

Pharmaceuticals and Medical Devices Safety Information

No. 342 April 2017

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Published by
Ministry of Health, Labour and Welfare



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Pharmaceuticals and Medical Devices Safety Information

No. 342 April 2017

Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Japan

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	Precautions for Dependence Associated with Hypnotics-sedatives, Anxiolytics, and Antiepileptics	C	From among hypnotics-sedatives, anxiolytics and antiepileptics, drugs for which adverse drug reactions related to dependence due to prolonged administration at a large dose, etc. are described in package inserts were investigated in terms of safety including dependence based on the accumulation status of adverse reaction reports in Japan and Japanese guidelines, etc. As a result, the Precautions section of package inserts of these drugs has been revised recently. Details of the revision and points to note, etc. for the use of these drugs will be introduced.	4
2	Optimal Clinical Use Guidelines		A commitment to the promotion of optimization of the use of innovative drugs was incorporated, as reform measures for social security, in the "Basic Policy for Economic and Fiscal Management and Reform 2016". In response to this, the Ministry of Health, Labour and Welfare decided that Optimal Clinical Use Guidelines for innovative drugs would be prepared to provide innovative drugs to most appropriate patients. Details of the decision and the guidelines will be introduced.	13
3	Aluminum potassium sulfate hydrate/Tannic acid	P C	Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated March 21, 2017, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.	18
4	Lamotrigine (and 37 others)	P	Revision of Precautions (No. 283)	21
5	List of Products Subject to Early Post-marketing Phase Vigilance		List of products subject to Early Post-marketing Phase Vigilance as of the end of February 2017 is provided.	38

P: Revision of Precautions C: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BA	Barbiturate
BUN	Blood urea nitrogen
BZ	Benzodiazepine
Chuikyo	Central Social Insurance Medical Council
CK (CPK)	Creatine kinase (Creatine phosphokinase)
CRP	C-reactive protein
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
GABA	γ-aminobutyric acid
Glu	Glucose
HbA1C	Hemoglobin A1c
JAS	Japan Atherosclerosis Society
K	Potassium
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDL-R	Low-density lipoprotein cholesterol receptors
MAH	Marketing authorization holder
MedDRA-PT	Medical Dictionary for Regulatory Activities-Preferred Term
MHLW	Ministry of Health, Labour and Welfare
MRI	Magnetic resonance imaging
Na	Sodium
PAFSC	Pharmaceutical Affairs and Food Sanitation Council
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-1 ligand 1
PD-L2	Programmed cell death-1 ligand 2
PED	Pharmaceutical Evaluation Division
PLT	Platelet
PMDA	Pharmaceuticals and Medical Devices Agency
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
RBC	Red blood cells
SD	Safety Division
WBC	White blood cells
γ-GTP	gamma-glutamyl transpeptidase

Precautions for Dependence Associated with Hypnotics-sedatives, Anxiolytics, and Antiepileptics

1. Introduction

Hypnotics or anxiolytics are prescribed by various specialties and widely used in clinical practice. Among these drugs, benzodiazepine (BZ) receptor agonists acting on BZ receptors promote neural transmission of the inhibitory system and show hypnotic-sedative action, anxiolytic action, muscle relaxant action, and anticonvulsant action by binding to the γ -aminobutyric acid (GABA)_A-BZ receptor complex and increasing the GABA_A receptor function. In Japan, since chlordiazepoxide was approved in March 1961, many BZ receptor agonists have been approved as hypnotics-sedatives and anxiolytics.

BZ receptor agonists when used continuously at a large dose are known to sometimes cause drug dependence. Mostly, in the Precautions section of package inserts, attention is called to the dependence when these agonists are used at a large dose over a long period of time. There were some reports on the dependence on BZ receptor agonists overseas from the beginning of the 1960s, but most of them were reports on the onset of withdrawal symptoms at the time of large-dose, long-term, and continuous use. There was probably an influence of the idea that the dependence occurs only when these agonists are administered at a large dose for a long period to patients who have a predisposition for the dependence.¹⁾ Nevertheless, perception of BZ receptor agonists changed in the 1980s, and the idea that the core of the problem is the dependence caused by neither abuse nor non-medical use but by medical use has become gradually more widespread.¹⁾

Considering such a situation, from among hypnotics-sedatives, anxiolytics and antiepileptics, drugs for which adverse drug reactions (ADRs) related to dependence are described in package inserts (refer to Table 1) were investigated in terms of safety including dependence based on the accumulation status of adverse reaction reports in Japan, literature papers, and Japanese guidelines on dependence and withdrawal symptoms.

As a result, it was considered appropriate to instruct marketing authorization holders (MAHs) to revise the Precautions section, and as such they were instructed to revise the Precautions section on March 21, 2017³⁾ after discussion at the 3rd Meeting of the Committee on Drug Safety in Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) in fiscal year (FY) 2016²⁾, held on March 17, 2017. The contents for the recent revision of the Precautions section and the points to note, etc. for the use of these drugs are provided in the present report.

Table 1 Hypnotics-sedatives¹, anxiolytics, and antiepileptics for which adverse reactions related to dependence are described in package inserts

(1) Benzodiazepine receptor agonists (hypnotics-sedatives/anxiolytics)	(2) Benzodiazepine receptor agonists (antiepileptics)
Zopiclone	Diazepam (suppository)
Eszopiclone	Clonazepam
Zolpidem tartrate	Clobazam
Oxazolam	Midazolam (a preparation indicated for status epilepticus)
Clorazepate dipotassium	
Chlordiazepoxide	
Diazepam (oral/injection ²)	(3) Barbiturate drugs (hypnotics-sedatives/anxiolytics)
Alprazolam	Amobarbital
Cloxazolam	Secobarbital sodium
Clotiazepam	Pentobarbital calcium
Fludiazepam	Phenobarbital (oral) ²
Etizolam	Phenobarbital sodium (suppository) ²
Estazolam	
Quazepam	
Triazolam	(4) Barbiturate drugs (antiepileptics)
Nimetazepam	Phenobarbital (injection)
Haloxazolam	Phenobarbital sodium (injection)
Flutazolam	Primidone
Medazepam	Phenytoin/Phenobarbital
Lorazepam	Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate
Flutoprazepam	
Bromazepam (oral)	
Mexazolam	(5) Non-barbiturate drugs (hypnotics-sedatives/anxiolytic)
Ethyl loflazepate	Triclofos sodium
Flunitrazepam (oral)	Bromovalerylurea
Flurazepam hydrochloride	
Brotizolam	
Rilmazafone hydrochloride hydrate	(6) Non-barbiturate drugs (antiepileptic)
Lormetazepam	Chloral hydrate
Nitrazepam ²	

¹ Drugs with the indication for either insomnia or sleep disorder

² Drugs with the indication for antiepileptics among others

2. Results of Survey on Dependence etc. on Hypnotics-sedatives, Anxiolytics, and Antiepileptics and Revisions of Package Inserts

Aggregate results of events related to serious and non-serious dependence or withdrawal symptoms, etc. in Japan obtained by MAHs between initial marketing in Japan and June 30, 2016 (hereinafter, dependence-related events) showed that ingredients for which there were 50 or more reports of dependence-related events were reported include etizolam for 720 events in 695 cases, alprazolam for 179 events in 171 cases, triazolam for 163 events in 158 cases, zolpidem tartrate for 129 events in 126 cases, clotiazepam for 121 events in 118 cases and ethyl loflazepate for 74 events in 64 cases. All of them were BZ receptor agonists. Also, regarding barbiturate (BA) drugs and non-BA drugs, the number of reports of dependence-related events was small, and the most reported ingredient among them was pentobarbital calcium for 17 events in 15 cases.

In adverse reaction reports in Japan, there were a total of 473 cases whose daily dose was within the approved doses range. Among these cases, the treatment duration was known in 116 cases, and the treatment duration was within 14 days in 15 cases and 15 days or more in 101 cases. On the other hand, there were a total of 442 cases whose daily dose exceeded the approved

doses. Among these cases, the treatment duration was known in 54 cases, and the treatment duration was within 14 days in 41 cases and 15 days or more in 13 cases. In total, of the 442 cases whose daily dose exceeded the approval doses, there were 369 cases that included “intentional overdose” and “intentional product misuses” as ADR/adverse event names (MedDRA-PT).

Considering these adverse reaction reports, the review paper and the descriptions in the Japanese guidelines on dependence, withdrawal symptoms, etc., it was decided that revisions are necessary as follows from (1) to (6).

- (1) Physical dependence may be formed due to the long-term use of BZ receptor agonists, and withdrawal symptoms may occur at the time of dose reduction or treatment discontinuation. Involvement of GABA_A receptor α 1 subunit is assumed as a mechanism of dependence formation, and therefore attention should be called to the effect that “dependence” may occur in the Clinically Significant Adverse Reactions section for BZ receptor agonists that are used as hypnotics-sedatives, anxiolytics or antiepileptics with a risk of long-term use or for which long-term use is expected.
- (2) Dependence on BZ receptor agonists may be formed by not only by “prolonged used of large doses” but also by “prolonged use” within the range of approved doses, and therefore the statement to call attention in case dependence occurs will be changed from “due to prolonged use of large doses” to “due to prolonged use,” and the statement to call attention in case withdrawal symptoms occur will be changed from “during administration of large doses or during prolonged use” to “during prolonged use”.
- (3) Dependence formation may occur for all BA drugs that bind to the BA binding site, and therefore attention should be called to the effect that “drug dependence” may occur in the Clinically Significant Adverse Reactions section for all BA drugs that are used as hypnotics-sedatives, anxiolytics or antiepileptics.
- (4) It is said that non-BA chloral drugs and bromovalerylurea drugs may also form dependence, and therefore the statement to call attention in case withdrawal symptoms occurs should be changed from “during administration of large doses or during prolonged use” to “during prolonged use”.
- (5) A statement to the effect “Caution should be exercised for dosage and treatment duration when administering this drug” should be added to the “dependence or drug dependence” in the Clinically Significant Adverse Reactions section for BZ receptor agonists and BA drugs.
- (6) For BZ receptor agonists, BA drugs, and non-BA drugs that are indicated for hypnotics-sedatives, and anxiolytics with the risk of long-term use, “Long-term use by chronic administration should be avoided” and “Therapeutic necessity should be carefully considered when continuing administration of these drugs” should be added to the Important Precautions section so that dependence that may be formed by long-term treatment can be avoided in advance.

Also, for BZ receptor agonists, attention is called by stating that when persons with mental disorders such as schizophrenia are treated with these drugs, adverse reactions such as irritable excitation and confusion that correspond to paradoxical reactions may occur. However, since these adverse reactions may occur in any patients treated, it was determined appropriate to delete descriptions such as “persons with mental disorders such as schizophrenia”.

Regarding the modified parts of the Precautions section dated March 21, 2017, please refer to “4. Revision of Precautions (No. 283) (P 21)” in this issue.

3. Points to Note for Use of Hypnotics-sedatives, Anxiolytics or Antiepileptics

Hypnotics-sedatives, anxiolytics, and antiepileptics as represented by BZ receptor agonists are drugs whose expected efficacy and safety can be ensured when they are properly used with attention paid to not only the dosage level but also the treatment duration.

Until now, in package inserts, attention has been called to dependence and withdrawal symptoms when large doses are used continuously. Considering that there have been reports of cases that developed adverse reactions related to dependence due to prolonged use of these drugs within the range of approved doses, it is requested that attention be paid to the precautions in Table

2 after carefully checking the latest package inserts, etc. when using these drugs which may cause dependence, and that patient adherence management and medication guidance be conducted for patients in an appropriate manner⁴).

Table 2

1. Even within the range of approved doses, drug dependence may occur due to prolonged use, and therefore
 - (1) Caution should be exercised for dosage and treatment duration when administering these drugs
 - (2) Long-term use by chronic administration should be avoided when using these drugs as hypnotics-sedatives or anxiolytics. Therapeutic necessity should be carefully considered when continuing administration of these drugs.
2. Even within the range of approved doses, the primary disease may worsen or withdrawal symptoms may occur due to rapid reduction in dose level during continuous use or due to discontinuation of administration. If administration of these drugs is to be discontinued, discontinuation should be done carefully by means such as gradual dose reduction.
3. For BZ receptor agonists, patients should be carefully monitored because these drugs may cause irritable excitation, confusion, etc. in cases not limited to patients with schizophrenia or elderly patients.

4. Case Summaries

Case 1 Etizolam

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Male 30s	Social anxiety disorder	1 mg for 603 days ↓ Dose increased to 2 mg for 556 days ↓ Discontinued ↓ 2 mg Administration resumed approximately 3 days after discontinuation. Treatment duration unknown.	Seizure The patient had nausea in the morning from around 7 months before administration of this drug. The skin inside the mouth started to peel off. The patient had headache and feeling hot all day. He was demotivated, feeling sluggish, and feeling frustrated. Anxiety. He was having trouble thinking clearly. Feeling depressed, feeling melancholy, and feeling down. He had severe nausea present before breakfast, thus breakfast was not taken recently. He had an appetite at night. He had no nausea in the morning of holidays. Day 1 of administration: He made the first visit to this hospital. For the diagnosis of social anxiety disorder, this drug, sulpiride (50 mg/day), and 1 capsule/day of a combination drug containing diastase started to be administered. Day 15 of administration: He said he was "rather comfortable" while taking this drug. Day 34 of administration: As he said he was "very comfortable" while taking this drug, this drug was continuously administered until 561 days thereafter (Day 594 of administration). Day 604 of administration: As he complained "I am out of shape, and don't want to talk with anyone at work" and "I suddenly don't feel like eating", this drug (0.5 mg × 2 tablets/day) was added to this drug (1 mg), sulpiride (50 mg/day) and 1 capsule/day

			<p>of the combination drug containing diastase.</p> <p>Day 622 of administration: The patient visited the hospital. As he said he was “very comfortable” while taking this drug, this drug (0.5 mg × 2 tablets/day) was administered until Day 1159 of administration, with this drug (1 mg), 1 tablet of sulpiride (50 mg/day), and 1 capsule/day of the combination drug containing diastase. After that, he did not take this drug because he ran out of it.</p> <p>Day 1162 of administration: At a regular visit, he developed a grand mal in the outpatient waiting room. He uttered a strange sound while sitting in a chair, lost consciousness after standing up from the chair, fell with his head bumping against the near desk, and had a convulsion for approximately 3 minutes, thrashing his arms and legs. While repeating deep breathing many times, he fell into a befogged state and tried to stand up. Because this state was persistent for approximately 10 minutes, he was placed in a bed. After that, he tried to hang around in a befogged state while coughing, so he was placed again in the bed. He developed nausea and vomiting several times, but probably because of not having taken breakfast, he only vomited mucosal fluid. In approximately 1 hour, he returned to sanity. He felt drugged but headache was mild. It was a tonic-clonic seizure. The previous night, nausea did not stop, so he went to a neighboring hospital for an emergency medical service and received a drug for nausea. He had no history of development of epileptic seizures in the past. As he awoke from the seizure, the same prescriptions were resumed. This drug (0.5 mg × 2 tablets/day) was administered with 1 tablet of this drug (1 mg), 1 tablet of sulpiride (50 mg), and 1 capsule/day of the combination product containing diastase.</p> <p>Day 1163 of administration: For electroencephalographic examination and MRI, the patient was referred to a neighboring hospital, but returned home without undergoing the examinations. Convulsive seizures resolved.</p>
	Laboratory Examination Values of laboratory examination are not available.		
	Suspected concomitant medication: Sulpiride Concomitant medication: Combination drug containing diastase		

Case 2 Zolpidem tartrate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Outcome
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures	
	Female 40s	Insomnia (ulcerous colitis, anxiety, numbness, large intestinal operation,	5 mg + 5 mg as needed for approximately	Hypnotic drug dependence Approximately 5 and a half years before administration: Subtotal colectomy and ileostomy	Improved

		enterostomy)	<p>43 days ↓ (suspended for 12 days) ↓ 10 mg for 80 days ↓ 5 mg for approximately 15 days ↓ (suspended for approximately 57 days) ↓ 10 mg for 1 day</p>	<p>were performed. The patient became aware of having become out of shape due to complications with the procedures, and subsequently showed excessive anxiety about medical procedures or drugs.</p> <p>118 days before administration: At the internal medicine department of Hospital A, administration of zopiclone 7.5 mg/day was started for insomnia.</p> <p>Approximately 2 days before administration: As the patient could feel the effect for only several days, administration of zopiclone was discontinued.</p> <p>Day 1 of administration: At the psychiatric department of Hospital B, administration of 5 mg/day of this drug started for insomnia.</p> <p>Date unknown: 5 mg/day of this drug was added on an as-needed basis.</p> <p>Day 13 of administration: Administration of lormetazepam 1 mg/day was started for insomnia.</p> <p>Day 27 of administration: Administration of diazepam 2 mg/day was started for anxiety.</p> <p>Approximately Day 43 of administration (suspension of this drug): Insomnia was improved by oral administration of hypnotic drugs, but the patient self-interrupted all psychotropic drugs (this drug, lormetazepam, diazepam), thinking "I don't want to rely on hypnotic drugs; I want to quit them".</p> <p>Approximately Day 50 of administration: Oral administration could be discontinued for approximately 1 week, but insomnia worsened more than the degree before the start of oral administration (rebound phenomenon), and withdrawal signs such as headache, photophobia, and dysphoria also occurred transiently. The oral drugs taken before discontinuation were resumed (lormetazepam, diazepam), but the patient could sleep for only 2-3 hours, without improvement of insomnia as seen before.</p> <p>Day 55 of administration</p>	
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			<p>(resumption of this drug): Because of inadequate response, 10 mg/day of this drug was added.</p> <p>Day 83 of administration: Administration of etizolam 0.5 mg as needed was started.</p> <p>Day 104 of administration: Diazepam 2 mg as needed was added.</p> <p>Day 105 of administration: Administration of triazolam 0.25 mg on an as-needed basis was started.</p> <p>Date unknown Administration of etizolam was discontinued.</p> <p>Approximately Month 4 of administration: Administration of triazolam was discontinued.</p> <p>Approximately Month 4 of administration: With self-adjustment of medications such as as-needed drugs to be used at the time of sleeping difficulty, the patient started to use them at dose levels higher than the levels instructed by the doctor. Even after that, improvement of insomnia was not achieved.</p> <p>Date unknown: Administration of etizolam was resumed at 3 mg on an as-needed basis.</p> <p>Approximately 4 and a half months of administration: Preexisting condition at initial visit to the psychiatric department of Hospital C: Consciousness was lucid. The patient was seemingly calm, but spoke of regret about the use of hypnotic drugs and suddenly cried, showing strong anxiety. The average sleep duration immediately before the visit, as reported by the patient, was approximately 2 hours, and there were days when she could not sleep at all. Psychological dependence, intolerance, withdrawal symptoms, and failure in discontinuation or restriction of hypnotic drugs were obvious based on medical history taking/medical interview, and therefore the patient was diagnosed with hypnotic drug dependence. Insomnia was determined to be neurotic insomnia based on the clinical</p>	
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				<p>course of symptoms and the premorbid personality. When a hypnotic drug was down-titrated (5 mg/day of this drug) while concomitantly using chlorpromazine hydrochloride 12.5 mg/day, dose reduction of the hypnotic drug was possible, but the drug could not be discontinued.</p> <p>Approximately Month 5 of administration (suspension of this drug):</p> <p>After that, chlorpromazine hydrochloride was up-titrated to 25-37.5 mg/day, and this drug and lormetazepam were down-titrated and discontinued sequentially, but no withdrawal sign occurred during the down-titration period.</p> <p>Day 208 of administration (resumption/discontinuation of this drug):</p> <p>When discontinuation of hypnotic drugs was tried, insomnia relapsed. As a drug to be used at the time of sleeping difficulty, 10 mg/day of this drug was used again, but there was no particular adverse reaction.</p> <p>Approximately 29 days after discontinuation:</p> <p>Hypnotic drug dependence improved. Finally, stable sleep for approximately 7 hours could be achieved with diazepam 5 mg/day, chlorpromazine hydrochloride 37.5 mg/day, and flunitrazepam 1.5 mg/day.</p>	
<p>Concomitant medications: zopiclone, lormetazepam, diazepam, etizolam, triazolam, chlorpromazine hydrochloride, combination drug containing clostridium butyricum</p>					

5. Closing Comments

Healthcare professionals are requested to understand the main purport of the present revision and also continuously cooperate for the proper use of these drugs. PMDA issued PMDA Alert for Proper Use of Drugs (for healthcare professionals): Dependence associated with BZ Receptor Agonists. Please refer to the document as appropriate.

<References>

- 1) *Journal of Practical Pharmacy* 2015; 66(12): 2949-2954
- 2) Materials 1-4 for the FY2016 Meeting of the Committee on Drug Safety in Pharmaceutical Affairs Department of the PAFSC (3rd meeting held on March 17, 2017)
URL: (only available in Japanese language)
<http://www.mhlw.go.jp/stf/shingi2/0000156310.html>
- 3) Revision of Precautions (Pharmaceutical Safety and Environmental Health Bureau [PSEHB]/ Safety Division [SD] Notification No. 0321-1, dated March 21, 2017)
URL: (only available in Japanese language)
<http://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-iyakushokuhinkyoku/0000155824.pdf>
- 4) Disseminating information on the Revision of Precautions for Hypnotics-sedatives, Anxiolytics and Antiepileptics (for Request) (PSEHB/SD Notification No. 0321-2 and-3, dated March 21, 2017)

URL: (only available in Japanese language)

<http://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-iyakushokuhinkyoku/0000155825.pdf>

5) PMDA Alert for Proper Use of Drugs (for healthcare professionals): Dependence associated with BZ Receptor Agonists

URL:

<https://www.pmda.go.jp/files/000217228.pdf>

Optimal Clinical Use Guidelines

Introduction

A commitment to the promotion of optimization of the use of innovative drugs was incorporated, as reform measures for social security, in the “Basic Policy on Economic and Fiscal Management and Reform 2016” (Cabinet decision on June 2, 2016). In response to this, the Ministry of Health, Labour and Welfare (MHLW) decided that Optimal Clinical Use Guidelines for innovative drugs would be prepared to provide innovative drugs to most appropriate patients.

Innovative drugs such as drugs with a new action mechanism tend to have large differences from existing products regarding the sign of effectiveness and safety profiles. To realize the optimal use of such products, it is important to clarify the types of patients who will be truly benefited from them and the requirements for doctors and medical institutions to appropriately use them. Therefore, “Optimal Clinical Use Guidelines” will be published following the marketing approval of such drugs. Optimal Clinical Use Guidelines will be developed based on scientific evidence with the cooperation of relevant academia and the Pharmaceuticals and Medical Devices Agency (PMDA).

As one of measures to deal with the issue of expensive drugs, MHLW will notice points of consider for insurance coverage according to the guidelines to use innovative drugs appropriately, based on recommendations from the Central Social Insurance Medical Council (Chuikyo).

For FY 2016, the guidelines were published as the pilots for an anti-PD-1 antibody; nivolumab (genetical recombination) (product name: Opdivo Intravenous Infusion 20 mg, 100 mg) and its similar drug, as well as an anti-PCSK9 antibody; evolocumab (genetical recombination) (product name: Repatha SC injection 140 mg syringe, Repatha SC injection 140 mg pen) and its similar drug. Their contents are presented in this section.

2. Contents in Optimal Clinical Use Guidelines

To use innovative drugs effectively and safely, it is important to use these drugs in patients who are expected to greatly benefit from the drugs and use the drugs at medical institutions that are able to take necessary action if adverse reactions occur, until information on the efficacy and safety are accumulated sufficiently.

For this reason, the guidelines are to describe necessary requirements, principles, and points to consider for promoting optimization of the use of the drug based on the medical/pharmaceutical and scientific viewpoints that have been obtained by the time of the publication of the guidelines. The guidelines are structured as follows.

(1) Introduction

Information such as the background/history and positioning of the guidelines and relevant academia that have cooperated for the formulation of the guidelines for the drugs are provided.

(2) Characteristics and action mechanisms of the drugs

For the use of the drugs, the action mechanisms, etc. are described to understand their characteristics.

(3) Clinical data

Clinical data obtained by the time of the formulation of the guidelines, such as information on the efficacy and safety of the drugs in clinical studies for marketing approval are included. In addition, reference information are provided for selection of patients who are administered the drugs.

(4) Requirements for medical institutions

To use the drugs in patients who are expected to greatly benefit from the drugs, the diagnosis/identification of patients for whom administration is most appropriate as well as

necessary appropriate action at the time of occurrence of serious adverse reactions are needed, and therefore requirements for medical institutions that may deal with these matters are described.

(5) Eligibility criteria of patients

Criteria of patients for the specification of cases where the use of the drugs is expected to be highly beneficial are shown from the viewpoints of the safety and efficacy of the drugs.

(6) Points to consider for administration

Points to consider when the drugs are used, such as characteristic adverse reactions and information on efficacy evaluation are shown for using the drugs safely and effectively.

3. Summary of Published Optimal Clinical Use Guidelines

The summary of the guidelines published in FY 2016 is as shown below. For the details of each guideline, please check the notification issued.

3-1. Nivolumab (genetical recombination) and Pembrolizumab (genetical recombination)

- Optimal Clinical Use Guidelines (Non-Small-Cell Lung Cancer and Malignant Melanoma) for Nivolumab (Genetical Recombination) and Pembrolizumab (Genetical Recombination) (PSEHB/PED Notification No. 0214-1, issued by the Director, Pharmaceutical Evaluation Division (PED), PSEHB, MHLW on February 14, 2017)
- Optimal Clinical Use Guidelines (Head and Neck Cancer) for Nivolumab (Genetical Recombination) (PSEHB/PED Notification No. 0324-11, issued by the Director, PED, PSEHB, MHLW on March 24, 2017)

In the human body, T cells recognize antigen-presenting cancer cells and exert cytotoxic activity. Cancer cells are considered to avoid attacks by T cells by expressing PD-1 (programmed cell death-1) ligands (PD-L1 and PD-L2) which bind to PD-1 receptor found on T cells and binding to PD-1.

The anti-PD-1 antibodies nivolumab (genetical recombination) and pembrolizumab (genetical recombination) are monoclonal antibodies against human PD-1. These are so-called "immune checkpoint inhibitors" which exert an anti-tumor effect through mechanisms such as inhibiting the interaction between the PD-1 receptor found on T cells and PD-1 ligands in cancer cells and enhancing/re-activating the cytotoxic activity in T cells. The action mechanisms of these drugs are very different from conventional anticancer agents.

So, anti-PD antibodies involve adverse reactions due to excessive immune response based on their action mechanisms, which is a characteristic largely different from conventional anticancer agents. It is necessary to administer these agents only to patients for whom the use of these agents is identified to be appropriate, under the direction of a doctor who has sufficient knowledge/experience of cancer chemotherapy, at medical institutions that can sufficiently deal with emergencies after being thoroughly familiar with such efficacy and safety profiles.

Such being the situation, the Optimal Clinical Use Guidelines describe the following requirements, etc.

Essential points for institutions and patients to be administered listed in the Optimal Clinical Use Guidelines for Nivolumab (Genetical Recombination) and Pembrolizumab (Genetical Recombination)

△ Requirements for medical institutions

Considering the drug use-results survey (all-case surveillance) required as a condition for approval, medical institutions must be able to conduct the survey properly. In addition, the medical institutions should be able to diagnose and identify patients for whom administration of the drugs are appropriate and to respond to serious ADRs that may occur associated with the drugs. Therefore, the drugs should be used in medical institutions that satisfy the requirements listed in the guidelines.

△ Eligibility criteria of patients

[Issues related to safety]

- These drugs should not be administered to patients corresponding to Contraindications.
- For patients corresponding to Careful Administration, etc., administration of these drugs is not

recommended, but careful administration of these drugs may be considered only when there are no other treatment options.

[Issues related to efficacy]

- Patients in whom the efficacy was confirmed in clinical trials
- Patients in whom the efficacy has not been established (e.g. combination with another anti-malignant tumor agent) are not to be administered.
- Information about PD-L1 expression rate (in cases of non-small-cell lung cancer) etc.

3-2. Evolocumab (genetical recombination) and Alirocumab (genetical gecombination)

- Optimal Clinical Use Guidelines for Evolocumab (Genetical Recombination) and Alirocumab (Genetical Recombination) (PSEHB/PED Notification No. 0331-1, issued by the Director, PED, PSEHB, MHLW dated March 31, 2017)

Uptake of plasma low-density lipoprotein cholesterol (LDL-C) into liver cells requires low-density lipoprotein cholesterol receptors (LDL-R) on the liver cell surface. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is considered to directly bind to LDL-R, and cause degradation of LDL-R after being taken up into liver cells, together with low density lipoprotein (LDL) and LDL-R, and then increase LDL-C in the bloodstream.

The anti-PCSK9 antibodies evolocumab (genetical recombination) and alirocumab (genetical recombination) are monoclonal antibodies against PCSK9. These drugs inhibit the binding of PCSK9 in the bloodstream to LDL-R on the liver cell surface by binding to PCSK9, increase the LDL-R count on the liver cell surface by inhibiting the degradation of LDL-R and promoting the recycle back to the liver cell surface, and finally reduce the plasma LDL-C level. They are antibody products with action mechanisms different from existing therapeutic drugs for hypercholesterolaemia.

Many of patients who need treatment for hypercholesterolaemia are very likely to require long-term use, and therefore when using an anti-PCSK9 antibody which is an injectable drug with a new action mechanism, it is necessary to appropriately select patients for whom the drug should be used and evaluate the start of administration after performing sufficient medical examinations and tests prior to its application, and sufficiently performing/considering treatment with dietary therapy, exercise therapy, existing medications and so on.

Such being the situation, the Optimal Clinical Use Guidelines describe the following requirements, etc.

Essential points for institutions and patients to be administered listed in the Optimal Clinical Use Guidelines for Evolocumab (Genetical Recombination) and Alirocumab (Genetical Recombination)

△ Requirements for medical institutions

It is important that these drugs are indicated for proper patients carefully when starting administration of these drugs. Moreover, since these patients are likely to need long-term use once these patients started these drugs, the convenient access to institutions must be ensured for these patients.

1) For the start of administration

(1) Medical institutions

- Institutions that have doctors who have sufficient knowledge for these drugs, perform comprehensive risk management of atherosclerotic cardiovascular diseases.
- Institutions that have doctors who sufficiently understand the contents of the JAS Guidelines 2012 (Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012) and are able to select high risks patients of atherosclerotic cardiovascular diseases and provide appropriate treatments.
- Institutions that have doctors with ample experience in patients with familial hypercholesterolaemia.
- Institutions that is able to appropriately conduct post-marketing surveys based on the Risk Management Plan (RMP), to evaluate the safety and efficacy after marketing of the drugs.

(2) In-hospital drug information management structure

2) For the continuation of administration

Institutions that meet the requirements in “1) For the start of administration” or can collaborate with an institution meeting the requirement in 1) and meet the following requirements:

- (1) Institutions that have doctors who have sufficient experience for the patients in hypercholesterolaemia and are able to appropriately decide whether these drugs should be continued or not.
- (2) In-hospital drug information management structure as above in 1).

△ Eligibility criteria of patients

[Patient selection]

It is important to use these drugs in high risk patients for atherosclerotic cardiovascular diseases who have not reached the management targets for dyslipidemic patients in the JAS Guidelines 2012 despite having taken statin at the maximum tolerated dose († Note) for a certain period.

The optimal patients for these drugs are assumed to be mainly those with familial hypercholesterolemia who have not reached the management targets for dyslipidemic patients and those with past history of coronary artery disease. For the use of these drugs in patients considered to have a high risk for cardiovascular events who do not fall under such criteria, statin adherence to or control status of other risk factors related to arteriosclerotic diseases should be carefully evaluated.

For deciding the necessity/unnecessity of administration of the drugs, the following requirements should be confirmed:

- 1) For patients with non-familial hypercholesterolemia, the risk of onset of cardiovascular events should be high. And in evaluating the risk, One or more of the following risk factors should be present:
 - (1) Past history of coronary artery disease (including coronary angioplasty for stable angina pectoris)
 - (2) Past history of non-cardiogenic cerebral infarction
 - (3) Diabetes mellitus
 - (4) Chronic kidney disease
 - (5) Peripheral arterial disease
- 2) The management targets for dyslipidemic patients has not been reached with the use of statin for the adequate period prior to the administration of these drugs. Adequate follow up periods using statin at the maximum tolerated dose († Note) are as below,
 - period that doctors think as clinically adequate period for using statin in patients with familial hypercholesterolemia and patients meeting the above (1) or (2),
 - 3 months or longer in other patientsMoreover, concomitant use of ezetimibe in addition to statin should be considered prior to the administration of the drugs.
- 3) Medical treatments, including dietary therapy, exercise therapy, smoking cessation as the basic approach for the treatment of hypercholesterolemia and reduction of other risk factors (diabetes mellitus, hypertension) for atherosclerotic cardiovascular diseases, have been performed sufficiently.

* It is important to suspect familial hypercholesterolemia in patients with hypercholesterolemia whose lipid control is poor despite the maximum tolerated dose of statin they are taking. Consulting with a doctor with ample experience in patients with familial hypercholesterolemia should be considered.

(† Note) The maximum tolerated dose refers to a dose that a doctor decides it would be inappropriate for his/her patient to exceed, considering the risk for ADRs associated with an increase or background of the patient (age, renal function disorders etc.)

3. Closing Comments

Until now, Optimal Clinical Use Guidelines have been published as the pilots for nivolumab (genetical recombination) and pembrolizumab (genetical recombination), as well as evolocumab (genetical recombination) and alirocumab (genetical recombination). In the future, Optimal Clinical Use Guidelines will be published in time with new approval of innovative drugs.

In addition, published Optimal Clinical Use Guidelines will be revised as necessary based on information of efficacy/safety obtained after marketing.

For using innovative drugs effectively and safely in patients who will be truly benefited from them, it is requested that the latest contents of Optimal Clinical Use Guidelines for each drug be

understood and efforts be made for more appropriate use when using drugs for which Optimal Clinical Use Guidelines have been published.

3

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated March 21, 2017, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Aluminum potassium sulfate hydrate/Tannic acid

Brand name (name of company)	Zione Injection/Lidocaine, Zione Injection (Mitsubishi Tanabe Pharma Corporation)
Therapeutic category	Hemorrhoidal preparations
Indications	Internal haemorrhoids associated with prolapse

PRECAUTIONS (underlined parts are revised)

Important Precautions

Caution should be exercised regarding the event as follows that may occur with the administration procedure.

Rectovaginal fistula [A rectovaginal fistula may occur when injecting into anterior hemorrhoids in women and in case the injection needle penetrates the entire thickness of the rectal wall and the product is inserted/injected into vaginal and proximal sites. Patients should be carefully monitored and appropriate measures such as surgery should be taken.

Adverse reactions (clinically significant adverse reactions)

Rectovaginal fistula: A rectovaginal fistula may occur after administration of the product. Patients should be monitored regularly. If a fistula is observed, appropriate measures such as surgery should be taken.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 8 months (April 2013 to December 2016)

Cases related to rectovaginal fistula: 1 case (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 46 000

Launched in Japan: March 2005

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Outcome
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures	
1	Female 40s	Internal haemorrhoids (hypertension)	20 mL for 1 day ↓ 20 mL for 1 day	Rectal ulcer, rectovaginal fistula Day of first dose: The patient received the first dose of this drug. Day of second dose: (157 days after first dose) The patient received the second dose of this drug (anterior: 4 cc; 4	Improved

			<p>o'clock direction: 8 cc; 7 o'clock direction: 8 cc).</p> <p>1 day after second dose: Due to pain, the patient visited the hospital.</p> <p>Swab containing lidocaine was inserted into the anus. She returned home. Rectal ulcer developed.</p> <p>2 days after second dose: Magnesium oxide (300 mg x 3T), acetaminophen (200 mg x 6T) and suvorexant (20 mg x 1T) were prescribed. Ceftriaxone sodium hydrate (1 g) + saline (100 ml) were intravenously administered.</p> <p>5% maltose - lactated Ringer's solution (500 mL x 2 vials) and 1% glucose (Glu) acetated Ringer's solution (500 mL x 2 vials) were infused.</p> <p>3 days after second dose: Loxoprofen sodium hydrate (3T), cefcapene pivoxil hydrochloride hydrate (3T) and pronase (3T) were prescribed. Ceftriaxone sodium hydrate (1 g) + physiological saline (100 ml) were intravenously administered.</p> <p>4 days after second dose: Diflucortolone valerate-lidocaine (2 g x 1 time/day x 7 vials) and bifidobacterium (3 T x 7 days) were prescribed.</p> <p>5 days after second dose: Pronase (3 T x 7 days) and lansoprazole (15 mg x 7 days) were prescribed.</p> <p>8 days after second dose: Rectovaginal fistula developed.</p> <p>23 days after second dose: The patient was transferred to another hospital.</p> <p>31 days after second dose: The patient was admitted to the hospital.</p> <p>32 days after second dose: Surgery was performed. Colostomy (sigmoid colon).</p> <p>40 days after second dose: The patient was discharged from the hospital. Rectovaginal fistula persisted.</p> <p>299 days after second dose: The patient was admitted to the hospital.</p> <p>300 days after second dose: The defective part of the vagina</p>	
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				<p>was closed with the right gluteal fold flap.</p> <p>321 days after second dose: The patient was discharged from the hospital.</p> <p>468 days after second dose: Closure of rectovaginal fistula was confirmed with barium enema.</p> <p>499 days after second dose: Intestinal epithelialization at the site of closure was confirmed with colonoscopy.</p> <p>535 days after second dose: The patient was admitted to the hospital.</p> <p>536 days after second dose: Sigmoid colon stoma was closed.</p> <p>543 days after second dose: The patient was discharged from the hospital.</p>	
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Laboratory Examination

Test item	2 days after second dose:	24 days after second dose:	51 days after second dose:
RBC (x 10000/mm ³)	440	439	443
WBC (/mm ³)	13200	7480	9950
Hemoglobin level (g/dL)	13.3	14.1	13.9
Hematocrit level (%)	41.6	41.9	41.7
PLT count (x 10000/mm ³)	31.3	43.5	46.4
AST(GOT) (IU/L)	40	33	18
ALT(GPT) (IU/L)	27	25	19
LDH (IU/L)	250	173	141
CK(CPK) (IU/L)	27	31	
γ-GTP (IU/L)	252	138	90
Total bilirubin (mg/dL)	0.6	0.4	0.2
Uric acid (mg/dL)	6.1	7.5	
BUN(mg/dL)	5.8	11	12
Serum creatinine (mg/dL)	0.48	0.56	0.54
Total protein (g/dL)	6.5	6.7	6.6
Neutral fat (mg/dL)	89	92	
CRP(mg/dL)	5.36	0.088	0.179
Na (mEq/L)	142	143	142
K (mEq/L)	3.2	4.2	4.0
Hemoglobin HbA1C (%)	5.2		
Blood Glu (mg/dL)	99		
Albumin (g/dL)		3.9	3.7
Concomitant medications: none			

Revision of Precautions (No. 283)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated March 21, 2017

1

Antiepileptics

Lamotrigine

Brand name

Lamictal Tablets 25 mg and 100 mg (GlaxoSmithKline K.K.),
Lamictal Tablets for pediatrics 2 mg and 5 mg (GlaxoSmithKline K.K.)

Precautions of dosage and administration

Caution should be exercised on drugs to be used in combination for the following category. In addition, drugs as combination therapy that are not known to affect the glucuronidation of lamotrigine should follow the dosage and administration of lamotrigine concomitantly used with sodium valproate. Drugs that do not affect the glucuronidation of lamotrigine are as follows: Aripiprazole, olanzapine, zonisamide, gabapentin, cimetidine, topiramate, pregabalin, lithium, levetiracetam, perampanel, and lacosamide

2

Hypnotics and sedatives, anxiolytics

Amobarbital

Brand name

Isomytal (Nippon Shinyaku Co., Ltd.)

**Important
Precautions**

Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.

**Adverse reactions
(clinically significant
adverse reactions)**

Drug dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. Careful attention should be paid especially to patients with alcoholism, tendency to develop drug dependence or medical history of drug dependence, and serious neurosis. In addition, withdrawal symptoms such as anxiety, insomnia, convulsions, nausea, hallucinations, delusion, excitation, confusion, or depressed state may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Extra cautions should be exercised for elderly or frail patients.

3

Hypnotics and sedatives, anxiolytics

(a) Alprazolam**(b) Ethyl Loflazepate**

Brand name (a) Constan 0.4 mg Tablets, 0.8 mg Tablets, and the others (Teva Takeda Yakuhin Ltd. and the others), Solanax Tablets 0.4 mg, 0.8 mg, and the others (Pfizer Japan Inc.)

(b) Meilax Fine Granules 1%, Meilax Tablets 1 mg, 2 mg, and the others (Meiji Seika Pharma Co., Ltd. and the others)

Important
Precautions

Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.

Adverse reactions
(clinically significant
adverse reactions)

Dependence, withdrawal symptoms: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

Irritable excitation, confusion: Irritable excitation or confusion, etc., may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

4

Hypnotics and sedatives, anxiolytics

Eszopiclone

Brand name Lunesta Tablets 1 mg, 2 mg, 3 mg (Eisai Co., Ltd.)

Important
Precautions

Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.

Adverse reactions
(clinically significant
adverse reactions)

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as anxiety, abnormal dreams, nausea, upset stomach, or rebound insomnia may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

5

Hypnotics and sedatives, anxiolytics

Estazolam

Brand name	Eurodin 1 mg Tablets, 2 mg Tablets, Eurodin Powder 1%, and the others (Teva Takeda Yakuhin Ltd. and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration when administering this drug.</u> In addition, withdrawal symptoms such as delirium, or convulsions may occur <u>due to rapid dose reduction or discontinuation of this drug during prolonged use.</u> Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion: Paradoxical reactions such as irritable excitation or confusion, etc., may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

6

Hypnotics and sedatives, anxiolytics

Oxazolam

Brand name	Serenal Tablets 5, 10, Serenal Powder 10%, and the others (Daiichi Sankyo Company, Limited and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration when administering this drug.</u> In addition, <u>withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use.</u> Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

7

Hypnotics and sedatives, anxiolytics

Quazepam

Brand name	Doral Tablets 15, 20, and the others (Hisamitsu Pharmaceutical Co., Inc. and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion: Irritable excitation or confusion, etc., may occur.

8

Hypnotics and sedatives, anxiolytics

Cloxazolam

Brand name	Sepazon Tablets 1, 2, Sepazon Powder 1% (Daiichi Sankyo Company, Limited)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation: Irritable excitation or insomnia, etc., may occur.

9

Hypnotics and sedatives, anxiolytics

Clorazepate Dipotassium

Brand name	Mendon Capsules 7.5 mg (Mylan EPD G.K.)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion: Irritable excitation or confusion may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

10

Hypnotics and sedatives, anxiolytics

(a) Chlordiazepoxide**(b) Diazepam (oral dosage form, injection)**

Brand name	(a) 5 mg Contol Tablets, 10 mg Contol Tablets, Contol Powder 1%, 10%, and the others (Teva Takeda Yakuhin Ltd. and the others) (b) (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) (injection) Cercine Injection 5 mg, 10 mg, and the others (Teva Takeda Yakuhin Ltd. and the others), Horizon Injection 10 mg and the others (Maruishi Pharmaceutical Co., td. and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion: Irritable excitation or confusion, etc., may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken such as discontinuing administration.

11

Hypnotics and sedatives, anxiolytics

Secobarbital Sodium

Brand name	Ional Sodium For Injection (0.2) (Nichi-Iko Pharmaceutical Co., Ltd.)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Drug dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. Careful attention should be paid especially to patients with alcoholism, tendency to develop drug dependence or medical history of drug dependence, and serious neurosis.

12

Hypnotics and sedatives, anxiolytics

Zopiclone

Brand name	Amoban Tablets 7.5, 10, and the others (Sanofi K.K. and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered</u> when continuing <u>administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as tremor, seizure, or insomnia may occur due to <u>rapid dose reduction or discontinuation of this drug during prolonged use.</u> Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

13

Hypnotics and sedatives, anxiolytics

Zolpidem tartrate

Brand name	Myslee Tablets 5 mg, 10 mg, and the others (Astellas Pharma Inc. and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered</u> when continuing <u>administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence, withdrawal symptoms: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as rebound insomnia, or irritation may occur due to <u>rapid dose reduction or discontinuation of this drug during prolonged use.</u> Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

14

Hypnotics and sedatives, anxiolytics

Triazolam

Brand name	Halcion Tablets 0.125 mg, 0.25 mg and the others (Pfizer Japan Inc. and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	<p>Drug dependence, withdrawal symptoms: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. In particular, when administering this drug to patients with a history of seizure, dose should be carefully reduced.</p> <p>Psychiatric symptoms: Psychiatric symptoms such as irritable excitation, confusion, aggression, somnambulism, hallucination, delusion, or agitation may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued.</p>

15

Hypnotics and sedatives, anxiolytics

(a) Triclofos Sodium**(b) Bromovalerylurea**

Brand name	(a) Tricloryl Syrup 10% (Alfresa Pharma Corporation) (b) Brovarin and the others (Nippon Shinyaku Co., Ltd. and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	<p>Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizures, delirium, tremor, or anxiety may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.</p>

16

Hypnotics and sedatives, anxiolytics

Nitrazepam

Brand name

Nelbon Tablets 5 mg, 10 mg, Nelbon Powder 1%, and the others (Daiichi Sankyo Company, Limited and the others), Benzalin Tablets 2, 5, and 10 Benzalin Fine Granules 1% and the others (Shionogi & Co., Ltd. and the others)

**Important
Precautions**

Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided except when used as an antiepileptic. Therapeutic necessity should be carefully considered when continuing administration of this drug.

**Adverse reactions
(clinically significant
adverse reactions)**

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion: Irritable excitation or confusion, etc., may occur.

17

Hypnotics and sedatives, anxiolytics

Nimetazepam

Brand name

Erimin Tablets 3 mg, 5 mg (Sumitomo Dainippon Pharma Co., Ltd.)

**Important
Precautions**

Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.

**Adverse reactions
(clinically significant
adverse reactions)**

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion, etc.: Irritable excitation or confusion, etc., may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

18

Hypnotics and sedatives, anxiolytics
Psychotropics

(a) Haloxazolam**(b) Clotiazepam**

Brand name	(a) Somelin Fine Granules 1%, Somelin Tablets 5 mg, 10 mg (Daiichi Sankyo Company, Limited) (b) Rize Tablets 5 mg, 10 mg, Rize Granules 10%, and the others (Mitsubishi Tanabe Pharma Corporation and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

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Hypnotics and sedatives, anxiolytics
Antiepileptics

(a) Phenobarbital (oral dosage form)**(b) Phenobarbital Sodium (suppository)**

Brand name	(a) (oral dosage form) Phenobal, Phenobal Powder 10%, Phenobal Tablets 30 mg, Phenobal Elixir 0.4%, and the others (Fujinaga Pharm. Co., Ltd. and the others) (b) (suppository) Wakobital Suppositories 15, 30, 50, 100 (TAKATA Pharmaceutical Co., Ltd.), Lupial Suppositories 25, 50, 100 (Hisamitsu Pharmaceutical Co., Inc.)
Important Precautions	Drug dependence may occur due to prolonged use. <u>Long-term use by chronic administration should be avoided except when used as treatments with an antiepileptic. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as anxiety, insomnia, convulsions, nausea, hallucinations, delusions, excitement, confusion, or depressed state may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

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Hypnotics and sedatives, anxiolytics

Antiepileptics

(a) Phenobarbital (injection)**(b) Phenytoin/Phenobarbital****(c) Phenytoin/Phenobarbital/Caffeine Sodium Benzoate****(d) Phenobarbital Sodium (injection)****Brand name**

- (a) Phenobarbital Injection 100 mg (Fujinaga Pharm. Co., Ltd.)
 (b) Aleviatin with Phenobarbital Combination Tablets (Sumitomo Dainippon Pharma Co., Ltd.)
 (c) Hydantol D Combination Tablets, Hydantol E Combination Tablets, Hydantol F Combination Tablets (Fujinaga Pharmaceutical Co., Ltd.)
 (d) Nobelbar 250 mg for Injection (Nobelpharma Co., Ltd.)

Adverse reactions (clinically significant adverse reactions)

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as anxiety, insomnia, convulsions, nausea, hallucinations, delusions, excitement, confusion, or depressed state may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

21

Hypnotics and sedatives, anxiolytics

Fludiazepam**Brand name**

Erispan Tablets 0.25 mg, Erispan Fine Granules 0.1% (Sumitomo Dainippon Pharma Co., Ltd.)

Important Precautions

Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.

Adverse reactions (clinically significant adverse reactions)

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.
 Irritable excitation, confusion, etc.: Irritable excitation or confusion, etc., may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

22

Hypnotics and sedatives, anxiolytics

Flutazolam

Brand name	Coreminal Tablets 4 mg, Coreminal Fine Granules 1% (Sawai Pharmaceutical Co., Ltd.)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	<p>Dependence: <u>Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.</u></p> <p>Irritable excitation, confusion: Irritable excitation or confusion, etc., may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.</p>

23

Hypnotics and sedatives, anxiolytics

Flutoprazepam

Brand name	Restas Tablets 2 mg (Nihon Generic Co., Ltd.)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	<p>Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.</p> <p>Irritable excitation, confusion etc.: Irritable excitation or confusion, etc., have been reported with the use of other BZ drugs.</p>

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Hypnotics and sedatives, anxiolytics

(a) Flunitrazepam (oral dosage form)**(b) Bromazepam (oral dosage form)**

Brand name	(a) Silece Tablets 1 mg, 2 mg, and the others (Eisai Co., Ltd. and the others) (b) Lexotan Tablets 1, 2, 5, Lexotan Fine Granules 1%, and the others (Chugai Pharmaceutical Co., Ltd. and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion: <u>Irritable excitation or confusion, etc.</u> , may occur.

25

Hypnotics and sedatives, anxiolytics

Flurazepam Hydrochloride

Brand name	Dalmate Capsules 15 (Kyowa Pharmaceutical Industry Co., Ltd.)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

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Hypnotics and sedatives, anxiolytics

Brotizolam**Brand name**

Lendormin D Tablets 0.25 mg, Lendormin Tablets 0.25 mg, and the others
(Nippon Boehringer Ingelheim Co., Ltd. and the others)

**Important
Precautions**

Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.

**Adverse reactions
(clinically significant
adverse reactions)**

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as insomnia, or anxiety may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

Unrest, excitement: Unrest or excitement may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

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Hypnotics and sedatives, anxiolytics

Pentobarbital calcium**Brand name**

Ravona 50 mg (Mitsubishi Tanabe Pharma Corporation)

**Important
Precautions**

Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.

**Adverse reactions
(clinically significant
adverse reactions)**

Drug dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. Careful attention should be paid especially to patients with alcoholism, tendency to develop drug dependence or medical history of drug dependence, and serious neurosis.

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Hypnotics and sedatives, anxiolytics

Chloral Hydrate**Brand name**

Escre Suppositories "250," Escre Suppositories "500", Escre Rectal Kit "500" (Hisamitsu Pharmaceutical Co., Inc.)

**Adverse reactions
(clinically significant
adverse reactions)**

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, or anxiety may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

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Hypnotics and sedatives, anxiolytics

Mexazolam

Brand name	Melex Tablets 0.5 mg, 1 mg, Melex Fine Granules 0.1% (Daiichi Sankyo Company, Limited)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion: Irritable excitation or confusion, etc., may occur

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Hypnotics and sedatives, anxiolytics

Medazepam

Brand name	Resmit Tablets 2, 5, and the others (Shionogi & Co., Ltd. and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion: Irritable excitation or confusion, etc., may occur.

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Hypnotics and sedatives, anxiolytics

Rilmazafone Hydrochloride Hydrate

Brand name	Rhythmy Tablets 1 mg, 2 mg and the others (Shionogi & Co., Ltd. and the others)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion: Irritable excitation or confusion, etc., may occur.

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Hypnotics and sedatives, anxiolytics

(a) Lorazepam**(b) Lormetazepam**

Brand name	(a) Wypax Tablets 0.5, 1.0, and the others (Pfizer Japan Inc. and the others) (b) Evamyl Tablets 1.0 (Bayer Yakuhin, Ltd.), LORAMET Tablets 1.0 (Asuka Pharmaceutical Co., Ltd.)
Important Precautions	<u>Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.</u>
Adverse reactions (clinically significant adverse reactions)	Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and <u>caution should be exercised for dosage and treatment duration</u> when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion: Irritable excitation or confusion, etc., may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

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Antiepileptics

Clonazepam

Brand name

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% (Sumitomo Dainippon Pharma Co., Ltd.)

Adverse reactions (clinically significant adverse reactions)

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion, etc.: Irritable excitation or confusion, etc., may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

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Antiepileptics

Clobazam

Brand name

Mystan Tablets 5 mg, 10 mg, Mystan Fine Granules 1% (Sumitomo Dainippon Pharma Co., Ltd.)

Adverse reactions (clinically significant adverse reactions)

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

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Antiepileptics

Diazepam (suppository)

Brand name

Diapp Suppositories 4, 6, 10 (TAKATA Pharmaceutical Co., Ltd.)

Adverse reactions (clinically significant adverse reactions)

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction. Irritable excitation, confusion, etc.: Irritable excitation or confusion, etc., may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

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Antiepileptics

Primidone**Brand name**

Primidone Tablets 250 mg “Nichi-Iko,” Primidone Fine Granules 99.5% “Nichi-Iko” (Nichi-Iko Pharmaceutical Co., Ltd.)

Adverse reactions (clinically significant adverse reactions)

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as anxiety, insomnia, convulsions, nausea, hallucinations, delusions, excitement, confusion, or depressed state have been reported due to rapid dose reduction or discontinuation of this drug during prolonged use.

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Antiepileptics

Midazolam (products with an indication to treat status epilepticus)**Brand name**

Midafresa Injection 0.1% (Alfresa Pharma Corporation)

Adverse reactions (clinically significant adverse reactions)

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. Withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, delusion, or involuntary movements may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

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Psychotropics

Etizolam**Brand name**

Depas Tablets 0.25 mg, 0.5 mg, 1 mg, Depas Fine Granules 1%, and the others (Mitsubishi Tanabe Pharma Corporation and the others)

Important Precautions

Drug dependence may occur due to prolonged use. Long-term use by chronic administration should be avoided. Therapeutic necessity should be carefully considered when continuing administration of this drug.

Adverse reactions (clinically significant adverse reactions)

Dependence: Drug dependence may occur due to prolonged use. Patients should be carefully monitored and caution should be exercised for dosage and treatment duration when administering this drug. In addition, withdrawal symptoms such as seizure, delirium, tremor, insomnia, anxiety, hallucination, or delusion may occur due to rapid dose reduction or discontinuation of this drug during prolonged use. Discontinuation of administration should be carefully carried out such as by gradual dose reduction.

5

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting ADR from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of February 28, 2017)

⊙: Products for which EPPV was initiated after February 1, 2017

Nonproprietary name		Name of the MAH	Date of EPPV initiate
Brand name			
⊙	Dimethyl Fumarate Tecfidera Capsules 120 mg, 240 mg	Biogen Japan Ltd.	February 22, 2017
⊙	Plerixafor Mozobil Subcutaneous Injection 24 mg	Sanofi K.K.	February 22, 2017
⊙	Tenofovir Alafenamide Fumarate Vemlidy Tablets 25 mg	Gilead sciences K.K.	February 15, 2017
⊙	Daclatasvir Hydrochloride / Asunaprevir / Beclabuvir Hydrochloride Ximency Combination Tablets	Bristol-Myers Squibb K.K.	February 15, 2017
⊙	Etelcalcetide Hydrochloride Parsabiv Intravenous Injection for Dialysis 2.5 mg, 5 mg, 10 mg	ONO Pharmaceutical Co., Ltd.	February 15, 2017
⊙	Pembrolizumab (Genetical Recombination) Keytruda Injection 20 mg, 100 mg ¹	MSD K.K.	February 15, 2017
⊙	Pembrolizumab (Genetical Recombination) Keytruda Injection 20 mg, 100 mg ²	MSD K.K.	February 15, 2017
⊙	Ticagrelor Brilinta Tablets 60 mg, 90 mg	AstraZeneca K.K.	February 8, 2017
	Emtricitabine/TenofovirAlafenamide Fumarate Descovy Combination Tablets LT and HT	Japan Tobacco Inc.	January 27, 2017
	DarunavirEthanolate/Cobicistat Prezcobix Combination Tablets	Janssen Pharmaceutical K.K.	January 4, 2017
	Carglumic Acid Carbaglu Dispersible Tablets 200 mg	Pola Pharma Inc.	December 22, 2016
	Canakinumab (Genetical Recombination) Ilaris for Subcutaneous Injection 150 mg ³	Novartis Pharma K.K.	December 19, 2016
	Eplerenone Selara Tablets 25, 50 mg ⁴	Pfizer Japan Inc.	December 19, 2016
	LomitapideMesilate Juxtapid Capsules 5, 10, 20 mg	Aegerion Pharmaceuticals Inc.	December 15, 2016

Nonproprietary name		Name of the MAH	Date of EPPV initiate
Brand name			
Dienogest	DINagest Tablets 1 mg, DINagest OD Tablets 1 mg ⁵	Mochida Pharmaceutical Co., Ltd.	December 2, 2016
PasireotidePamoate	Signifor LAR Kit for I. M. Injection 20, 40, 60 mg	Novartis Pharma K.K.	December 2, 2016
Trafermin (genetical recombination)	Regroth Dental Kit 600µg, 1200µg	Kaken Pharmaceutical Co., Ltd.	December 1, 2016
Albutrepenonacog Alfa (Genetical Recombination)	Idelvion I.V. Injection 250, 500, 1000, 2000	CSL Behring K.K.	November 29, 2016
Rifaximin	Rifaxima Tablets 200 mg	Aska Pharmaceutical Co., Ltd.	November 29, 2016
Budesonide	Zentacort Capsules 3 mg	Zeria Pharmaceutical Co., Ltd.	November 29, 2016
Alogliptin Benzoate/Metformin Hydrochloride	Inisync Combination Tablets	Takeda Pharmaceutical Company Limited	November 29, 2016
Zoledronic Acid Hydrate	Reclast for I.V. Injection 5 mg	Asahi Kasei Pharma Corporation	November 25, 2016
Ponatinib Hydrochloride	Iclusig Tablets 15 mg	Otsuka Pharmaceutical Co., Ltd.	November 21, 2016
Selexipag	Upravi Tablets 0.2 mg, 0.4 mg	Nippon Shinyaku Co., Ltd.	November 21, 2016
Ixekizumab (Genetical Recombination)	Taltz 80 mg Syringe for SC Injection, Taltz 80 mg Auto-Injector for SC Injection	Eli Lilly Japan K.K.	November 21, 2016
Grazoprevir Hydrate	Grazyna Tablets 50 mg	MSD K.K.	November 18, 2016
Elbasvir	Erelsa Tablets 50mg	MSD K.K.	November 18, 2016
Elotuzumab (Genetical Recombination)	Empliciti I.V. Injection 300 mg, 400 mg	Bristol-Myers Squibb K.K.	November 18, 2016
Bilastine	Bilanoa Tablets 20 mg	Taiho Pharmaceutical Co., Ltd.	November 18, 2016
Telmisartan/Amlodipine Besilate/Hydrochlorothiazide	Micatrio Combination Tablets	Nippon Boehringer Ingelheim Co., Ltd.	November 18, 2016
Idarucizumab (Genetical Recombination)	Prizbind Intravenous Solution 2.5 g	Nippon Boehringer Ingelheim Co., Ltd.	November 18, 2016
Desloratadine	Desalex Tablets 5 mg	MSD K.K.	November 18, 2016
Adapalene/Benzoyl Peroxide	Epiduo Gel	Galderma S.A.	November 4, 2016
Brodalumab (Genetical Recombination)	Lumicef Subcutaneous Injection 210 mg Syringe	Kyowa Hakko Kirin Co., Ltd.	September 30, 2016
Adalimumab (Genetical Recombination)	Humira for SC Injection 40 mg syringe 0.8 mL, 40 mg syringe 0.4 mL, 80 mg syringe 0.8 mL ⁶	AbbVie GK	September 28, 2016

Nonproprietary name		Name of the MAH	Date of EPPV initiate
Brand name			
	Aripiprazole	Otsuka Pharmaceutical Co., Ltd.	September 28, 2016
	Abilify Tablets 1 mg, 3 mg, 6 mg, 12 mg, OD Tablets 3 mg, 6 mg, 12 mg, powder 1%, oral solution 0.1% ^{*7}		
	Propranolol Hydrochloride	Maruho Co., Ltd.	September 16, 2016
	Hemangiol Syrup for Pediatric 0.375% ^{*8}		
	Progesterone	Merck Serono Co., Ltd.	September 7, 2016
	OneCrinone 90 mg Progesterone Vaginal Gel		
	Alirocumab (Genetical Recombination)	Sanofi K.K.	September 5, 2016
	Praluent Subcutaneous Injection pen 75 mg, 150 mg, Syringe 75 mg, 150 mg		
	Levodopa/Carbidopa Hydrate	AbbVie GK	September 1, 2016
	Duodopa enteral combination solution		

*1 PD-L1-positive, unresectable, advanced or relapsed non-small-cell lung cancer

*2 Radically unresectable malignant melanoma

*3 Familial mediterranean fever, Tumour necrosis factor receptor-associated periodic syndrome, Mevalonate kinase deficiency/Hyper IgD syndrome

*4 Chronic cardiac failure

*5 Improvement of pain in adenomyosis uteri

*6 Non-infectious intermediate, posterior and panuveitis

*7 Irritability associated with autism spectrum disorder in childhood

*8 Infantile haemangioma