Pharmaceuticals and Medical Devices Safety Information

No. 365 August 2019

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Available information is listed here

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No. 365 August 2019

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

[Outline of Information]

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

If providers of medical care and pharmaceutical products 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 providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

CI	Confidence Interval
CRP	C-reactive protein
CT	Computed tomography
CV	Cardiovascular
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
HbA1c	Hemoglobin A1c
HPB/MSPO	Office of Medical Safety Promotion, Health Policy Bureau
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
NIPPV	Nasal-intermittent Positive Pressure Ventilation
NSCLC	Non-small cell lung cancer
OTC	Over-the-counter
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB/PSD	Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau
SP-D	Surfactant protein D
SpO2	Oxygen saturation
WBC	White blood cell

1
Review of Contraindications of Metformin including "renal impairment"

1. Introduction

Metformin hydrochloride (metformin) is a biguanide antidiabetic agent, which has been approved for marketing in 100 or more countries including the United States and the EU as of the end of 2018 since it was approved for marketing in France in 1959.

Metformin has a risk of lactic acidosis, and particularly there was a concern that patients with renal impairment would be at a higher risk of lactic acidosis because the blood concentration of metformin was increased due to delay in its excretion in those patients. Consequently, the use in patients with renal impairment had been contraindicated.

The package insert of metformin was revised based on the consideration at the third Subcommittee on Drug Safety, Committee on Drug Safety, Pharmaceutical Affairs and Food Sanitation Council held on May 31, 2019 (Subcommittee on Safety Measures) and the details are introduced below.

2. Background

Since multiple cases of death from lactic acidosis induced by phenformin hydrochloride, a drug from the same biguanide class, were reported overseas in the 1970s, the package inserts of metformin in Japan and overseas have provided a precaution to restrict the patient use, the dosage, etc. in order to minimize the risk of lactic acidosis. In the process of package-insert revision regarding lactic acidosis in Japan, there was a concern that patients with renal impairment would be at a higher risk of lactic acidosis because the blood concentration of metformin was increased due to delay in its excretion in those patients. Consequently, the use in patients with renal impairment was more tightly restricted in May 1977, for example, by revising the description of patients with renal impairment to whom the drug should be contraindicated from "patients with serious renal impairment" to "patients with mild or more severe renal impairment."

In recent years, the restriction on metformin's use in patients with renal impairment has been reviewed overseas based on the updated scientific findings on metformin's safety in patients with renal impairment. The FDA and the EMA reviewed published papers and other sources and both concluded that metformin may be used in patients with mild to moderate renal impairment. As a result, in April and October 2016 respectively, FDA and EMA announced that they would limit the contraindication only to patients with estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73m^2 and that they would revise the package insert in order to add precautions for the use in patients with mild to moderate renal impairment. Based on the announcement, the package inserts of all metformin-containing preparations were revised in Europe and the US.

In light of the above circumstances in Europe and the US, the revision of the alert for patients with renal impairment and lactic acidosis in the package inserts of metformin-containing preparation was considered with the support of the Japan Diabetes Society.

3. Considerations at Subcommittee on Drug Safety

(1) Results of PMDA investigation related to metformin

The results of the investigation related to metformin are as described in the following 1) to 4).

1) Descriptions in foreign package inserts (at the time of the Subcommittee on Drug Safety)
   - Package insert in the US: Metformin is contraindicated in patients with estimated Glomerular Filtration Rate (eGFR) < 30 (mL/min/1.73m^2). Initiation of metformin administration is not recommended in patients with 30 ≤ eGFR < 45.
   - Package insert in the UK: Dose should be adjusted as shown in Table 1 for patients with renal impairment (the maximum daily dose for patients with normal renal function is 3 000 mg).

Table 1. Dose adjustment in the UK package insert

eGFR (mL/min)	Maximum daily dose
60≤eGFR<90	3 000 mg
45≤eGFR<60	2 000 mg
30≤eGFR<45	1 000 mg
eGFR<30	Contraindication

- Package insert in Japan: Preparations with a maximum daily dose of 2 250 mg (Metgluco Tablets 250 mg and the others, “high-dose preparations.”) and preparations with a maximum daily dose of 750 mg (Glycoran Tablets 250 mg and the others, “low-dose preparations.”) are available.

  For the use in patients with renal impairment, the contraindication applies to patients with moderate to more severe renal impairment for high-dose preparations and to patients with mild to severe renal impairment for low-dose preparations. The difference in contraindication between low-dose and high-dose preparations derives from the judgment at the review for marketing approval that Metgluco Tablets 250 mg (approved in January 2010), which had been filed for marketing approval after a low-dose preparation (approved in January 1961), might be used in patients with mild renal impairment based on clinical studies conducted in Japan. The use in patients with hepatic impairments and in the elderly is also restricted more tightly for low-dose preparations than for high-dose preparations for the same reason (Table 2).

Table 2. Major differences in the package inserts in Japan at the time of the Subcommittee on Drug Safety

	Low-dose preparation	High-dose preparation
Major product names	Glycoran Tablets 250 mg and the others	Metgluco Tablets 250 mg and the others
Marketing authorization	Approved in January 1961	Approved in January 2010
Maximum daily dose	750 mg	2 250 mg
Use in patients with renal impairment	Contraindicated to patients with mild to severe renal impairment	Contraindicated to patients with moderate or more severe renal impairment
Use in patients with hepatic impairment	Contraindicated to patients with mild to severe hepatic impairment	Contraindicated to patients with severe hepatic impairment
Use in geriatric patients	Contraindication	Careful administration

2) Pharmacokinetic study in patients with renal impairment
   - Metformin is cleared by the kidneys, and the blood concentration of metformin increases according to the severity of the renal impairment. It is possible to decrease the blood concentration of metformin in patients with moderate renal impairment to the levels comparable to those of patients with normal renal function by dose reduction.
   - It has been reported that the blood concentration of metformin was higher in Japanese patients compared to those of non-Japanese patients.

3) Japanese and overseas published literature, academic society guidelines

- Drug levels generally remain within the therapeutic range and lactate concentrations are not substantially increased even when metformin is used in patients with mild to moderate renal impairment. There is no statement that the risk of lactic acidosis varies depending on the preparation.
- "Recommendation for Proper Use of Metformin" published by the Japan Diabetes Society, assesses renal function by eGFR, and it is stated that metformin is contraindicated in patients with an eGFR below 30 mL/min/1.73m^2 and metformin should be carefully administered in patients with eGFR of 30-45 mL/min/1.73m^2.
- Multiple practice guidelines overseas allow administration of metformin to patients with mild and moderate renal impairment.

4) Adverse reaction reports in Japan
   - The severe adverse reaction reports of lactic acidosis in Japan in 347 cases include 43 cases with moderate renal impairment (eGFR 30-60 mL/min/1.73m^2), most had risk factors other than renal function (e.g., dehydration, cardiovascular diseases) indicating an influence of non-renal impairment risk factors.

(2) Results of considerations at Subcommittee on Drug Safety

Based on these results, the subcommittee on Drug Safety judged that it is appropriate to revise the package insert of metformin as the following 1) to 4).

1) Administration to patients with renal impairment will be contraindicated only to patients with severe renal impairment (eGFR < 30) provided that risk minimization strategies (initiation with low doses, dose adjustment in response to patients' conditions, careful monitoring of patients' clinical courses) are implemented. Descriptions related to assessment for renal function will be revised to provide descriptions based on the recommended assessment by eGFR in the package inserts of metformin-containing preparations in Europe and the US and Recommendation published by the Japan Diabetes Society.
2) Approximate maximum daily doses of metformin in patients with renal impairment based on eGFR will be included (Table 3).

Table 3. Approximate maximum daily doses of metformin in patients with renal impairment

eGFR (mL/min/1.73m^2)	Approximate dose
60≤eGFR<90	2 250 mg
45≤eGFR<60	1 500 mg
30≤eGFR<45	750 mg

3) A statement that a particular caution is required for risk factors other than renal impairment, factors such as dehydration in case of poor oral intake, and excessive alcohol consumption, and other precautions related to lactic acidosis will also be reorganized.
4) Differences in the precautions related to lactic acidosis between low-dose and high-dose preparations will be corrected.

4. Closing comments

The contraindications of low-dose and high-dose metformin preparations were revised to apply only to patients with severe renal impairment (eGFR < 30), allowing administration in patients with mild to moderate renal impairment in this revision. However, caution should be exercised, particularly in patients with moderate renal impairment since administration of metformin to patients with mild to moderate renal impairment may increase the blood concentration of the drug, which may lead to a higher risk of lactic acidosis. Administration should be initiated at a low dose and the clinical course of patients should be monitored closely through methods such as more frequent assessment of renal function (eGFR) during administration. Appropriateness of administration of metformin or necessity of dose adjustment should be considered based on the monitoring of the patient as well. Doses should be gradually increased, if to be increased, considering the approximate maximum daily doses included in the package insert if appropriate while the patient's response is closely monitored.

Regardless of the presence of renal impairment, cases of lactic acidosis have been reported as occurring subsequent to a sudden change in condition due to dehydration or excessive alcohol consumption, etc. caused by poor oral intake like anorexia. Therefore, adequate patient education on the prevention of lactic acidosis, its initial symptoms, and required initial responses for the symptoms by healthcare professionals are requested.

We sincerely request your continuous cooperation for proper use of metformin.

[Reference]

- Documents 1-1 to 1-4 of the third Subcommittee on Drug Safety, Committee on Drug Safety, Pharmaceutical Affairs and Food Sanitation Council in 2019 (held on May 31, 2019) http://www.mhlw.go.jp/stf/shingi2/0000183979_00004.html (only in Japanese)
- Revision of Precautions (PSEHB/PSD Notification No. 0618-1 dated June 18, 2019) http://www.mhlw.go.jp/content/11120000/000518508.pdf (only in Japanese) http://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0007.html (June 18, 2019)

2
Safety Measures for Febuxostat

1. Introduction

Febuxostat is a drug that inhibits xanthine oxidase used to treat hyperuricemia, which has been available in 78 countries and regions worldwide including the United States as of May 2019 since it obtained manufacturing and marketing approval in Europe in 2008.

Considering the higher incidences of cardiovascular (CV) death and all-cause death observed in the febuxostat group compared to the allopurinol group reported in an overseas clinical study in patients with gout who had CV diseases (CARES study), it was decided that measures taken in Japan for the CV risks associated with febuxostat would be considered.

Recently, the package insert of febuxostat was revised based on the consideration at the fourth Subcommittee on Drug Safety, Committee on Drug Safety, Pharmaceutical Affairs and Food Sanitation Council held on June 26, 2019 (Subcommittee on Drug Safety), and the details are introduced below.

2. Background

Febuxostat was approved in the United States in February 2009. The Food and Drug Administration (FDA) in the United States instructed that a post-marketing clinical study (CARES study conducted during the period between April 2010 and May 2017) be conducted since the incidence of CV events was suggested to be higher than the control group (placebo group or allopurinol group) in the approval review of febuxostat.

In Japan, febuxostat was granted marketing approval for the indications of “gout and hyperuricemia” in January 2011. On this occasion, collection of information on CV risks in a special drug use-results survey (conducted during the period between April 2012 and June 2018) was instructed based on the overseas findings and others, although there was no particularly higher tendency in the incidence of CV events in the febuxostat group than the control group (placebo group or allopurinol group) in Japanese clinical studies.

In Japan, the Risk Management Plan including “CV events” in important potential risks was developed for febuxostat at the time of the partial change approval for “hyperuricemia associated with chemotherapy” in May 2016.

In November 2017, FDA announced that they would start a safety assessment of febuxostat since the results from the CARES study showed a higher risk of CV death in the febuxostat group compared to the allopurinol group. Furthermore, FDA ordered a revision of the package insert (*alerting CV deaths in the Boxed Warning section and restricting the use of febuxostat to certain patients who have an inadequate response or intolerance to allopurinol.) to alert CV death in February 2019 based on the CARES study results and the deliberation of the Advisory Committee.

In light of the above overseas trend and submission of the results of the special drug use-results survey in May 2019, safety measures would be considered in Japan.

In Europe, the European Medicine Agency ordered a post-marketing clinical study (FAST study) to assess CV risks of febuxostat since CV risk was suggested in the approval review of febuxostat (approved in April 2008), which is currently ongoing.

3. Considerations at Subcommittee on Drug Safety

(1) Results of PMDA investigation related to febuxostat

The results of the investigation of the 1) outline of CARES study, 2) Japanese and overseas published literature, 3) special drug use-results survey, and 4) adverse reaction reports in Japan related to febuxostat are as follows.

1) Outline of CARES study (Tables 1 and 2)

- A double-blind randomized study conducted to compare the CV outcomes of febuxostat and allopurinol in patients with gout who have CV disease.
- Non-inferiority of febuxostat to allopurinol was shown for the primary endpoint (onset of any of CV death, nonfatal myocardial infarction, nonfatal cerebral stroke, or urgent revascularization for unstable angina).
- Among the secondary endpoints, the incidence of CV death was higher in the febuxostat group compared to the allopurinol group.
- The incidence of all-cause death was also higher in the febuxostat group than the allopurinol group.

Table 1 Results of primary endpoint, secondary endpoints (safety), and all-cause death (Modified-ITT analysis)

	Febuxostat group[a)] (3 098 patients)	Allopurinol group[a)] (3 092 patients)	Hazard ratio [95%CI]	P value[c)]
Primary endpoint	335 (10.8)	321 (10.4)	1.03 [0.87-1.23][b)]	0.66 (0.002)
Secondary endpoints				
CV death	134 (4.3)	100 (3.2)	1.34 [1.03-1.73]	0.03
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 [0.72-1.21]	0.61
Nonfatal cerebral stroke	71 (2.3)	70 (2.3)	1.01 [0.73-1.41]	0.94
Urgent revascularization for unstable angina	49 (1.6)	56 (1.8)	0.86 [0.59-1.26]	0.44
Composite endpoint composed of 3 factors: CV death, nonfatal myocardial infarction, and nonfatal cerebral stroke	296 (9.6)	271 (8.8)	1.09 [0.92-1.28]	0.33
All-cause death	243 (7.8)	199 (6.4)	1.22 [1.01-1.47]	0.04

a) Number of patients who developed adverse events [incidence (%)]
b) 97%CI (Confidence Interval)
c) The P value in parentheses is a one-sided P value of a test for a null hypothesis assuming that the hazard ratio with the objective of showing non-inferiority is 1.3 or greater. All other P values are to show the superiority of the febuxostat group to the allopurinol group and are calculated by Cox regression analysis.

Table 2 Incidence of deaths in the CARES study

	Febuxostat group (3 098 patients)	Allopurinol group (3 092 patients)
CV death	134 (4.3)	100 (3.2)
Sudden cardiac death	83 (2.7)	56 (1.8)
Cardiac failure	20 (0.6)	13 (0.4)
Cerebral stroke	8 (0.3)	11 (0.4)
Myocardial infarction	11 (0.4)	6 (0.2)
Arrhythmia	7 (0.2)	9 (0.3)
Valvular disease	3 (<0.1)	2 (<0.1)
Cardiac failure and respiratory failure	1 (<0.1)	1 (<0.1)
Cardiovascular haemorrhage	0	1 (<0.1)
Peripheral arterial disease	0	1 (<0.1)
Other	1 (<0.1)	0
Noncardiovascular death	109 (3.5)	99 (3.2)

Number of patients who developed adverse events [incidence (%)]

2) Japanese and overseas published literature
   - Published clinical studies / epidemiological studies and meta-analyses assessing CV risks and risks of death of febuxostat were extracted.
   - Of the 7 extracted articles, 1 article (meta-analysis including the CARES study results)

reports a higher incidence of CV death in the febuxostat group compared to the control groups (placebo group or allopurinol group), 6 other articles do not report a presence of particular CV risks or risks of death in the febuxostat group compared to the control group.

3) Special drug use-results survey
   - Between April 2012 and June 2018, 3 245 cases were collected as the safety analysis set.
   - The number of cerebrovascular and CV deaths was 35 cases, which was comparable to the number of onsets calculated from the expectation at the start of the survey.

4) Adverse reaction reports in Japan
   - Of 555 serious adverse reactions in 397 cases reported to the PMDA, there were 70 CV related events in 63 patients (including 18 cases of death outcome).
   - Although cases such as patients who have CV disease, patients who used concomitant drugs during treatment with febuxostat, and patients who have adverse events which may be caused by other adverse events developed at the same time, in which the causal relationship is difficult to determine are included, there were no cases where the causal relationship between febuxostat and the reported CV related events or febuxostat and death could not be ruled out.

(2) Results of considerations at Subcommittee on Drug Safety

Based on these results, the subcommittee on safety measures determined the safety measures for febuxostat as the following 1) to 4).

1) Necessity of changing the positioning of febuxostat

PMDA considers that measures such as restricting the use of febuxostat to certain patients are not required at this point for the following reasons.

   - Considering the CARES study results indicate the relative risk ratio of febuxostat and allopurinol and some studies show that allopurinol controls CV events and reduces all-cause deaths, it is not necessarily interpreted that febuxostat itself increases the risk of CV death.
   - In light of the report that CV risk is lower in Japanese individuals compared to European and American individuals and there was no difference in the incidence of CV events and CV death between febuxostat and allopurinol in Eastern Asian patients, it is unknown whether the difference of the risk of CV death between allopurinol and febuxostat observed in the CARES study with 3% Asian subjects can be extrapolated to the Japanese population.
   - There are several population-based cohort studies reporting that there was no difference in CV risk or risk of death between febuxostat and allopurinol.
   - In the CARES study, the urate-lowering efficacy of febuxostat was confirmed and the usefulness of febuxostat as a uric acid inhibitor was not denied.

2) Necessity of an alert in the package insert
   - Considering the results obtained in the CARES study with a certain level of accuracy, and given CV death itself is a serious event, it is decided that the CARES study results should be included in the Other Precautions section in the package insert and a cautionary statement regarding the onset of CV disease should be included in the Important Precautions section as a preventive measure.

3) Future measures
   - Observational studies using databases for the evaluation and the collection of information on CV events of febuxostat in Japanese patients will be considered.

4) Necessity of an alert in similar drugs
   - Although no concerns were expressed about CV risks in a similar drug with a xanthine oxidase inhibitory effect, topiroxostat (indications: gout, hyperuricemia) at the time of its review, and the relation between the xanthine oxidase inhibitory effect and CV risk onset

is unknown, it is considered appropriate to add the CARES study results to Other Precautions section in the package insert to inform healthcare professionals, in light of the event with a difference observed among similar drugs confirmed in the CARES study being a serious event, CV death.

4. Closing comments

Although no measures such as restricting febuxostat to certain patients will be taken in Japan based on the information on adverse reactions in Japanese patients available at present, the package insert has been revised to alert the risks. Furthermore, conducting observational studies using databases to collect and assess information on the onset of CV events in Japanese patients will also be considered.

Since the adverse reactions due to febuxostat reported in Japan included cases in which the causal relationship between the drug and CV disease is difficult to determine, we sincerely request the continuous proper use of febuxostat and the cooperation of healthcare professionals for provision of information on more detailed adverse reaction reports.

[Reference]

- Documents 1-1 to 1-4 of the fourth Subcommittee on Drug Safety, Committee on Drug Safety, Pharmaceutical Affairs and Food Sanitation Council in 2019 (held on June 26, 2019) http://www.mhlw.go.jp/stf/newpage_05441.html (only in Japanese)
- Revision of Precautions (PSEHB/PSD Notification No. 0709-10 dated July 9, 2019)
  http://www.mhlw.go.jp/content/11120000/000526988.pdf (only in Japanese)
  http://www.pmda.go.jp/files/000230437.pdf
  http://www.pmda.go.jp/files/000230438.pdf

3
Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)]

1. Introduction

In association with the growth of aging population, safety problems readily occur by concomitant administration of multiple drugs due to physiological change by age and treatment of multiple comorbidities. The Review Committee on the Appropriate Medication for Elderly Patients was established in April 2017 and has been working on investigations and consideration of the matters necessary to secure safety of drug therapy in the elderly, and the Guidance of Appropriate Medication for Elderly Patients (general) were compiled in May 2018.

Following the last fiscal year's version, Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)] has been compiled this year. This section introduces their details.

2. Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)]

(Joint HPB/MSPO Notification No. 0614-1 and PSEHB/PSD No. 0614-1 by the Director, Office of Medical Safety Promotion, General Affairs Division, Health Policy Bureau and by the Director, Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated June 14, 2019)

[Objective]

This guidance was prepared for the purpose of optimization of drug therapy in the elderly (avoidance of [1]adverse drug events, improvement of drug adherence, avoidance of insufficient medical treatment) and to provide reference information on treatment and prescription as the guidelines summarizing the basic considerations for better drug therapy considering the characteristics of the elderly. The particulars (by recuperation environment) compiled this time are intended to clarify the considerations by patient's recuperation environment taking changeable considerations into account for the persons concerned associated with the changes in patient's condition, life, and environment.

Although the main intended users of the particulars (by recuperation environment) are physicians, dentists, and pharmacists similar to the general version, the involvement of nurses and other healthcare professionals is also important for promotion of drug adherence and information sharing especially in the recuperation environment addressed here. Therefore, the occupations and the roles are described when healthcare professionals other than physicians, dentists, and pharmacists are involved.

[Composition of particulars (by recuperation environment)]

The recuperation environment is divided into the following 3 parts, and concepts for confirmation and review of prescription, considerations during and after changing the recuperation environment, and considerations when considering prescriptions are described as characteristic points for each recuperation environment. The common considerations across recuperation environments are described as the "common considerations among recuperation environments."

- Part 1: Facilities without full-time physicians, such as outpatient clinics, home care, and special nursing homes for the elderly

[1] In the present guidance the term "adverse drug event" is used as the concept of an adverse symptom or sign that occurred after drug use with or without a causal relationship with the drug. The term "adverse reaction" is used as a reaction in which a causal relationship with the drug is suspected or cannot be ruled out.

- Part 2: Hospital treatment during convalescent phase and chronic phase following acute phase
- Part 3: Other environments for recuperation (e.g., nursing homes with full-time physicians)

Common considerations among recuperation environments

- **Optimization of medical care with drugs when ACP is implemented**
- **Significance of nondrug measures**
  - ✓ **Improvement of lifestyle, environmental adjustment, contrivance of care**
  - ✓ **Consideration of switching to drug therapy**
  - ✓ **Consideration of switching from drug therapy**
- **Roles and alliance of multiple occupations**
  - ✓ **Cooperation with persons involved in medical care and nursing responsible for comprehensive community care, and information sharing and team formation with multiple occupations within the facility or within the community**
  - ✓ **Sharing of considerations with persons involved in medical care and nursing responsible for comprehensive community care, etc.**
  - ✓ **Alliance and collaboration using a prescription book, etc.**
  - ✓ **Improvement of drug adherence**

Part 1 Facilities without full-time physicians, such as outpatient clinics, home care, and special nursing homes for the elderly

- **Concept of confirmation and review of prescriptions**
  - ✓ **Confirmation and review of prescriptions**
  - ✓ **Long-term safety and risk-benefit balance viewpoints**
  - ✓ **Confirmation of prescriptions during long-term outpatient treatment (during long-term care for home care), etc.**
- **Considerations when changing to outpatient or home care**
  - ✓ **Discussion and collaboration with specialists**
  - ✓ **Implementation of information collection from multiple occupations and review process of prescription**
- **Considerations when considering prescription**
  (1) Assessment of polypharmacy related issues
  (2) Priority of prescription and dose reduction / discontinuation
    - ✓ **Expected outpatient / home care situations and monitoring**
    - ✓ **Expected situations and monitoring at facilities**

Part 2 Inpatient treatment during convalescent phase / chronic phase following acute phase *including comprehensive community care ward

- **Concept of confirmation and review of prescriptions at the time of admission**
  - ✓ **Confirmation and review of prescriptions**
  - ✓ **Consideration for changing to home care and facility care environments**
  - ✓ **Information sharing with physicians, dentists, and pharmacists before admission**
- **Considerations during admission to discharge from hospital**
  - ✓ ***Discussion and collaboration with specialists**
  - ✓ ***Implementation of information collection from multiple occupations within the hospital and review process of prescription**
  - ✓ **Collaboration and information transfer with community home doctors and pharmacists for discharge from hospital**
- **Considerations when considering prescription**
  (1) Assessment of polypharmacy related issues
  (2) Priority of prescription and dose reduction / discontinuation
    - ✓ **Expected situations and monitoring during convalescent phase / chronic phase**

Part 3 Other recuperation environments (e.g., nursing facilities with full-time physicians)

- **Concept of confirmation and review of prescriptions at the time of admission**
  - ✓ **Confirmation and review of prescriptions**
  - ✓ **Long-term safety and risk-benefit balance viewpoints**
- **Considerations during admission to discharge from care facility**
  - ✓ **Discussion / collaboration with specialists and home doctors, dentists, and pharmacists (according to need)**
  - ✓ **Implementation of information collection from multiple occupations and review process of prescription**
  - ✓ **Coordination of drug administration environment for home care**
  - ✓ **Collaboration and information transfer with community home doctors and pharmacists for discharge from care facility**
- **Considerations when considering prescription**
  - **(1) Assessment of polypharmacy related issues**
  - **(2) Priority of prescription and dose reduction / discontinuation**
    - ✓ **Expected situations and monitoring at healthcare facilities for the elderly, sanatorium type medical care facilities for the elderly requiring care, and nursing care centers**
    - ✓ **Confirmation of adverse drug event risks under prescription environment at each facility**

[APPENDIX]

The information on drug selection considering the characteristics of the elderly, dosage, precautions for usage, and precautions for interactions with drugs in other therapeutic categories are summarized as an appendix to the present guidance as well as a case example series of dose reduction based on an actual case for prescription review at each recuperation environment (extracted from Table 1: Appendix to Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)]. Note that an attempt at dose reduction may fail. For example, the number of drugs may increase by review or the patient may return to the original prescription due to aggravation of the symptom caused by dose reduction. Since it also includes patient's life conditions and the involvement of multiple occupations based on the conditions, this appendix can also be utilized as a material at study groups, etc. of multiple occupations.

Table 1 Case example

Case 1: A case of adverse drug event associated with decreased activity level associated with cerebral hemorrhage		
	Recuperation environment	**Changing the environment during convalescent phase / chronic phase**
	Issue	Drugs were not reviewed according to decreased ADL
	Patient background	**An 85-year-old female** **Hypertension, diabetes mellitus, a history of myocardial infarction, atrial fibrillation, dyslipidemia, iron deficiency anemia**
	Prescription	**Before intervention: A total of 7 drugs, 4 times daily** Amlodipine Tablets 5 mg — 1 tablet (1 tablet per day) once daily after breakfast Azilsartan Tablets 20 mg — 1 tablet (1 tablet per day) once daily after breakfast Bisoprolol Tablets 5 mg — One-half tablet (one-half tablet per day) once daily after breakfast Nateglinide Tablets 90 mg — 1 tablet (3 tablets per day) 3 times daily just before meals Teneligliptin Tablets 20 mg — 1 tablet (1 tablet per day) once daily after breakfast Sodium Ferrous Citrate Tablets 50 mg — 1 tablet (1 tablet per day) once daily after breakfast Pravastatin Tablets 5 mg — 1 tablet (1 tablet per day) once daily after breakfast **After intervention: A total of 5 drugs, once daily**

		Azilsartan Tablets 20 mg	1 tablet (1 tablet per day) once daily after breakfast
		Bisoprolol Tablets 5 mg	One-half tablet (one-half tablet per day) once daily after breakfast
		Teneligliptin Tablets 20 mg	1 tablet (1 tablet per day) once daily after breakfast
		Sodium Ferrous Citrate Tablets 50 mg	1 tablet (1 tablet per day) once daily after breakfast
		Pravastatin Tablets 5 mg	1 tablet (1 tablet per day) once daily after breakfast

	Course	**Intervention points** Although the patient had decreased activity level and hypotension associated with cerebral hemorrhage, 2 different hypotensive drugs, amlodipine and azilsartan, were administered continuously. Since the patient could not maintain standing and sitting positions and was at a high risk of falling, amlodipine was discontinued. Additionally, hypoglycemia was also observed although the patient was not aware of hypoglycemic symptoms, nateglinide was discontinued among nateglinide and teneligliptin considering adherence.
		Course after intervention After discontinuation of amlodipine, blood pressure increased to 120-135/65-75 mmHg and the symptoms of orthostatic hypotension improved. Hypoglycemia also improved with an increase of HbA1c to 7.2%.

3. Closing comments

The present guidance was prepared to provide better drug therapy considering the characteristics of the elderly. We encourage healthcare professionals to utilize the guidance as references for treatment and prescription. Understanding of the general public including patients who receive medical care and their families is essential for correction of polypharmacy issues. We sincerely request your continuous cooperation in educational activities by healthcare professionals for dissemination of knowledge of proper use of drugs to the general public.

Please also refer to the significance of education of patients and the public described in Closing Comments of the present guidance.

4. Reference information

* Study Group on the Appropriate Medication for Elderly Patients
  http://www.mhlw.go.jp/stf/shingi/other-iyaku.html?tid=431862 (only in Japanese)
* Working Group for the Creation of Guidelines of Appropriate Medication for Elderly Patients
  http://www.mhlw.go.jp/stf/shingi/other-iyaku.html?tid=475677 (only in Japanese)
* Guidance of Appropriate Medication for Elderly Patients (general) (Joint HPB/MSPO Notification No. 0529-1 and PSEHB/PSD No. 0529-1 by the Director, Office of Medical Safety Promotion, General Affairs Division, Health Policy Bureau and by the Director, Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated May 29, 2018)
  http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000209384.pdf (only in Japanese)
* Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)] (Joint HPB/PMSO Notification No. 0614-1 and PSEHB/PSD No. 0614-1 by the Director, Office of Medical Safety, General Affairs Division, Health Policy Bureau and by the Director, Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated June 14, 2019)
  http://www.mhlw.go.jp/content/11120000/000517943.pdf (only in Japanese)

4
Proper Use of Over-the-Counter (OTC) Drugs that May Lead to Abuse

The Minister of Health, Labour and Welfare designates some of the ingredients used in over-the-counter drugs as “drugs that may lead to abuse, etc.” Specifically, 6 ingredients of ephedrine, codeine (antitussives and expectorants only), dihydrocodeine (antitussives and expectorants only), bromovalerylurea, pseudoephedrine, and methylephedrine (oral solution only among antitussives and expectorants) are designated. For over-the-counter drugs containing such ingredients, confirmation of purchases at other pharmacies and the reason for purchasing, and quantity restriction at purchase are required. These requirements were notified by the Implementation of Pharmaceuticals that May Lead to Abuse as Designated by the Minister of Health, Labour and Welfare based on the provisions under Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices Article 15-2, PFSB Notification No. 0604-2 by the Director, Pharmaceuticals and Food Safety Bureau, Ministry of Health, Labour and Welfare dated June 4, 2014 (announcement).

In the meantime, it was reported that there is a certain number of suspected cases of dependence etc. by use of over-the-counter drugs in the Nationwide Research on the Actual State of Drug-related Mental Diseases at Psychiatric Facilities (lead investigator: Dr. Toshihiko Matsumoto, Director, Department of Drug Dependence Research, National Center of Neurology and Psychiatry, National Institute of Mental Health), an assigned research funded by FY2018 Health and Labour Sciences Research Grant (Pharmaceuticals and Medical Devices Regulatory Science Policy Research Project).

In this article, Dr. Toshihiko Matsumoto, who conducted the above research, describes the current status of abuse and dependence of over-the-counter drugs and challenges for prevention. Upon understanding the possibility of dependence by the use of over-the-counter drugs, healthcare professionals are requested to cooperate with reporting such suspected cases encountered by using the adverse drug reaction reporting system for better understanding of more accurate status. In addition, in order to improve public awareness of possible dependence by the use of over-the-counter drugs, pharmacies and those involved in the distribution of pharmaceuticals are requested to provide proper information to the purchasers and to disseminate the information in the community.

Current status of abuse and dependence of over-the-counter (OTC) drugs and challenges to prevention

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Department of Drug Dependence Research

1. Introduction

Recently, the word “self-medication” is drawing attention. According to the WHO’s definition, self-medication is “the selection and use of medicines by individuals to treat self-recognized illness or symptoms,” which is expected to broadly promote the spontaneous effort of the public for health management and disease prevention and contribute to reduction of medical expenses.

Indeed, over-the-counter drugs are becoming more and more accessible to us. If we walk in a town, drug stores compete with each other side-by-side and over-the-counter drugs are now easily available even on the Internet due to relaxation of regulations.

Does it mean that the public has become healthier than before as a result? Of course, it is too soon to make any statement on this point. However, the number of concerning situations of drug dependence is growing in the clinical setting in association with improvement of access to over-the-counter drugs.

In this article, I would like to address the issues of abuse and dependence of over-the-counter drugs which have become visible from the clinical setting of drug dependence in Japan and give outlines of its actual status and clinical characteristics.

2. Nationwide Research on the Actual State of Drug-related Mental Diseases at Psychiatric Facilities

In order to understand the actual status of patients with drug-related disorders in psychiatric practice, we have been conducting a chronological and complete enumeration called Nationwide Research on the Actual State of Drug-related Mental Diseases at Psychiatric Facilities (hospital research) almost every other year since 1987. This research is conducted for all patients with drug-related disorders who received treatment as outpatients or were hospitalized during the 2-month period between September and October of the research year at approximately 1 600 psychiatric facilities with beds nationwide, and the information is collected by filling in the case report forms by the physicians in charge of treatment. The findings obtained from the hospital research are utilized as the basic data for consideration/implementation of government policies on drugs such as prescription restriction on ritalin in 2007 and designation of etizolam as a psychotropic drug in 2016, playing key roles in drug governance in Japan.

Although it is limited to psychiatric facilities, this hospital research can be considered to reflect the trend of drugs of abuse in Japan to some extent. In order to understand the trend of such drugs of abuse, we define the drugs with the greatest impact on the symptoms of drug-related disorders as “major drugs” and follow up the changes in the percentage of each drug in all patients with drug-related disorders chronologically.

Figure 1 shows the percentage of each drug defined as a “major drug” in the most recent 2018 research (a total of 2 609 patients) and the previous research conducted in 2016 (a total of 2 262 patients). As you can see from this figure, the consistently problematic drugs of abuse in psychiatric practice in Japan are stimulants and the percentage remains more than half both in 2016 (53.4%) and 2018 (56.0%) research. The second problematic drugs of abuse are hypnotics/anxiolytics (excluding over-the-counter drugs), which also remain high in the research (2016: 17.0%, 2018: 17.1%).

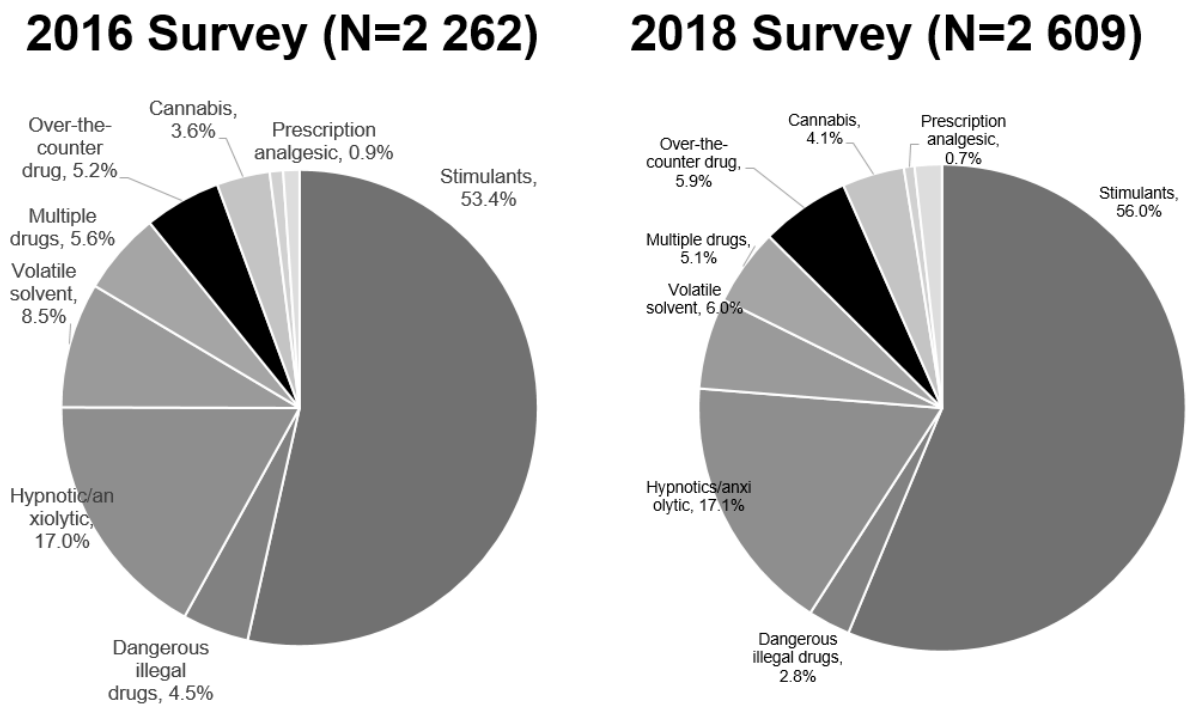

Fig. 1: Proportion of “major drugs” in 2016 research and 2018 research

In the meantime, some drugs show a decreasing tendency or an increasing tendency in their percentage. Drugs with a decreasing tendency are volatile solvents (2016: 8.5% => 2018: 6.0%) and dangerous illegal drugs (2016: 4.5% => 2018: 2.8%). The former keeps decreasing in all research since the 1990s while the latter has become difficult to obtain due to comprehensive control and eradication of actual distributors at present. While on the other hand, 2 drugs show an increasing tendency. One is cannabis in which the number of persons in custody under the Cannabis Control Law is increasing in recent years (2016: 3.6% => 2018: 4.1%) and the other is the theme of this article, over-the-counter drugs (2016: 5.2% => 2018: 5.9%).

3. Clinical characteristics and actual state of patients with over-the-counter drug-related disorders

What are the clinical characteristics of the patients with over-the-counter drug-related disorders compared to patients with disorders related to other types of drugs?

Figure 2 shows the selected data on the 5 key drugs that are stimulants, hypnotics/anxiolytics, volatile solvents, over-the-counter drugs, and cannabis based on the 2018 hospital research data, and there is a comparison of the percentages of patients with each drug-related disorder falling under the diagnostic subclassification of “F1: Mental and behavioral disorders due to psychoactive substance use” of the ICD-10. As you can see from the figure, it is characterized that many patients with stimulant-, volatile solvent-, and cannabis-related disorders fall under psychotic disorder (a condition that presents hallucination / delusion due to drug use) and residual / late-onset psychotic disorder (a condition with persistent hallucination / delusion as sequelae regardless of years of drug deprivation). To the contrary, you can see that very few patients with over-the-counter drug-related disorders present with hallucination / delusion or sequelae along with patients with hypnotic/anxiolytic-related disorders while many of them present dependence syndrome (literally, a pathological condition of “being unable to discontinue or stop”).

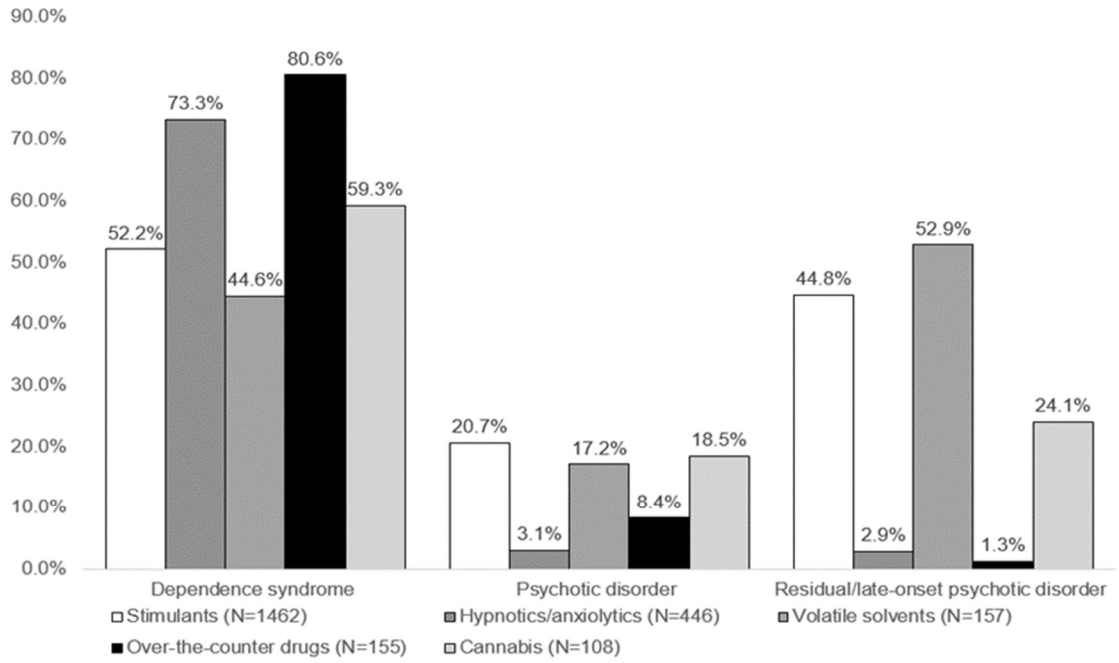

Fig. 2: Comparison of ICD-10 F1 subclassification by “major drugs”

Please look at Figure 3 next. This is a graph indicating the component ratio of the “major drugs” by age group in patients with drug-related disorders due to the top 5 drugs of abuse, which are stimulants, hypnotics/anxiolytics, volatile solvents, over-the-counter drugs, and cannabis. This figure shows that over-the-counter drugs account for the largest part, as much as 40%, in teenage patients with drug-related disorders.

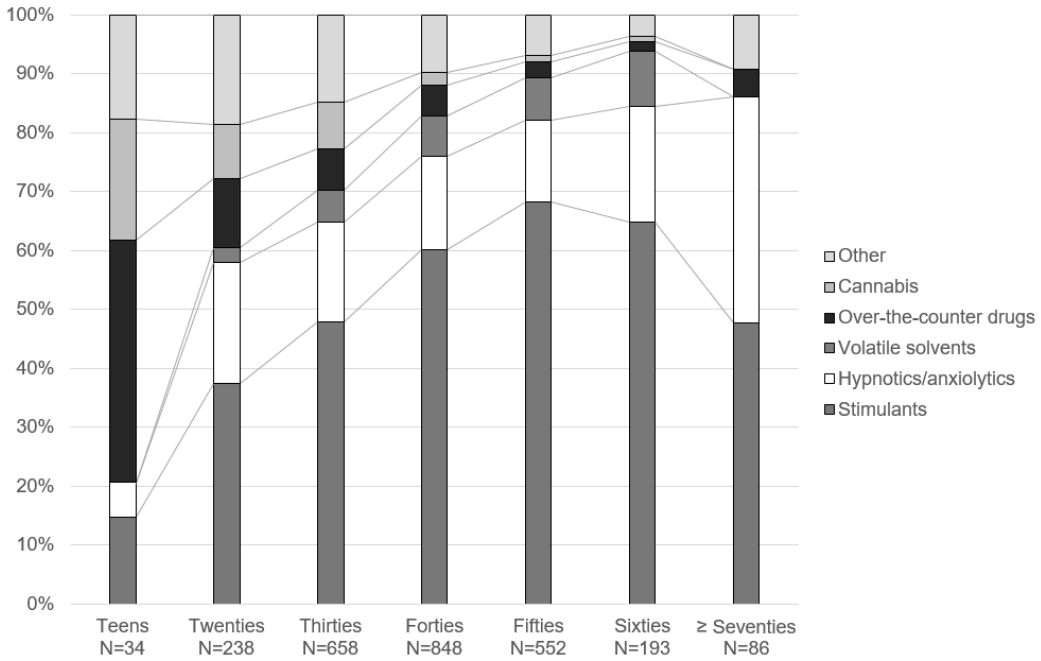

Fig. 3: Proportion of “major drugs” by age group

Figure 4 extracts only the data on teenage patients with drug-related disorders from the database of the 3 most recent hospital research studies, those in 2014, 2016, and 2018, and

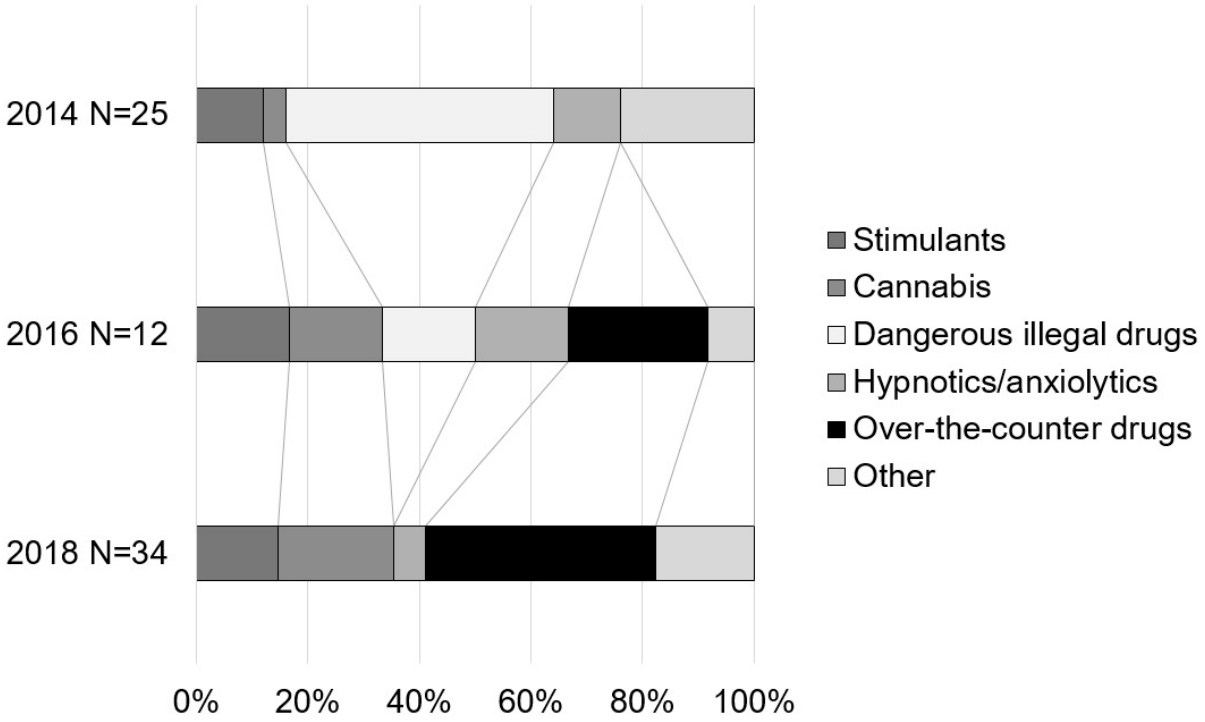

Fig. 4: Chronological change in “major drugs” in teens

compares the “major drugs” in the patients with drug-related disorders in each research year. This figure indicates the following reality. That is, while dangerous illegal drugs accounted for more than half of the “major drugs” in the 2014 research, it decreased in the 2016 research. However, with a decrease in dangerous illegal drugs in the 2016 research, teenage patients with over-the-counter drugs as the “major drugs” emerged, which the previous 2014 research had not observed. Moreover, while there is no patient with dangerous illegal drugs as the “major drugs,” the percentage of patients with over-the-counter drugs as the “major drugs” grew rapidly in the 2016 research.

The above research results can be summarized in 2 points as the characteristics of patients with over-the-counter drug-related disorders. Firstly, the main symptom of the patients with over-the-counter drug-related disorders is not toxic psychosis such as hallucination / delusion, but dependence itself that “cannot be discontinued or stopped.” And secondly, currently the over-the-counter drugs are the representative drugs used by teenage patients with drug-related disorders.

In addition, in this 2018 hospital research, we also investigated to the extent possible the product names of the over-the-counter drugs used outside the original intended use and the results in all age groups are shown in Table 1.

Table 1: Over-the-counter drugs used for purposes other than the original intended use (drugs observed in more than 2 cases)

Product name	Number of patients	Product name	Number of patients
Bron Tablets/Bron Syrup (antitussive/expectorant)	158	Restamin (antiallergic)	6
Pabron/Pabron Gold (combination cold remedy)	34	Loxonin (analgesic)	6
Wutt (hypnotic)	32	Lulu (combination cold remedy)	5
Naron/Naron Ace (analgesic)	16	Estrone Mocha (drowsiness remover)	4
Eve/Eve Quick/Ibuprofen (analgesic)	15	Rislon (hypnotic)	4
Drewell (hypnotic)	12	PA/PL/Pylon PL (cold remedy)	3
Bufferin (analgesic)	12	Norshin (analgesic)	3
Contac (combination cold remedy)	10	Kaigen (antitussive/expectorant)	2
Tonin/New Tonin/New Tonin (antitussive/expectorant)	10	Kerorin (analgesic)	2
Sedes (analgesic)	6	Precol (combination cold remedy)	2
Benza/Benza Block	6		

4. Who abuses over-the-counter drugs?

Based on my own experience, most patients who abuse or are dependent on over-the-counter drugs I encounter at the drug dependence clinic are teenagers who have difficulties with living, suffer from slashing their wrists, and have feelings that they want to “disappear” or “die” before becoming drug abusers. Teenagers who cannot talk to their parents about their psychological distress at home or school candidly for various reasons (or not willing to talk due to distrust) and brood by themselves.

Quite a few of them have already visited a psychiatric department. The hospital research results also show that psychiatric diagnoses are made for many of the patients with over-the-counter drug-related disorders such as “F3: Mood disorders,” “F4: Neurotic, stress-related and somatoform disorders,” “F6: Disorders of adult personality and behaviour,” and “F8: Disorders of psychological development” in the ICD-10 psychiatric diagnosis. However, they cannot tell their attending psychiatrist their honest feelings and pretend to be “good patients” who are easy to take care of by saying “there is no change” or “I am OK,” and they are also overadaptive to treatment.

They use over-the-counter antitussives “for non-indication purposes” to motivate themselves to work, go out with friends, or study, improve their mood, or divert their anxiety. However, they soon develop tolerance to such pharmacological effects, and will be overwhelmed by emotional distress that they cannot control by such a makeshift usage.

In short, teenage patients who abuse or are dependent on over-the-counter drugs are people who cannot talk to surrounding people who they should be talking to primarily and who are trying to overcome the difficulties with drugs only. In other words, they are “people who can only be dependent on drugs” or “people who cannot rely on people with ease.” Moreover, it is an important point that they do not abuse over-the-counter drugs for pleasure or enjoyment. The compensation for enforcing their drug-taking behavior is definitely not pleasure, rather “temporal alleviation of distress.” Therefore, it is also necessary to understand that their problems cannot be solved simply by discontinuing abuse of over-the-counter drugs and continuous and considerate mental health support is required.

Based on the above, I would like to reorganize the criteria for judging patients for over-the-

counter drug abuse / dependence requiring specialized treatment. Note that this is based on the author's personal clinical experience and it is unknown how far this can be generalized.

The author recognizes that the patients require specialized treatment if they fall under 2 or more items among the following 3 items.

- Drug use for non-indication purposes: Use of over-the-counter drugs in expectation of effects different from the original indications of the over-the-counter drugs (antitussive, analgesic, cold remedy) such as hyperbulia or alleviation of anxiety / tension
- Life disability: Family life or social life is interfered with because he/she has to spend more money or time in order to obtain over-the-counter drugs
- Difficulty in discontinuing drugs: He/she cannot be deprived of drugs or fail to be deprived of drugs repeatedly because he/she suffers from withdrawal symptoms such as hypobulia, severe general malaise, and unbearable impatience (these are withdrawal syndromes peculiar to Bron Tablet-dependent patients) or emotional distress such as suicidal ideation and depressed mood (these are natural psychiatric symptoms) when he/she tries to stop abusing over-the-counter drugs

I would like to add that in abuse of over-the-counter drugs, the amount of consumption and frequency of use varies greatly between individuals and it is difficult to establish unified criteria.

5. Closing comments

In this article, I explained the clinical characteristics of recent over-the-counter drug abuse / dependence based on the findings obtained from the hospital research conducted by the author.

Healthcare professionals pay attention to the drugs prescribed for patients by other clinical departments, but we are apt to neglect confirmation of their regular over-the-counter drugs at times. Patients also tend to hesitate about honest declaration because they think that it may offend healthcare professionals, or they might receive a reprimand from healthcare professionals when they find out about the patients' use of over-the-counter drugs. Moreover, in actual circumstances, it is considered that there are not many healthcare professionals who can recall which product contains which ingredients at once even when they obtain information on the over-the-counter drugs that the patient is taking. In this sense, it is required for many healthcare professionals to be concerned about the ingredients of over-the-counter drugs and strive to collect information in the future.

5

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated July 9, 2019, this section presents the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Nivolumab (genetical recombination)

Branded name (name of company)	Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Malignant melanoma Unresectable advanced or recurrent non-small cell lung cancer Unresectable or metastatic renal cell carcinoma Relapsed or refractory classical Hodgkin lymphoma Relapsed or metastatic head and neck cancer Unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy Unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy

PRECAUTIONS (revised language is underlined)

[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions)	**Colitis, <u>enteritis,</u> severe diarrhea**: Colitis, <u>enteritis,</u> and severe diarrhea may occur<u>, and cases of enterocolitis that resulted in perforation or ileus have been reported.</u> The patient should be carefully monitored. If symptoms such as persisted diarrhea, abdominal pain, blood stool, etc. are observed, drug discontinuation or other appropriate measures should be taken.
[Under New instructions]	
11. Adverse Reactions	Colitis, <u>enteritis,</u> severe diarrhea
11.1 Clinically Significant Adverse Reactions	<u>Cases of enterocolitis that resulted in perforation or ileus have been reported.</u> If symptoms such as persisted diarrhea, abdominal pain, blood stool, etc. are observed, drug discontinuation or other appropriate measures should be taken.
Reference information	Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 35-month period (April 2016 to February 2019) Cases of enteritis: 5 (1 patient mortality) Cases involving intestinal perforation: 4 (no patient mortalities) Cases involving ileus: 1 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 17 000 Japanese market launch: September 2014

Case summary

No.	Patient		Daily dose Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Male 60s	Recurrent Non-small cell lung cancer recurrent (NSCLC) (metastases to lymph nodes, metastases to lung, metastases to central nervous system, pulmonary artery thrombosis, deep vein thrombosis, diverticulum)	3 mg/kg 5 courses at 2-week intervals	**Intestinal obstruction, small intestinal perforation** The patient had a history of appendicitis. Day 1 of administration: Nivolumab was administered 3 mg/kg/day in the patient with unresectable advanced and recurrent NSCLC (treated site: right upper lobe, stage 4, TNM stage: T2N2M1 [the name of organ metastasized: brain]). Abdominal pain was observed. 8 days after administration: Queasy, abdominal pain, and black stools (melaena) were observed. 15 days after administration: Large bowel endoscopy revealed many diverticula in the ascending colon, but did not show any lung cancer metastasis foci. Date unknown: No abnormalities were found by imaging procedure (systemic CT, etc.) or blood test after the first dose of nivolumab. Date unknown: No abnormalities were found by upper gastrointestinal tract endoscopy or large bowel endoscopy, and the symptom improved without treatment. Date unknown: Abdominal pain, vomiting, and black stools were observed every time nivolumab was administered. 57 days after administration (day of discontinuation): The patient received the 5th dose of nivolumab. CRP results were negative with no abdominal pain, etc. 7 days after discontinuation: The patient felt severe abdominal pain and was rushed to a local physician because of increased pain. [Physical findings] Flat, board-like abdomen, and severe tenderness as well as spontaneous pain in the epigastric area. Bloody drainage was detected in the nasogastric tube with an occult blood test result of 4+. [Blood gas analysis findings] Hyperventilation due to pain was suspected. [Blood test findings] No abnormalities were found in the hepatic and renal functions. [Abdominal imaging procedure (CT)] A small amount of free air in the abdominal cavity, especially around the upper abdomen, and wall thickening of the small intestine, a small amount of ascites, and an increased concentration of mesenteric fat in the lower abdomen were observed. Based on the above, the patient was diagnosed with gastrointestinal perforation (small intestinal perforation) and perforative peritonitis associated with upper gastrointestinal perforation. Nivolumab was discontinued, and the patient was hospitalized. Conservative treatment with an antibiotic (ampicillin hydrate) and fluid replacement (drip infusion) under a fasted condition, using a nasogastric tube was started.

				8 days after discontinuation	An ileus-tube was inserted due to development of intestinal obstruction. Upper gastrointestinal tract endoscopy did not show ulcerative lesions, which could rule out upper gastrointestinal perforation. As physical findings and clinical course ruled out the possibility of lower gastrointestinal perforation, small intestinal perforation was suspected. Small-bowel radiography, however, through the ileus tube did now show any outflow from the intestine, and definitive diagnosis was not possible.
				11 days after discontinuation	Hydrocortisone sodium succinate (300 mg/day) was administered for 3 days.
				Date unknown	Abdominal pain and intestinal obstruction symptoms improved.
				17 days after discontinuation	Liquid food was started.
				Date unknown	Conservative treatment with corticosteroids was continued, and the patient was followed up with the ileus tube for drainage inserted.
				24 days after discontinuation	The medication was switched to prednisolone (20 mg/day).
				31 days after discontinuation	Lesions at the terminal ileum were suspected. Endoscopy (lower gastrointestinal endoscopy) was performed up to the terminal ileum, but no abnormalities were observed.
				Date unknown	The diet was resumed, and the dose of prednisolone was titrated down to 5 mg/day.
				38 days after discontinuation	Abdominal pain and intestinal obstruction symptoms recurred, and hernia and intestinal obstruction developed. Contrast CT scan revealed stenosis in the more oral side of the ileum than the observed range detected by endoscopy large bowel.
				Date unknown	Corticosteroid was effective but the patient had repeated symptoms of abdominal pain and intestinal obstruction after the diet was resumed. Therefore, they were diagnosed as structurally small intestinal stenosis lesions following small intestinal perforation.
				41 days after discontinuation	Laparotomy was performed. The ileum was perforated 40 cm wide from the site which was located 30 cm of the Bauhin's valve. The ilea at both oral sides adhered to each other in a loop, which induced stenosis. They also adhered to the intestinal wall as well and showed penetration. No fistulae were formed. Since an abscess was formed between the intestinal walls, a surgery was performed to partially resect the small intestine to remove the abscess as a mass, then end-to-end anastomosis was performed. No adhesion or lesions in the other small-intestine regions were observed.

					[Histopathology findings] Granulation tissue formation with conspicuous inflammatory cellular infiltration, food residue, foreign-body reaction, and fibrosis were observed under the muscle layer of the small intestine. The site apparently had been perforated once and then the penetration had been closed. Neither epithelioid granuloma formation nor malignancy findings were observed in the cut sections including the site once perforated.
				52 days after discontinuation	The clinical course after surgery was favorable with no recurrence of abdominal pain, gastrointestinal haemorrhage or intestinal obstruction. The patient was discharged from the hospital. Gastrointestinal perforation (small intestinal perforation) and intestinal obstruction improved.
				Date unknown	Perforative peritonitis improved.
	Concomitant medications: Edoxaban tosilate hydrate				

2 Palbociclib

Branded name (name of company)	Ibrance Capsules 25 mg, 125 mg (Pfizer Japan Inc.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Inoperable or recurrent breast cancer

PRECAUTIONS (revised language is underlined)

[Under Old instructions]

Warnings (Newly added)	Cases of interstitial lung disease resulting in mortality have been reported. Patients should be carefully monitored for initial symptoms (such as dyspnoea, cough, and pyrexia) and by performing a chest X-ray, etc. If any abnormalities are observed, administration of this drug should be discontinued and a chest CT scan or serum marker test, etc. should be performed as necessary and appropriate measures should be taken.
Careful Administration (Newly added)	Patients with interstitial lung disease or a history of the disease (interstitial lung disease may exacerbate.)
Important Precautions	Interstitial lung disease may occur. When using this drug, patients should be carefully monitored for initial symptoms (such as dyspnoea, cough, and pyrexia) and by performing a chest X-ray, etc. Patients or their families should be adequately informed of adverse reactions associated with this drug and instructed to immediately contact medical institutions when they experience any initial symptoms of the disease.
Adverse Reactions (Clinically Significant Adverse Reactions)	**Interstitial lung disease:** Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities are observed, this drug should be discontinued and a chest CT scan or serum marker test, etc. should be performed as necessary, and appropriate measures should be taken.
Reference information	Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 19-month period (December 2017 to June 2019). Cases involving interstitial lung disease : 14 (1 patient mortality) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 15 000 Japanese market launch: December 2017

Case summary 1

No.	Patient		Daily dose Treatment duration	Adverse reactions		
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures		Outcome
1	Female 60s	Breast cancer	125 mg for 21 days 100 mg for 21 days 100 mg for 21 days 100 mg for 21 days 100 mg for 21 days 100 mg for 21 days 100 mg for 21 days 100 mg for 21 days 100 mg for 7 days 100 mg for 21 days ↓ Discontinued	**Interstitial lung disease** Bronchiectasis Breast cancer recurrent (metastasis to lungs, liver, bones, and lymph nodes)		Improved
				10 days before administration	Chest X ray did not show any significant findings.	
				3 days before administration	Diagnosis by chest CT scan: after surgery for breast cancer, metastases to bone, metastases to lymph nodes. The patient was on chemotherapy; metastases to lymph nodes were decreasing in size.	
				Day 1 of administration	Treatment with palbociclib 125 mg/day and fulvestrant 500 mg/month was started.	
				Day 35 of administration	The dose of palbociclib was reduced to 100 mg/day.	
				Day 63 of administration	Treatment with palbociclib was started at a dose of 100 mg/day.	
				Day 91 of administration	Treatment with palbociclib was started at a dose of 100 mg/day.	
				Day 119 of administration	Treatment with palbociclib was started at a dose of 100 mg/day.	
				Day 147 of administration	Treatment with palbociclib was started at a dose of 100 mg/day.	
				Day 175 of administration	Treatment with palbociclib was started at a dose of 100 mg/day.	
				Day 203 of administration	Treatment with palbociclib was started at a dose of 100 mg/day.	
				Day 238 of administration	Treatment with palbociclib was started at a dose of 100 mg/day.	
				Day 267 of administration	Treatment with palbociclib was started at a dose of 100 mg/day.	
				Day 287 of administration	Treatment with palbociclib was started at a dose of 100 mg/day.	

				Day 323 of administration (day of discontinuation)	Interstitial lung disease (Grade 2) was observed. No subjective symptoms. Chest X ray revealed ground-glass opacity in the left lower lung. The CT scan, which was performed to evaluate the recurrent breast-cancer foci, revealed segmental ground-glass opacity in the middle lobe/lingular segment and the bilateral lungs. Palbociclib was discontinued.	
				6 days after discontinuation	Chest X ray revealed ground-glass opacity in the left lower lung.	
				14 days after discontinuation	CT scan did not show improvement or aggravation in the pulmonary interstitial shadow. Treatment with prednisolone 20 mg was started.	
				27 days after discontinuation	As a reduced KL-6 level was observed, prednisolone was reduced to 15 mg.	
				34 days after discontinuation	Chest X ray did not show aggravation and prednisolone was reduced to 10 mg.	
				41 days after discontinuation	CT scan showed an improvement trend on pulmonary interstitial shadow	
				69 days after discontinuation	The dose of prednisolone was reduced to 7.5 mg.	
				84 days after discontinuation	The dose of prednisolone was reduced to 5 mg.	
				97 days after discontinuation	CT scan did not show aggravation of pulmonary interstitial shadow, and the dose of prednisolone was reduced to 2.5 mg. Chest X ray showed an improvement in the shadow.	
				111 days after discontinuation	Treatment with prednisolone at 2.5 mg was to be continued.	

Laboratory Examination:

	176 days before administration	10 days before administration	Day of discontinuation	6 days after discontinuation	27 days after discontinuation	97 days after discontinuation	111 days after discontinuation
β-D-glucan (pg/ml)	<5.0	-	<5.0	-	<5.0	<5.0	-
SpO2 (%)	93	-		-	96	95	-
KL-6 (IU/mL)	272	-	1100	-	946	824	953
LDH (IU/L)	-	238	-	225	220	254	238
CRP (mg/dl)	-	0.80	-	0.38	0.08	0.11	0.23
WBC (/mm3)	-	8290	-	6280	11490	6940	7040
Lymphocytes (%)	-	27.0	-	46.0	20.1	35.3	27.0

Concomitant medications: Fulvestrant

Case summary 2

No.	Patient		Daily dose Treatment duration	Adverse reactions		
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures		Outcome
1	Female 80s	Breast cancer metastatic	100 mg for 43 days ↓ Discontinued	**Lung disorder** Breast cancer multiple bone metastasis, recurrence of advanced breast cancer		Fatal
				84 days before administration	Treatment with fulvestrant was started.	
				Day 1 of administration	Treatment with palbociclib was started at a dose of 100 mg/day.	
				Day 43 of administration (day of discontinuation)	Facial paralysis symptom developed (diagnosed as Bell's palsy), and the patient was started on prednisolone 20 mg. Palbociclib was discontinued.	
				(Date unknown)	The dose of prednisolone was down-titrated.	
				25 days after discontinuation	The patient experienced pyrexia (above 38°C) and then gradually had dyspnoea.	
				35 days after discontinuation	Oxygen saturation 80%, and the patient was diagnosed with acute respiratory failure. CT scan revealed ground-glass opacity in the bilateral lungs. Pneumocystis carinii and other infections were suspected to have caused pneumonia, and the patient was started on treatment with trimethoprim/sulfamethoxazole, tazobactam/piperacillin hydrate, and prednisolone 80 mg/day.	
				36 days after discontinuation	Since her respiratory failure symptom further aggravated, non-invasive positive pressure ventilation (NIPPV) was introduced. Tests for several infections were negative.	
				Date unknown	The patient was diagnosed with drug-induced lung disorder.	
				41 days after discontinuation	The ground-glass opacity in the right upper lobe improved to some extent, but other parts slightly worsened and pleural effusion occurred.	
				43 days after discontinuation	Since the symptom did not improve well, steroid pulse therapy (methylprednisolone 1 g/day for 3 days) was started. Subsequently, treatment with prednisolone was always maintained at a dose of 45 mg/day.	

				48 days after discontinuation	The patient responded to the steroid pulse therapy and respiratory failure improved. On the same day, NIPPV was discontinued, and the dose of steroids was to be down-titrated. The ground-glass opacity improved. No evident traction bronchiectasis or honeycomb lung formation was observed.	
				56 days after discontinuation	The dose of prednisolone was reduced to 30 mg/day.	
				70 days after discontinuation	The dose of prednisolone was reduced to 20 mg/day.	
				84 days after discontinuation	The dose of prednisolone was reduced to 10 mg/day.	
				87 days after discontinuation	Dyspnoea developed again.	
				88 days after discontinuation	The second steroid pulse therapy was performed, but the patient poorly responded to it and respiratory failure gradually worsened. The ground-glass opacity worsened again, and marked traction bronchiectasis was observed.	
				107 days after discontinuation	The patient's death was confirmed.	

Laboratory Examination:

	25 days after discontinuation	35 days after discontinuation	37 days after discontinuation	44 days after discontinuation	55 days after discontinuation	90 days after discontinuation
β-D-glucan (pg/ml)	-	7.1	-	-	-	<5.0
Body temperature (°C)	38	-	-	-	-	-
KL-6 (IU/mL)	-	9000<	-	9000<	-	-
Urinary Legionella antigen	-	(-)	-	-	-	-
Mycoplasma antibody	-	(-)	-	-	-	-
Carinii diagnosis	-	No	-	-	-	-
SP-D (ng/mL)	-	-	895	-	154	340

Concomitant medications: Fulvestrant, famotidine, mecobalamin, valaciclovir, chondroitin, combination drug of calcium carbonate/cholecalciferol/magnesium carbonate

6

Revision of Precautions (No.305)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated July 9, 2019.

1 Circulatory organ agents-miscellaneous

Epoprostenol sodium

Branded name	Flolan for Injection 0.5 mg, 1.5 mg, (GlaxoSmithKline K.K.) and the others
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (Newly added)	Thrombocytopenia may occur. Patients should be carefully monitored through methods such as periodic clinical laboratory tests. If any abnormalities are observed, dose reduction, discontinuation of administration, or other appropriate measures should be taken.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Thrombocytopenia may occur. Patients should be carefully monitored through methods such as periodic clinical laboratory tests.
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	**Thrombocytopenia**

2 Antineoplastics-miscellaneous

Nivolumab (genetical recombination)

Branded name	Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions)	**Colitis, enteritis, severe diarrhea:** Colitis, enteritis, and severe diarrhea may occur, and cases of enterocolitis that resulted in perforation or ileus have been reported. The patient should be carefully monitored. If symptoms such as persisted diarrhea, abdominal pain, blood stool, etc. are observed, drug discontinuation or other appropriate measures should be taken.
[Under New instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions	**Colitis, enteritis, severe diarrhea** : Cases of enterocolitis that resulted in perforation or ileus have been reported. If symptoms such as persisted diarrhea, abdominal pain, blood stool, etc. are observed, drug discontinuation or other appropriate measures should be taken.

3 Antineoplastics-miscellaneous

Palbociclib

Branded name	Ibrance Capsules 25 mg, 125 mg (Pfizer Japan Inc.)
[Under Old instructions]	
Warnings	Cases of interstitial lung disease resulting in mortality have been reported. Patients should be carefully monitored for initial symptoms

(newly added)	(such as dyspnoea, cough, and pyrexia) and by performing a chest X ray, etc. If any abnormalities are observed, administration of this drug should be discontinued and a chest CT scan or serum marker test, etc. should be performed as necessary and appropriate measures should be taken.
Careful Administration (newly added)	Patients with interstitial lung disease or a history of the disease (interstitial lung disease may exacerbate.)
Important Precaution	Interstitial lung disease may occur. When using this drug, patients should be carefully monitored for initial symptoms (such as dyspnoea, cough, and pyrexia) and by performing a chest X-ray, etc. Patients or their families should be adequately informed of adverse reactions associated with this drug and instructed to immediately contact medical institutions when they experience any initial symptoms of the disease.
Adverse Reactions (Clinically Significant Adverse Reactions)	**Interstitial lung disease:** Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities are observed, this drug should be discontinued and a chest CT scan or serum marker test, etc. should be performed as necessary, and appropriate measures should be taken.

4 Antineoplastics-miscellaneous

Pembrolizumab (genetical recombination)

Branded name	Keytruda Injection 20 mg, 100 mg (MSD K.K.)
[Under New instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions)	**Colitis, enteritis, severe diarrhea**: Colitis, enteritis, and severe diarrhea may occur, and cases of enterocolitis that resulted in perforation or ileus have been reported. Patients should be carefully monitored. If symptoms such as persisted diarrhoea, abdominal pain, blood stool, etc. are observed, drug discontinuation or other appropriate measures should be taken.

5 Allergic agents-miscellaneous

[1] Cedar pollen extract powder
[2] Dermatophagoides pteronyssinus extract/dermatophagoides farina extract

Branded name	[1] Cedarcure Japanese Cedar Pollen Sublingual Tablets 2,000 JAU and the others (Torii Pharmaceutical Co., Ltd.) [2] Miticure House Dust Mite Sublingual Tablets 3,300 JAU and the others (Torii Pharmaceutical Co., Ltd.)
[Under Old instructions]	
Important Precautions	Intense exercise, alcohol consumption, bathing, etc., should be avoided before and 2 hours after taking this drug. Patients should be alert for the onset of adverse reactions such as anaphylaxis when engaged in such activities 2 hours or more after taking this drug.

6 Allergic agents-miscellaneous

[1] Standardized cedar pollen extract (liquid, those for sublingual administration only)
[2] Dermatophagoides pteronyssinus extract bulk powder/dermatophagoides farinae extract bulk powder

Branded name	[1] Cedartolen Japanese cedar pollen sublingual drop 200 JAU/mL bottle and the others (Torii Pharmaceutical Co., Ltd.) [2] Actair house dust mite sublingual tablets 100 units (IR) and the others (Torii Pharmaceutical Co., Ltd.)

[Under Old instructions]

Important Precautions	Patients should be instructed to avoid intense exercise, alcohol consumption, bathing, etc., before and 2 hours after taking this drug, and to be alert for the onset of adverse reactions such as anaphylaxis when engaged in such activities 2 hours or more after taking this drug.

7 Antipyretics and analgesics, anti-inflammatory agents

[1] Tramadol hydrochloride (oral dosage form)
[2] Tramadol hydrochloride/acetaminophen

Branded name	[1] Tramal OD Tablets 25 mg, 50 mg (Nippon Shinyaku Co., Ltd), and the others [2] Tramcet Combination Tablets (Janssen Pharmaceutical K.K. / Mochida Pharmaceuticals Co. Ltd.), and the others
[Under Old instructions]	
Contraindications (newly added)	Children younger than 12 years old
Important Precautions	(deleted) note 1
[Under New instructions]	
2. Contraindications (newly added)	Children younger than 12 years old

Note 1: The current language “This drug should not be used in children younger than 12 years old because serious respiratory depression may occur.” should be deleted.

8 Antipyretics and analgesics, anti-inflammatory agents

Tramadol hydrochloride (injection)

Branded name	Tramal Injection 100 (Nippon Shinyaku Co., Ltd.)
[Under Old instructions]	
Contraindications (newly added)	Children younger than 12 years old Use in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy
Important Precautions	(deleted) note 2
[Under New instructions]	
Contraindications (newly added)	Children younger than 12 years old Use in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS	
9.1 Patients with Complication or History of Diseases, etc.	(deleted) note 3
9.7 Pediatric use	(deleted) note 4

Note 2: The current language “This drug should not be used in children younger than 12 years old because serious respiratory depression may occur. This drug should not be used in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy because the risk of serious respiratory depression may increase.” should be deleted.

Note 3: The current language “This drug should not be used in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy because the risk of serious respiratory depression may increase.” should be deleted

Note 4: The current language “Children after tonsillectomy or adenoidectomy; this drug should not be used for pain relief. The risk of serious respiratory depression may increase.” should be deleted.

9 Antitussives and expectorants, opium alkaloids

[1] Codeine phosphate hydrate (prescription drugs)
[2] Dihydrocodeine phosphate (prescription drugs)

Branded name	[1] 1% Codeine Phosphate Powder Sioe (Sioe Pharmaceutical Co., Ltd./ Nippon Shinyaku Co., Ltd.) , and the others [2] 1% Dihydrocodeine Phosphate Powder Sioe (Sioe Pharmaceutical Co., Ltd./ Nippon Shinyaku Co., Ltd.) , and the others
[Under Old instructions]	
Contraindications	Children younger than 12 years old
（**newly added**）	Use in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy
Important Precautions	(deleted) note 5
[Under New instructions]	
2. CONTRAINDICATIONS	Children younger than 12 years old
（**newly added**）	Use in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS	
9.1 Patients with Complication or History of Diseases, etc.	(deleted) note 6
9.7 Pediatric use	(deleted) note 7

Note 5: The current language “This drug should not be used in children younger than 12 years old because serious respiratory depression may occur. This drug should not be used in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy because the risk of serious respiratory depression may increase.” should be deleted.
Note 6: The current language “Patients younger than 18 years old and after tonsillectomy or adenoidectomy this drug should not be used for pain relief. The risk of serious respiratory depression may increase.” should be deleted.
Note 7: The current language “Children after tonsillectomy or adenoidectomy
This drug should not be used for pain relief. The risk of serious respiratory depression may increase.” should be deleted.

10 Antitussives and expectorants

[1] Dihydrocodeine phosphate/platycodon fluidextract/glycyrrhiza extract/plantago herb extract/peony root extract (prescription drugs)
[2] Dihydrocodeine phosphate/*dl*-methylephedrine hydrochloride/ chlorpheniramine maleate (prescription drugs)
[3] Dihydrocodeine phosphate/diprophylline/*dl*-methylephedrine hydrochloride/ diphenhydramine salicylate/acetaminophen/bromovalerylurea (prescription drugs)
[4] Dihydrocodeine phosphate/ephedrine hydrochloride/ ammonium chloride (prescription drugs)

Branded name	[1] Opisezol Codeine Solution (Nichi-Iko Pharmaceutical Co., Ltd.) [2] Lightgen Combination Syrup (Teijin Pharma Limited.) and the others [3] Coughcode-N Combination Tablets (Pfizer Japan Inc.) [4] Sekicode Combination Syrup (Nichi-Iko Pharmaceutical Co., Ltd.)
[Under Old instructions]	
Contraindications （newly added）	Children younger than 12 years old
Important Precautions	(deleted) note 8

Note 8: The current language ”This drug should not be used in children younger than 12 years old because serious respiratory depression may occur.” should be deleted

11 Cold medicine, antitussives and expectorants

[1] Products containing codeine phosphate hydrate (OTC drugs)
[2] Products containing dihydrocodeine phosphate (OTC drugs)

When not to use the product	
This product should not be used in the following persons: （newly added）	Children younger than 12 years old note 9
Precaution concerning Dosage and Administration	(deleted) note 10

Note 9: In the When not to use the product section, on an outer container, or a wrapper of the product, any minimum ages of 13 years or older as approved in the current dosage and administration should replace the “younger than 12 years old” Tin this revision.
Note 10:The current language “For children younger than 12 years old, examination by a physician should always precede administration of this drug.” should be deleted.

7

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect ADR data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of 30 June, 2019)

◎: Products for which EPPV was initiated after June 1, 2019

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Ceftolozane sulfate/tazobactam sodium Zerbaxa Combination for Intravenous Drip Infusion	MSD K.K.	June 25, 2019
◎	Romiplostim (genetical recombination) *1 Romiplate for s.c. injection 250 μg	Kyowa Hakko Kirin Co., Inc	June 18, 2019
◎	Tocilizumab (genetical recombination) *2 Actemra Intravenous Infusion 80 mg, 200 mg, 400 mg	Chugai Pharmaceutical Co., Ltd.	June 12, 2019
◎	Sodium selenite Aselend Injection 100 μg	Fujimoto Pharmaceutical Corporation	June 6, 2019
	Apalutamide Erleada Tablets 60 mg	Janssen Pharmaceutical K.K.	May 30, 2019
	Thiotepa Rethio Intravenous Infusion 100 mg	Sumitomo Dainippon Pharma Co., Ltd.	May 28, 2019
	Risankizumab (genetical recombination) Skyrizi Subcutaneous Injection 75 mg Syringe 0.83 mL	AbbVie GK	May 24, 2019
	Fluticasone furoate/vilanterol trifenatate/umeclidinium bromide Trelegy 100 Ellipta 14 doses, 30 doses	Glaxo Smith Kline K.K.	May 22, 2019
	Esaxerenone Minnebro Tablets 1.25mg, 2.5mg, 5mg	Daiichi Sankyo Co., Ltd.	May 13,2019
	Bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate Biktarvy Combination Tablets	Gilead Sciences Inc.	April 8, 2019
	Tafamidis meglumine*3 Vyndaqel capsules 20 mg	Pfizer Japan Inc.	March 26, 2019
	Landiolol hydrochloride*4 Onoact for Intravenous Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	March 26, 2019
	Dupilumab (genetical recombination) *5	Sanofi K.K.	March 26, 2019

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
	Dupixent Subcutaneous Injection 300 mg Syringe		
	Dapagliflozin propylene glycolate hydrate*6 Forxiga Tablets 5 mg, 10 mg	AstraZeneca K.K.	March 26, 2019
	Nalmefene hydrochloride hydrate Selincro tablets 10 mg	Otsuka Pharmaceutical Co., Ltd	Match 5, 2019
	Romosozumab (genetical recombination) Evenity subcutaneous injection 105 mg syringe	Amgen Astellas Bi-Pharma K.K.	March 4, 2019
	Dacomitinib Hydrate Vizimpro Tablets 15 mg, 45 mg	Pfizer Japan Inc.	March 1, 2019
	Relugolix Relumina Tablets 40 mg	Takeda Pharmaceutical Company Limited.	March 1, 2019
	Lorazepam Lora-pita Intravenous Injection 2mg	Pfizer Japan Inc.	March 1, 2019
	Binimetinib Mektovi Tablets 15 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
	Encorafenib Braftovi Capsules 50 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
	Sofosbuvir/velpatasvir Epclusa Combination Tablets	Gilead Sciences Inc.	February 26, 2019
	Metirosine Demser Capsules 250 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
	Damoctocog alfa pegol (genetical recombination) Jivi for i.v. injection 250, 500, 1000, 2000, 3000 Refixia I.V. Injection 500, 1000, 2000	Bayer Yakuhin Ltd	February 12, 2019

*1 Aplastic anemia inadequately controlled with existing therapies

*2 Cytokine release syndrome induced by tumor-specific T cell infusion treatment

*3 Transthyretin cardiac amyloidosis (wild type and mutant type)

*4 The following life-threatening arrhythmias when they are refractory and time-critical
Ventricular fibrillation, ventricular tachycardia accompanied by haemodynamic instability

*5 Bronchial asthma (only for sever or refractory cases whose symptoms are not adequately controlled with existing treatments)

*6 Type 1 diabetes mellitus