep disorder in neurosis • Anxiety, tension, sleep disorder in depression • Somatic symptoms in psychosomatic disease (hypertension, gastroduodenal ulcer), and anxiety, tension, depressed mood, sleep disorder • Sleep disorder in schizophrenia • Anxiety, tension, depressed mood, and muscle tightness in the following diseases Cervical spondylosis, lumbago, tension headache | <p>In neurosis and depression: The usual adult dosage of etizolam is 3 mg daily given orally in 3divided doses.</p> <p>In psychosomatic disease, cervical spondylosis, lumbago, and tension headache: The usual adult dosage of etizolam is 1.5 mg daily given orally in 3 divided doses.</p> <p>In sleep disorder: The usual adult dosage of etizolam is 1 to 3 mg daily given orally before going to bed.</p> <p>For each indication, the dose may be adjusted according to the patient's age and symptoms, but in elderly patients, should not exceed a daily dose of 1.5 mg.</p> |
| 5 | <p>Oxazolam</p> <p>Serenal Tablets 5, 10, Serenal Powder 10%, and the others</p> <p>(Daiichi Sankyo Company, Limited and the others)</p> | <ul style="list-style-type: none"> • Anxiety, tension, depressed mood, sleep disorder in neurosis • Somatic symptoms in psychosomatic disease (gastrointestinal disease, cardiovascular disease, endocrine system disease, dysautonomia), and anxiety, tension, depressed mood • Anaesthetic premedication | <ol style="list-style-type: none"> 1. The usual adult dose of oxazolam is 10 to 20 mg, given orally 3 times daily. The dose may be adjusted according to the patient's age and symptoms. 2. In anaesthetic premedication, the usual dose of oxazolam is 1 to 2 mg/kg, given orally before going to bed or before surgery. The dose may be adjusted according to the patient's age, symptoms, and disease. |
| 6 | <p>Quazepam</p> <p>Doral Tablets 15, 20, and the others</p> <p>(Hisamitsu Pharmaceutical Co.,</p> | <ol style="list-style-type: none"> 1. Insomnia 2. Anaesthetic premedication | <ol style="list-style-type: none"> 1. Insomnia The usual adult dosage of quazepam is 20 mg given orally before going to bed. The dose may be adjusted according to the patient's age, symptoms, and disease, but the maximum |

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| | Inc. and the others) | | <p>daily dose is 30 mg.</p> <p>2. Anaesthetic premedication</p> <p>The night before surgery: The usual adult dosage of quazepam is 15 to 30 mg given orally before going to bed. The dose may be adjusted according to the patient's age, symptoms, and disease, but the maximum daily dose is 30 mg.</p> |
| 7 | <p>Cloxazolam</p> <p>Sepazon Tablets 1, 2, Sepazon Powder 1% (Daiichi Sankyo Company, Limited)</p> | <ul style="list-style-type: none"> • Anxiety, tension, depressed mood, obsession , fear, sleep disorder in neurosis • Somatic symptoms in psychosomatic disease (gastrointestinal disease, cardiovascular disease, climacteric disturbance, dysautonomia), and anxiety, tension, depressed mood • Relief of preoperative anxiety | <ol style="list-style-type: none"> 1. The usual adult dose of cloxazolam is 3 to 12 mg daily given orally in 3 divided doses. The dose may be adjusted according to the patient's age and symptoms. 2. To relieve preoperative anxiety, the usual dose of cloxazolam is 0.1 to 0.2 mg/kg given orally before surgery. The dose may be adjusted according to the patient's age and symptoms. |
| 8 | <p>Clotiazepam</p> <p>Rize Tablets 5 mg, 10 mg, Rize Granules 10%, and the others (Mitsubishi Tanabe Pharma Corporation and the others)</p> | <ul style="list-style-type: none"> ○ Somatic symptoms in psychosomatic disease (gastrointestinal disease, cardiovascular disease), and anxiety, tension, hypochondria, depressed mood, sleep disorder ○ Dizziness, shoulder muscle stiffness, inappetence in the following disease Dysautonomia ○ Anaesthetic premedication | <p>The dosage should be determined according to the patient's age and symptoms, but the usual adult dose of clotiazepam is 15 to 30 mg daily given orally in 3 divided doses.</p> <p>In anaesthetic premedication, the dose of clotiazepam is 10 to 15 mg given orally before going to bed or before surgery.</p> |
| 9 | <p>Clorazepate Dipotassium</p> <p>Mendon Capsules 7.5 mg (Mylan EPD G.K.)</p> | <p>Anxiety, tension, feeling irritated, depressed mood in neurosis</p> | <p>The usual adult dosage of clorazepate dipotassium is 9 to 30 mg daily given orally in 2 to 4 divided doses.</p> <p>The dosage of this drug is 2 to 4 capsules (15 to 30 mg of</p> |

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| | | | clorazepate dipotassium) daily given orally in 2 to 4 divided doses. The dose may be adjusted according to the patient's age and symptoms. |
| 10 | Chlordiazepoxide 5 mg Contol Tablets, 10 mg Contol Tablets, Contol Powder 1%, 10%, and the others (Teva Takeda Yakuhin Ltd. and the others) | Anxiety, tension, depressed mood in neurosis Anxiety, tension in depression Somatic symptoms in psychosomatic disease (gastroduodenal ulcer, hypertension), and anxiety, tension, depressed mood | The dose may be adjusted according to the patient's age and symptoms, but it should generally be administered as follows. Adults: The dose of chlordiazepoxide is 20 to 60 mg daily given orally in 2 to 3 divided doses. Children: The dose of chlordiazepoxide is 10 to 20 mg daily given orally in 2 to 4 divided doses. |
| 11 | Diazepam (oral dosage form) 2mg Cercine Tablets, 5 mg Cercine Tablets, 10 mg Cercine Tablets, Cercine Powder 1%, Cercine Syrup 0.1%, and the others (Teva Takeda Yakuhin Ltd. and the others) Horizon Tablets 2 mg, 5 mg, Horizon Powder 1%, and the others (Maruishi Pharmaceutical Co., Ltd. and the others) | <ul style="list-style-type: none"> ○ Anxiety, tension, depressed mood in neurosis ○ Anxiety, tension in depression ○ Somatic symptoms in psychosomatic disease (gastrointestinal disease, cardiovascular disease, dysautonomia, climacteric disturbance, lumbago, cervical syndrome), and anxiety, tension, depressed mood ○ Reduction of muscle tightness in the following diseases Muscle cramps and pain with cerebrospinal disease ○ Anaesthetic premedication | The usual adult dosage of diazepam is 2 to 5 mg given orally 2 to 4 times daily. However, in principle, the daily dosage for outpatients should not exceed 15 mg of diazepam. In pediatric use, the daily dosage of diazepam is 1 to 5 mg in children up to 3 years old and 2 to 10 mg in children 4 to 12 years old, each given orally in 1 to 3 divided doses. For patients with muscle cramps, the usual adult dose of diazepam is 2 to 10 mg given orally 3 to 4 times daily. The dose may be adjusted according to the patient's age and symptoms. In anaesthetic premedication, the usual adult dose of diazepam is 5 to 10 mg given orally before going to bed or before surgery. The dose may be adjusted according to the patient's age, symptoms, and disease. |

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| 12 | <p>Diazepam (injection) Cercine Injection 5 mg, 10 mg, and the others (Teva Takeda Yakuhin Ltd. and the others)</p> | <p>Anxiety, tension, depressed mood in neurosis Reduction of anxiety, excitement, depressed mood in the following disease and condition</p> <ul style="list-style-type: none"> ● Preanesthesia, during anesthetic induction, during anesthesia, after the operation ● Withdrawal symptoms of alcohol dependence ● During delivery <p>Prophylaxis of convulsion in epileptiform conditions</p> | <p>When administering this drug, factors such as the type of disease, severity of symptoms, and the patient's age and body weight should be taken into account.</p> <p>Generally, the initial dose in adults is 2 mL (10 mg of diazepam) injected intravenously or intramuscularly, as gradually as possible, repeated as necessary every 3 to 4 hours.</p> <p>The vein chosen for intravenous administration should be as thick as possible, and intravenous injection should be as gradual as possible (over at least 2 minutes).</p> |
| | <p>Diazepam (injection) Horizon Injection 10 mg and the others (Maruishi Pharmaceutical Co., Ltd. and the others)</p> | <ul style="list-style-type: none"> ○ Anxiety, tension, depressed mood in neurosis ○ Reduction of anxiety, excitement, depressed mood in the following diseases and condition Preanesthesia, during anesthetic induction, during anesthesia, after the operation, withdrawal symptoms of alcohol dependence, during delivery ○ Prophylaxis of convulsion in the following conditions Epileptiform conditions, organophosphate poisoning, carbamate poisoning | |
| 13 | <p>Zopiclone Amoban Tablets 7.5, 10, and the others (Sanofi K.K. and the others)</p> | <ul style="list-style-type: none"> ○ Insomnia ○ Anaesthetic premedication | <p>1. Insomnia The usual adult dosage of zopiclone is 7.5 to 10 mg given orally before going to bed. The dose may be adjusted according to the patient's age and symptoms, but should not exceed 10 mg.</p> <p>2. Anaesthetic premedication</p> |

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| | | | The usual adult dosage of zopiclone is 7.5 to 10 mg given orally before going to bed or before surgery. The dose may be adjusted according to the patient's age, symptoms, and disease, but should not exceed 10 mg. |
| 14 | Zolpidem tartrate Myslee Tablets 5 mg, 10 mg, and the others (Astellas Pharma Inc. and the others) | Insomnia (except for insomnia associated with schizophrenia and manic depressive) | The usual adult dosage of zolpidem tartrate is 5 to 10 mg given orally just before going to bed. In elderly patients, therapy should be initiated at 5 mg. The dose may be adjusted according to the patient's age, symptoms, and disease, but should not exceed 10 mg daily. |
| 15 | Triazolam Halcion Tablets 0.125 mg, 0.25 mg and the others (Pfizer Japan Inc. and the others) | <ul style="list-style-type: none"> ○ Insomnia ○ Anaesthetic premedication | <ul style="list-style-type: none"> ○ Insomnia The usual adult dosage of triazolam is 0.25 mg given orally before going to bed. For severe insomnia, a dose of 0.5 mg may be given. The dose may be adjusted according to factors such as the patient's age, symptoms, and disease, but in elderly patients, the doses should be 0.125 mg to 0.25 mg. ○ Anaesthetic premedication The night before surgery: The usual adult dosage of Triazolam is 0.25 mg given orally before going to bed. If necessary, a dose of 0.5 mg may be administered, taking into account factors such as the patient's age, symptoms, and disease. |
| 16 | Nimetazepam Erimin Tablets 3 mg, 5 mg (Sumitomo Dainippon Pharma Co., Ltd.) | Insomnia | The usual adult dosage of nimetazepam is 3 to 5 mg given orally before going to bed. The dose may be adjusted according to the patient's age and symptoms. |

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| 17 | Haloxazolam Somelin Fine Granules 1%, Somelin Tablets 5 mg, 10 mg (Daiichi Sankyo Company, Limited) | Insomnia | The usual adult dosage of haloxazolam is 5 to 10 mg given orally before going to bed. The dose may be adjusted according to the patient's age and symptoms. |
| 18 | Fludiazepam Erispan Tablets 0.25 mg, Erispan Fine Granules 0.1% (Sumitomo Dainippon Pharma Co., Ltd.) | Somatic symptoms in psychosomatic disease (gastrointestinal disease, hypertension, cardiac neurosis, dysautonomia), and anxiety, tension, depressed mood and feeling irritated, fatigability, sleep disorder | The usual adult dosage of fludiazepam is 0.75 mg daily given orally in 3 divided doses. The dose may be adjusted according to the patient's age and symptoms. |
| 19 | Flutazolam Coreminal Tablets 4 mg, Coreminal Fine Granules 1% (Sawai Pharmaceutical Co., Ltd.) | Somatic symptoms in psychosomatic disease (irritable bowel syndrome, chronic gastritis, gastroduodenal ulcer), and anxiety, tension, depressed mood | The usual adult dosage of Flutazolam is 12 mg daily given orally in 3 divided doses. The dose may be adjusted according to the patient's age and symptoms. |
| 20 | Flutoprazepam Restas Tablets 2 mg (Nihon Generic Co., Ltd.) | Anxiety, tension, depressed mood, fatigability, sleep disorder in neurosis Somatic symptoms in psychosomatic disease (hypertension, gastroduodenal ulcer, chronic gastritis, irritable bowel syndrome), and anxiety, tension, depressed mood, fatigability, sleep disorder | The usual adult dosage of flutoprazepam is 2 to 4 mg daily given orally in 1 to 2 divided doses. The dose may be adjusted according to the patient's age and symptoms, but in elderly patients, the daily dose should not exceed 4 mg. |
| 21 | Flunitrazepam (oral dosage form) Silece Tablets 1 mg, 2 mg, and the others (Eisai Co., Ltd. and the others) | Insomnia Anaesthetic premedication | The usual adult dosage of flunitrazepam is 0.5 to 2 mg given orally before going to bed or before surgery. The dose may be adjusted according to the patient's age and symptoms, but in elderly patients, the dose should not exceed 1 mg. |

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| | Rohypnol Tablets 1, 2, and the others (Chugai Pharmaceutical Co., Ltd. and the others) | | |
| 22 | Flurazepam Hydrochloride Dalmate Capsules 15 (Kyowa Pharmaceutical Industry Co., Ltd.) | 1. Insomnia 2. Anaesthetic premedication | The usual adult dosage is 1 to 2 capsules given orally before going to bed or before surgery. However, the dose of flurazepam hydrochloride should be 10 to 30 mg. The dose may be adjusted according to the patient's age and symptoms. |
| 23 | Brotizolam Lendormin D Tablets 0.25 mg, Lendormin Tablets 0.25 mg, and the others (Nippon Boehringer Ingelheim Co., Ltd. and the others) | Insomnia, Anaesthetic premedication | The dose of this drug may be adjusted according to factors such as the patient's age, symptoms, and disease, but generally, the adult dosage is as follows. <ul style="list-style-type: none"> • Insomnia A dose of 0.25 mg of brotizolam given orally before going to bed. • Anaesthetic premedication The night before surgery: A dose of 0.25 mg of brotizolam given orally before going to bed. Preanesthetic: A dose of 0.5 mg of brotizolam given orally. |
| 24 | Bromazepam (oral dosage form) Lexotan Tablets 1, 2, 5, Lexotan Fine Granules 1%, and the others (Chugai Pharmaceutical Co., Ltd. and the others) | <ul style="list-style-type: none"> • Anxiety, tension, depressed mood and obsession, fear in neurosis • Anxiety, tension in depression • Somatic symptoms in psychosomatic disease (hypertension, gastrointestinal disease, dysautonomia), and anxiety, tension, depressed mood, sleep disorder • Anaesthetic premedication | <ul style="list-style-type: none"> • In neurosis and depression: The usual adult dosage of bromazepam is 6 to 15 mg daily given orally in 2 to 3 divided doses. The dose may be adjusted according to the patient's age and symptoms. • In psychosomatic disease: The usual adult dosage of bromazepam is 3 to 6 mg daily given orally in 2 to 3 divided doses. The dose may be adjusted according to the patient's age and symptoms. • In anaesthetic premedication: |

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| | | | The usual adult dosage of bromazepam is 5 mg given orally before going to bed or before surgery. The dose may be adjusted according to the patient's age, symptoms, and disease. |
| 25 | Mexazolam Melex Tablets 0.5 mg, 1 mg, Melex Fine Granules 0.1% (Daiichi Sankyo Company, Limited) | <ul style="list-style-type: none"> ○ Anxiety, tension, depressed mood, fatigability, obsession, fear, sleep disorder in neurosis ○ Somatic symptoms in psychosomatic disease (gastroduodenal ulcer, chronic gastritis, irritable bowel syndrome, hypertension, cardiac neurosis, dysautonomia), and anxiety, tension, depressed mood, fatigability, sleep disorder | The usual adult dosage of mexazolam is 1.5 to 3 mg daily given orally in 3 divided doses. The dose may be adjusted according to the patient's age and symptoms, but in elderly patients, the daily dose should not exceed 1.5 mg. |
| 26 | Medazepam Resmit Tablets 2, 5, and the others (Shionogi & Co., Ltd. and the others) | <ul style="list-style-type: none"> ○ Anxiety, tension, depressed mood in neurosis ○ Somatic symptoms in psychosomatic disease (gastrointestinal disease, cardiovascular disease, endocrine system disease, dysautonomia), and anxiety, tension, depressed mood | The usual adult dosage of medazepam is 10 to 30 mg daily given orally. However, the dose may be adjusted according to the patient's age and symptoms. |
| 27 | Rilmazafone Hydrochloride Hydrate Rhythmy Tablets 1 mg, 2 mg and the others (Shionogi & Co., Ltd. and the others) | <ol style="list-style-type: none"> 1. Insomnia 2. Anaesthetic premedication | <ol style="list-style-type: none"> 1. Insomnia The usual adult dosage of rilmazafone hydrochloride hydrate is 1 to 2 mg given orally before going to bed. The dose may be adjusted according to the patient's age, disease, and symptoms, but in elderly patients, the dose should not exceed 2 mg. 2. Anaesthetic premedication The usual adult dosage of rilmazafone hydrochloride hydrate is 2 mg given orally before going to bed or before surgery. The dose may be adjusted according to factors such as |

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| | | | patient's age, s disease, and symptoms, but in elderly patients, the dose should not exceed 2 mg. |
| 28 | Ethyl Loflazepate Meilax Fine Granules 1%, Meilax Tablets 1 mg, 2 mg, and the others (Meiji Seika Pharma Co., Ltd. and the others) | <ul style="list-style-type: none"> ○ Anxiety, tension, depressed mood, sleep disorder in neurosis ○ Somatic symptoms in psychosomatic disease (gastroduodenal ulcer, chronic gastritis, irritable bowel syndrome, dysautonomia), and anxiety, tension, depressed mood, sleep disorder | <p>The usual adult dosage of ethyl loflazepate is 2 mg daily given orally in 1 to 2 divided doses.</p> <p>The dose may be adjusted according to the patient's age and symptoms.</p> |
| 29 | Lorazepam Wypax Tablets 0.5, 1.0, and the others (Pfizer Japan Inc. and the others) | <ul style="list-style-type: none"> ○ Anxiety, tension, depressed mood in neurosis ○ Somatic symptoms in psychosomatic disease (dysautonomia, cardiac neurosis), and anxiety, tension, depressed mood | <p>The usual adult dosage of lorazepam is 1 to 3 mg daily given orally in 2 to 3 divided doses. The dose may be adjusted according to the patient's age and symptoms.</p> |
| 30 | Lormetazepam Evamyl Tablets 1.0 (Bayer Yakuhin, Ltd.) LORAMET Tablets 1.0 (Asuka Pharmaceutical Co., Ltd.) | Insomnia | <p>The usual adult dosage of lormetazepam is 1 to 2 mg given orally before going to bed. The dose may be adjusted according to the patient's age and symptoms, but in elderly patients, the dose should not exceed 2 mg.</p> |
| 31 | Clonazepam Rivotril Tablets 0.5 mg, 1 mg, 2 mg, Rivotril Fine Granule 0.1%, 0.5% (Chugai Pharmaceutical Co., Ltd.) Landsen Tablets 0.5 mg, 1 mg, 2 mg, Landsen Fine Granules 0.1%, 0.5% | <p>Small (motor) seizures [myoclonic seizures, atstatic (akinesia) seizures, infantile spasms (infant spasms seizures, BNS convulsions, etc.)]</p> <p>Psychomotor seizures</p> <p>Autonomic seizures</p> | <p>The usual initial adult and pediatric dosage of clonazepam is 0.5 to 1 mg daily given orally in 1 to 3 divided doses. Thereafter, the dosage should be increased gradually according to symptoms until optimal effect is obtained. The usual maintenance dosage of clonazepam is 2 to 6 mg daily given orally in 1 to 3 divided doses. The initial infantile dosage of clonazepam is 0.025 mg per kilogram of body weight daily given orally in 1 to 3 divided doses. Thereafter, the dosage should be increased gradually according to symptoms until optimal effect is obtained. The usual maintenance</p> |

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| | (Sumitomo Dainippon Pharma Co., Ltd.) | | dosage of clonazepam is 0.1 mg per kilogram of body weight daily given orally in 1 to 3 divided doses. The dose may be adjusted according to the patient's age and symptoms. |
| 32 | Clobazam Mystan Tablets 5 mg, 10 mg, Mystan Fine Granules 1% (Sumitomo Dainippon Pharma Co., Ltd.) | Coadministration with other antiepileptics in the following convulsion types when other antiepileptic drugs fail to show satisfactory response Partial seizures Simple partial seizures, complex partial seizures, tonic-clonic seizures with secondary generalization Generalized seizures Tonic-clonic seizures, tonic seizures, atypical absence attacks, myoclonic seizures, atonic seizures | The usual adult dosage of clobazam is an initial dose of 10 mg daily given orally, and gradually increased according to symptoms. The maintenance dosage is 10 to 30 mg daily given orally in 1 to 3 divided doses. The dose may be adjusted according to the patient's symptoms (the maximum daily dose is 40 mg). The usual pediatric dosage of clobazam is an initial dose of 0.2 mg/kg daily given orally, and gradually increased according to symptoms. The maintenance dosage is 0.2 to 0.8 mg/kg daily given orally in 1 to 3 divided doses. The dose may be adjusted according to the patient's symptoms (the maximum daily dose is 1.0 mg/kg). |
| 33 | Diazepam (suppository) Diapp Suppositories 4, 6, 10 (TAKATA Pharmaceutical Co., Ltd.) | Used for the following indications in children Improvement of febrile convulsions and convulsive epileptic seizures | The usual pediatric dosage of diazepam is 0.4 to 0.5 mg/kg inserted rectally once to twice daily. The dose may be adjusted according to the patient's symptoms, but the daily dose should not exceed 1 mg/kg. |
| 34 | Midazolam (products with an indication to treat status epilepticus) Midafresa Injection 0.1% (Alfresa Pharma Corporation) | Status epilepticus | Intravenous injection The usual pediatric dose of midazolam in patients with a corrected gestational age of 45 weeks or longer (gestational age in weeks + weeks after birth) is 0.15 mg/kg injected intravenously. The recommended infusion speed is 1 mg/minute. If necessary, additional doses may be administered within the range 0.1 to 0.3 mg/kg per dose, but the total of the |

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| | | | <p>initial and additional doses should not exceed 0.6 mg/kg.</p> <p>Continuous intravenous infusion</p> <p>The usual initial pediatric dose of midazolam in patients with a corrected gestational age of 45 weeks or longer (gestational age in weeks + weeks after birth) is 0.1 mg/kg/hour by continuous intravenous infusion, with the dosage increased as necessary in steps of 0.05 to 0.1 mg/kg/hour. The maximum dose is 0.4 mg/kg/hour.</p> |
| 35 | <p>Nitrazepam</p> <p>Nelbon Tablets 5 mg, 10 mg, Nelbon Powder 1%, and the others (Daiichi Sankyo Company, Limited and the others)</p> <p>Benzalin Tablets 2, 5, and 10 Benzalin Fine Granules 1% and the others (Shionogi & Co., Ltd. and the others)</p> | <ol style="list-style-type: none"> 1. Insomnia 2. Anaesthetic premedication 3. Atypical petit mal seizures <p>Infantile spasms, myoclonic seizures, astatic seizure, etc.</p> <p>Focal seizures</p> <p>Focal epileptic seizures, psychomotor seizures, autonomic seizures, etc.</p> | <ol style="list-style-type: none"> 1. For insomnia: The usual adult dosage of nitrazepam is 5 to 10 mg given orally before going to bed. The dose may be adjusted according to the patient's age and symptoms. 2. In anaesthetic premedication: The usual adult dosage of nitrazepam is 5 to 10 mg given orally before going to bed or before surgery. The dose may be adjusted according to the factor such as patient's age, symptoms, and disease. 3. Used as an antiepileptic: The usual adult and pediatric dose of nitrazepam is 5 to 15 mg daily given in divided doses as necessary. The dose may be adjusted according to the patient's age and symptoms. |
| 36 | <p>Amobarbital</p> <p>Isomytal (Nippon Shinyaku Co., Ltd.)</p> | <p>Insomnia, sedation of anxiety tension state</p> | <p>For insomnia, the usual adult dosage of amobarbital is 0.1 to 0.3 g daily given orally before going to bed.</p> <p>For sedation of anxiety tension state, the usual adult dosage of amobarbital is 0.1 to 0.2 g daily given orally in 2 to 3 divided doses.</p> <p>The dose may be adjusted according to the patient's age and</p> |

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| 37 | Secobarbital Sodium lonal Sodium For Injection (0.2) (Nichi-Iko Pharmaceutical Co., Ltd.) | Insomnia, anaesthetic premedication, induction of general anesthesia, sedation of anxiety tension state | The usual adult dosage of secobarbital sodium is 100 to 200 mg (2 to 4 mL of 5% solution*) injected gradually, intravenously or intramuscularly. The dose may be adjusted according to the patient's age and symptoms, but the total dose should preferably not exceed 500 mg (10 mL of 5% solution*). *5% solution: 1 vial of this drug dissolved in 4 mL of water for injection or similar vehicle |
| 38 | Pentobarbital calcium Ravona 50 mg (Mitsubishi Tanabe Pharma Corporation) | Insomnia, anaesthetic premedication, sedation of anxiety tension state, adjustment of sleep in continuous sleep therapy | <ul style="list-style-type: none"> ○ Insomnia The usual adult dosage of pentobarbital calcium is 50 to 100 mg given orally before going to bed. The dose may be adjusted according to the patient's age and symptoms. ○ Anaesthetic premedication The usual adult dosage of pentobarbital calcium is 100 to 200 mg the night before surgery or 100 mg 1 to 2 hours before surgery, given orally. The dose may be adjusted according to the patient's age and symptoms. ○ Sedation of anxiety tension state The usual adult dosage of pentobarbital calcium is 25 to 50 mg given orally 2 to 3 times daily. The dose may be adjusted according to the patient's age and symptoms. |
| 39 | Phenobarbital (oral dosage form) Phenobal, Phenobal Powder 10%, | Insomnia Sedation of anxiety tension state | The usual adult dosage of phenobarbital is 30 to 200 mg daily given orally in 1 to 4 divided doses. |

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| | Phenobal Tablets 30 mg, Phenobal Elixir 0.4%, and the others (Fujinaga Pharm. Co., Ltd. and the others) | Convulsive epileptic seizures Tonic-clonic seizures (generalized convulsive seizures and grand mal), focal convulsion (including Jacksonian seizure) Autonomic seizures, psychomotor seizures | For insomnia, the usual adult dosage of phenobarbital is 30 to 200 mg given orally before going to bed. The dose may be adjusted according to the patient's age and symptoms. |
| 40 | Phenobarbital (injection) Phenobal Injection 100 mg (Fujinaga Pharm. Co., Ltd.) | Sedation of anxiety tension state (when urgently necessary) Convulsive epileptic seizures Tonic-clonic seizures (generalized convulsive seizures and grand mal), focal convulsion (including Jacksonian seizure) Autonomic seizures, psychomotor seizures | The usual adult dosage of phenobarbital is 50 to 200 mg injected once to twice daily, subcutaneously or intramuscularly. The dose may be adjusted according to the patient's age and symptoms. |
| 41 | Phenobarbital Sodium (suppository) Wakobital Suppositories 15, 30, 50, 100 (TAKATA Pharmaceutical Co., Ltd.) Lupial Suppositories 25, 50, 100 (Hisamitsu Pharmaceutical Co., Inc.) | Used for the following indications in pediatric if oral administration is not possible 1. Hypnogenesis 2. Sedation of anxiety tension state 3. Improvement of febrile convulsions and convulsive epileptic seizures | The usual pediatric dosage of phenobarbital sodium is 4 to 7 mg/kg daily as standard, inserted rectally. The dose may be adjusted according to the patient's symptoms and indications. |
| 42 | Phenobarbital Sodium (injection) Nobelbar 250 mg for Injection (Nobelpharma Co., Ltd.) | Neonatal convulsions Status epilepticus | Neonatal convulsions: Initial dose: 20 mg/kg of phenobarbital injected intravenously. If convulsions cannot be controlled, additional dose, adjusted according to the patient's condition, should be injected intravenously, within a range that does not exceed the initial |

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| | | | <p>dose.</p> <p>Maintenance dose: 2.5 to 5 mg/kg of phenobarbital once daily injected intravenously.</p> <p>Status epilepticus:</p> <p>15 to 20 mg/kg of phenobarbital once daily injected intravenously.</p> |
| 43 | <p>Phenytoin/Phenobarbital Aleviatin with Phenobarbital Combination Tablets (Sumitomo Dainippon Pharma Co., Ltd.)</p> | <p>Convulsive epileptic seizures</p> <p>Tonic-clonic seizures (generalized convulsive seizures and grand mal)</p> <p>Focal convulsion (including Jacksonian seizure)</p> <p>Autonomic seizures</p> <p>Psychomotor seizures</p> | <p>The usual adult dosage is 1 to 4 tablets daily given orally in divided doses.</p> <p>The dose may be adjusted according to the patient's age and symptoms.</p> |
| 44 | <p>Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate Hydantol D Combination Tablets, Hydantol E Combination Tablets, Hydantol F Combination Tablets (Fujinaga Pharmaceutical Co., Ltd.)</p> | <p>Convulsive epileptic seizures</p> <p>Tonic-clonic seizures (generalized convulsive seizures and grand mal)</p> <p>Focal convulsion (including Jacksonian seizure)</p> <p>Autonomic seizures</p> <p>Psychomotor seizures</p> | <p>The usual adult dosage is 6 to 12 tablets daily given orally in divided doses.</p> <p>The dose may be adjusted according to the patient's age and symptoms.</p> |
| 45 | <p>Primidone Primidone Tablets 250 mg "Nichi-Iko," Primidone Fine Granules 99.5% "Nichi-Iko" (Nichi-Iko Pharmaceutical Co., Ltd.)</p> | <p>Convulsive epileptic seizures</p> <p>Tonic-clonic seizures (generalized convulsive seizures and grand mal)</p> <p>Focal convulsion (including Jacksonian seizure)</p> <p>Psychomotor seizures</p> <p>Small (motor) seizures [myoclonic seizures, astatic (akinesia) seizures, infantile spasms (infant</p> | <p>The usual adult dosage of primidone for the first 3 days of treatment is 250 mg daily given orally before going to bed.</p> <p>Thereafter, the dosage should be gradually increased by 250 mg every 3 days, according to the patient's symptoms, taking into account the disappearance or aggravation of seizures, up to a daily dose of 1,500 mg given orally in 2 to 3 divided doses. If necessary, the daily dose may be increased to 2,000 mg.</p> |

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| | | spasms seizures, BNS convulsions, etc.)] | <p>The pediatric dosage for the first 3 days of treatment is 125 mg daily given orally before going to bed. Thereafter, the dosage should be gradually increased by 125 mg every 3 to 4 days, up to the next standard dosage, given orally in 2 to 3 divided doses.</p> <p>Up to 2 years 250 to 500 mg 3 to 5 years 500 to 750 mg 6 to 15 years 750 to 1,000 mg</p> <p>According to the patient's symptoms, taking into account the disappearance or aggravation of seizures, the dosage may be increased further.</p> |
| 46 | Triclofos Sodium Tricloryl Syrup 10% (Alfresa Pharma Corporation) | Insomnia Sleep in electroencephalography or electrocardiography, etc. | <p>The usual adult dosage of triclofos sodium is 1 to 2 g (10 to 20 mL of syrup) given orally before going to bed or before the test. For young children, the dose may be adjusted according to the patient's age. Taking into account factors such as the patient's age, condition, and the indication, a standard dose of 20 to 80 mg/kg (0.2 to 0.8 mL/kg of syrup) should be used, and the total dose should not exceed 2 g (20 mL of syrup).</p> |
| 47 | Bromovalerylurea Brovarin and the others (Nippon Shinyaku Co., Ltd. and the others) | Insomnia, sedation of anxiety tension state | <p>For insomnia, the usual adult dosage of bromovalerylurea is 0.5 to 0.8 g given orally once daily before going to bed or at bedtime.</p> <p>For sedation of anxiety tension state, the dosage of bromovalerylurea is 0.6 to 1.0 g daily given orally in 3 divided doses.</p> <p>The dose may be adjusted according to the patient's age and symptoms.</p> |

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| 48 | Chloral Hydrate Escre Suppositories "250," Escre Suppositories "500" (Hisamitsu Pharmaceutical Co., Inc.) | Sedation and hypnogenesis in physical examination Status epilepticus where intravenous injection is not possible | The usual pediatric dose of chloral hydrate is 30 to 50 mg/kg as standard, inserted rectally. The dose may be adjusted according to factors such as the patient's age, symptoms, and indications. The total dose should not exceed 1.5 g. |
| | Chloral Hydrate Escre Rectal Kit "500" (Hisamitsu Pharmaceutical Co., Inc.) | | The usual pediatric dosage of chloral hydrate is 30 to 50 mg/kg as standard, infused rectally. The dose may be adjusted according to factors such as the patient's age, symptoms, and indications . The total dose should not exceed 1.5 g. |
| 49 | Tofisopam Grandaxin Tab. 50, Grandaxin Fine gran. 10%, and the others (Mochida Pharmaceutical Co., Ltd. and the others) | Autonomic nervous symptoms such as headache, heaviness of head, malaise, palpitations, and sweating in the following diseases Dysautonomia, head or neck injury, climacteric disturbance or ovarian deficiency symptom | The usual adult dosage of tofisopam is 50 mg given orally 3 times daily. The dose may be adjusted according to the patient's age and symptoms. |

Adverse Drug Reactions (ADR) Investigated As Part of ADR Reports in Japan MedDRA-PT (version 19.0) Attachment 2

| MedDRA-PT | Total number of serious/non-serious ADRs (Number of events) | | | | | | | | | | | | | | |
|---|---|-------------|-----------|----------|----------|----------|------------|-------------|-------------------------|------------------|-----------------|----------------------|-----------|-------------------|-----------|
| | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | (10) | (11) | (12) | (13) | (14) | (15) |
| | Alprazolam | Eszopiclone | Estazolam | Etizolam | Oxazolam | Quazepam | Cloxazolam | Clotiazepam | Clorazepate Dipotassium | Chlordiazepoxide | Diazepam (Oral) | Diazepam (Injection) | Zopiclone | Zolpidem Tartrate | Triazolam |
| Drug withdrawal syndrome neonatal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug withdrawal syndrome | 35 | 1 | 3 | 79 | 0 | 2 | 0 | 16 | 0 | 0 | 8 | 0 | 0 | 8 | 10 |
| Drug withdrawal maintenance therapy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug withdrawal headache | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug withdrawal convulsions | 2 | 0 | 0 | 4 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Dopamine dysregulation syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intentional overdose | 60 | 0 | 10 | 340 | 0 | 0 | 4 | 55 | 0 | 0 | 11 | 0 | 20 | 67 | 66 |
| Intentional product misuse | 9 | 0 | 1 | 118 | 0 | 0 | 3 | 15 | 0 | 0 | 6 | 0 | 0 | 1 | 18 |
| Maternal use of illicit drugs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Substance dependence | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Substance abuse | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Substance abuser | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Neonatal complications of substance abuse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug dependence | 35 | 0 | 2 | 65 | 1 | 0 | 3 | 6 | 1 | 0 | 3 | 0 | 2 | 35 | 27 |
| Drug dependence, postpartum | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug dependence, antepartum | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug abuse | 5 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Drug abuser | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dependence | 12 | 0 | 0 | 62 | 0 | 0 | 0 | 13 | 0 | 0 | 1 | 1 | 0 | 9 | 13 |
| Withdrawal syndrome | 19 | 0 | 0 | 48 | 0 | 0 | 5 | 14 | 0 | 0 | 4 | 0 | 2 | 7 | 26 |
| Total | 179 | 1 | 16 | 720 | 1 | 2 | 16 | 121 | 1 | 0 | 33 | 1 | 24 | 129 | 163 |

| MedDRA-PT | Total number of serious/non-serious ADRs (Number of events) | | | | | | | | | | | | | | |
|---|---|-------------|-------------|------------|---------------|----------------------|--------------------------|------------|-------------------|-----------|-----------|------------------------------------|------------------|-----------|--------------|
| | (16) | (17) | (18) | (19) | (20) | (21) | (22) | (23) | (24) | (25) | (26) | (27) | (28) | (29) | (30) |
| | Nimetazepam | Haloxazolam | Fludiazepam | Flutazolam | Flutoprazepam | Flunitrazepam (Oral) | Flurazepam Hydrochloride | Brotizolam | Bromazepam (Oral) | Mexazolam | Medazepam | Rilimazafone Hydrochloride Hydrate | Ethyl Lofazepate | Lorazepam | Lormetazepam |
| Drug withdrawal syndrome neonatal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug withdrawal syndrome | 1 | 0 | 0 | 0 | 2 | 5 | 0 | 4 | 5 | 0 | 0 | 0 | 30 | 17 | 6 |
| Drug withdrawal maintenance therapy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug withdrawal headache | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Drug withdrawal convulsions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dopamine dysregulation syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intentional overdose | 0 | 0 | 0 | 0 | 0 | 7 | 0 | 10 | 2 | 0 | 0 | 0 | 20 | 8 | 0 |
| Intentional product misuse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 |
| Maternal use of illicit drugs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Substance dependence | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Substance abuse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Substance abuser | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Neonatal complications of substance abuse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug dependence | 0 | 0 | 0 | 0 | 1 | 6 | 0 | 11 | 4 | 2 | 0 | 0 | 8 | 10 | 22 |
| Drug dependence, postpartum | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug dependence, antepartum | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug abuse | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 10 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Drug abuser | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dependence | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 6 | 2 | 0 | 0 | 0 | 5 | 3 | 0 |
| Withdrawal syndrome | 0 | 0 | 0 | 0 | 1 | 6 | 0 | 3 | 1 | 1 | 0 | 0 | 10 | 5 | 2 |
| Total | 1 | 0 | 0 | 0 | 4 | 34 | 0 | 49 | 16 | 3 | 0 | 0 | 74 | 46 | 30 |

| MedDRA-PT | Total number of serious/non-serious ADRs (Number of events) | | | | | | | | | | | | | | |
|---|---|----------|------------------------|--|------------|-------------|---------------------|-----------------------|----------------------|---------------------------|------------------------------------|----------------------------------|-------------------------|--|-----------|
| | (31) | (32) | (33) | (34) | (35) | (36) | (37) | (38) | (39) | (40) | (41) | (42) | (43) | (44) | (45) |
| | Clonazepam | Clobazam | Diazepam (Suppository) | Midazolam (Product indicated for status) | Nitrazepam | Amobarbital | Secobarbital Sodium | Pentobarbital Calcium | Phenobarbital (Oral) | Phenobarbital (Injection) | Phenobarbital Sodium (Suppository) | Phenobarbital Sodium (Injection) | Phenytoin/Phenobarbital | Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate | Primidone |
| Drug withdrawal syndrome neonatal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug withdrawal syndrome | 20 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug withdrawal maintenance therapy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug withdrawal headache | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug withdrawal convulsions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dopamine dysregulation syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intentional overdose | 2 | 0 | 0 | 0 | 7 | 0 | 0 | 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intentional product misuse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Maternal use of illicit drugs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Substance dependence | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Substance abuse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Substance abuser | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Neonatal complications of substance abuse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug dependence | 3 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug dependence, postpartum | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug dependence, antepartum | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug abuse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Drug abuser | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dependence | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Withdrawal syndrome | 14 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 39 | 0 | 0 | 0 | 15 | 0 | 0 | 17 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

| MedDRA-PT | Total number of serious/non-serious ADRs (Number of events) | | | |
|---|--|---------------------|-----------------|-----------|
| | (46) | (47) | (48) | (49) |
| | Triclofos Sodium | Bromvalerylure a | Chloral Hydrate | Tofisopam |
| Drug withdrawal syndrome neonatal | 0 | 0 | 0 | 0 |
| Drug withdrawal syndrome | 0 | 0 | 0 | 1 |
| Drug withdrawal maintenance therapy | 0 | 0 | 0 | 0 |
| Drug withdrawal headache | 0 | 0 | 0 | 0 |
| Drug withdrawal convulsions | 0 | 0 | 0 | 0 |
| Dopamine dysregulation syndrome | 0 | 0 | 0 | 0 |
| Intentional overdose | 0 | 0 | 0 | 0 |
| Intentional product misuse | 0 | 0 | 0 | 0 |
| Maternal use of illicit drugs | 0 | 0 | 0 | 0 |
| Substance dependence | 0 | 0 | 0 | 0 |
| Substance abuse | 0 | 0 | 0 | 0 |
| Substance abuser | 0 | 0 | 0 | 0 |
| Neonatal complications of substance abuse | 0 | 0 | 0 | 0 |
| Drug dependence | 0 | 0 | 0 | 2 |
| Drug dependence, postpartum | 0 | 0 | 0 | 0 |
| Drug dependence, antepartum | 0 | 0 | 0 | 0 |
| Drug abuse | 0 | 0 | 0 | 0 |
| Drug abuser | 0 | 0 | 0 | 0 |
| Dependence | 0 | 0 | 0 | 0 |
| Withdrawal syndrome | 5 | 0 | 0 | 2 |
| Total | 5 | 0 | 0 | 5 |