Pharmaceuticals and Medical Devices Safety Information

No. 365  August 2019

Table of Contents

1. Review of Contraindications of Metformin including “renal impairment” ................................................................. 5

2. Safety Measures for Febuxostat ..................................................... 9

3. Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)] ..................................................... 13

4. Proper Use of Over-the-Counter (OTC) Drugs that May Lead to Abuse ................................................................................. 17

5. Important Safety Information .......................................................... 24
   1. Nivolumab (genetical recombination) ........................................ 24
   2. Palbociclib .............................................................................. 28

6. Revision of Precautions (No. 305)
   Epoprostenol sodium (and 10 others) ............................................ 33

7. List of Products Subject to Early Post-marketing Phase Vigilance ....................................................................................... 38

This Pharmaceuticals and Medical Devices Safety Information (PMDSI) publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only in Japanese).

Access to the latest safety information is available via the PMDA Medi-navi.

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### Outline of Information

<table>
<thead>
<tr>
<th>No.</th>
<th>Subject</th>
<th>Measures</th>
<th>Outline of Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Review of Contraindications of Metformin including “renal impairment”</td>
<td>( P )</td>
<td>Based on Japanese and overseas regulations, pharmacokinetic studies in patients with renal impairment, Japanese and overseas published literature, academic society guidelines, and adverse reaction reports in Japan, revision of contraindications of metformin including “renal impairment” was considered at the Subcommittee on Safety Measures, Committee on Drug Safety, Pharmaceutical Affairs and Food Sanitation Council. As a result, MHLW instructed the marketing authorization holders (MAHs) to alert by revision of Precautions in the package insert on June 18, 2019. The details are introduced in this section.</td>
</tr>
<tr>
<td>2</td>
<td>Safety Measures for Febuxostat</td>
<td>( P )</td>
<td>Based on the outline of the CARES study, Japanese and overseas published literature, special drug use-results survey, and adverse reaction reports in Japan, safety measures for febuxostat were considered at the Subcommittee on Drug Safety, Committee on Drug Safety, Pharmaceutical Affairs and Food Sanitation Council. As a result, MHLW instructed MAHs to alert by revision of Precautions in the package insert on July 9, 2019. The details are introduced in this section.</td>
</tr>
<tr>
<td>3</td>
<td>Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)]</td>
<td></td>
<td>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, the Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)] has been compiled this year. The details are introduced in this section.</td>
</tr>
<tr>
<td>4</td>
<td>Proper Use of Over-the-Counter (OTC) Drugs that May Lead to Abuse</td>
<td></td>
<td>It was reported that there is a certain number of suspected cases of dependence 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 Institute of Mental Health, National Center of Neurology and Psychiatry) assigned research funded by FY2018 Health Labour Sciences Research Grant (Pharmaceuticals and Medical Devices Regulatory Science Policy Research Project).</td>
</tr>
</tbody>
</table>
In this article, Dr. Toshihiko Matsumoto who conducted the above research explains the actual status based on the research results.

<table>
<thead>
<tr>
<th></th>
<th>Important Safety Information</th>
<th>P</th>
<th>C</th>
<th>Nivolumab (genetical recombination) and palbociclib. Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated July 9, 2019, the contents of important revisions and case summaries that served as the basis for these revisions are presented in this section.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Revision of Precautions (No. 304)</th>
<th>P</th>
<th>Eletriptan hydrobromide and 10 others</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>List of Products Subject to Early Post-marketing Phase Vigilance</th>
<th>List of products subject to Early Post-marketing Phase Vigilance as of June 30, 2019.</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Hemoglobin A1c</td>
</tr>
<tr>
<td>HPB/MSPO</td>
<td>Office of Medical Safety Promotion, Health Policy Bureau</td>
</tr>
<tr>
<td>KL-6</td>
<td>Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing authorization holder</td>
</tr>
<tr>
<td>MHLW</td>
<td>Ministry of Health, Labour and Welfare</td>
</tr>
<tr>
<td>NIPPV</td>
<td>Nasal-intermittent Positive Pressure Ventilation</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>OTC</td>
<td>Over-the-counter</td>
</tr>
<tr>
<td>PMDA</td>
<td>Pharmaceuticals and Medical Devices Agency</td>
</tr>
<tr>
<td>PMDSI</td>
<td>Pharmaceuticals and Medical Devices Safety Information</td>
</tr>
<tr>
<td>PSEHB/PSD</td>
<td>Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau</td>
</tr>
<tr>
<td>SP-D</td>
<td>Surfactant protein D</td>
</tr>
<tr>
<td>SpO2</td>
<td>Oxygen saturation</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
</tr>
</tbody>
</table>
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/1.73m² 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/1.73m². 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

<table>
<thead>
<tr>
<th>eGFR (mL/min)</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>60≤eGFR&lt;90</td>
<td>3000 mg</td>
</tr>
<tr>
<td>45≤eGFR&lt;60</td>
<td>2000 mg</td>
</tr>
<tr>
<td>30≤eGFR&lt;45</td>
<td>1000 mg</td>
</tr>
<tr>
<td>eGFR&lt;30</td>
<td>Contraindication</td>
</tr>
</tbody>
</table>

- Package insert in Japan: Preparations with a maximum daily dose of 2250 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

<table>
<thead>
<tr>
<th>Major product names</th>
<th>Low-dose preparation</th>
<th>High-dose preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketing authorization</td>
<td>Glycoran Tablets 250 mg and the others</td>
<td>Metgluco Tablets 250 mg and the others</td>
</tr>
<tr>
<td>Approved in January 1961</td>
<td>Approved in January 2010</td>
<td></td>
</tr>
<tr>
<td>Maximum daily dose</td>
<td>750 mg</td>
<td>2250 mg</td>
</tr>
<tr>
<td>Use in patients with renal impairment</td>
<td>Contraindicated to patients with moderate or more severe renal impairment</td>
<td>Contraindicated to patients with mild to severe renal impairment</td>
</tr>
<tr>
<td>Use in patients with hepatic impairment</td>
<td>Contraindicated to patients with mild to severe hepatic impairment</td>
<td>Contraindicated to patients with mild to severe hepatic impairment</td>
</tr>
<tr>
<td>Use in geriatric patients</td>
<td>Contraindication</td>
<td>Careful administration</td>
</tr>
</tbody>
</table>

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/1.73m² and metformin should be carefully administered in patients with eGFR of 30-45 mL/min/1.73m².

- 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/1.73m²), 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>
<thead>
<tr>
<th>eGFR (mL/min/1.73m²)</th>
<th>Approximate dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>60≤eGFR&lt;90</td>
<td>2 250 mg</td>
</tr>
<tr>
<td>45≤eGFR&lt;60</td>
<td>1 500 mg</td>
</tr>
<tr>
<td>30≤eGFR&lt;45</td>
<td>750 mg</td>
</tr>
</tbody>
</table>

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)
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)

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

<sup>a)</sup> Number of patients who developed adverse events [incidence (%)]
<sup>b)</sup> 97%CI (Confidence Interval)
<sup>c)</sup> 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

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

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 pa-
     tients 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 ob-
     served 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 state-
     ment 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)
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 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

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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
[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

<table>
<thead>
<tr>
<th>Case 1: A case of adverse drug event associated with decreased activity level associated with cerebral hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recuperation environment</strong></td>
</tr>
<tr>
<td><strong>Issue</strong></td>
</tr>
<tr>
<td><strong>Patient background</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Prescription</strong></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>After intervention: A total of 5 drugs, once daily</strong></td>
</tr>
</tbody>
</table>
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
* Working Group for the Creation of Guidelines of Appropriate Medication for Elderly Patients
* 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)
* Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)] (Joint HPB/PMPSO 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

Toshihiko Matsumoto
National Center of Neurology and Psychiatry, National Institute of Mental Health
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%).
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. 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%).

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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.
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-

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

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

<table>
<thead>
<tr>
<th>Branded name (name of company)</th>
<th>Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic category</td>
<td>Antineoplastics-miscellaneous</td>
</tr>
</tbody>
</table>

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, 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

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.

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

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/Age</th>
<th>Patient Reason for use (complications)</th>
<th>Daily dose Treatment duration</th>
<th>Adverse reactions</th>
<th>Clinical course and Therapeutic measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male 60s</td>
<td>Recurrent Non-small cell lung cancer (NSCLC) (metastases to lymph nodes, metastases to lung, metastases to central nervous system, pulmonary artery thrombosis, deep vein thrombosis, diverticulum)</td>
<td>3 mg/kg 5 courses at 2-week intervals</td>
<td><strong>Intestinal obstruction, small intestinal perforation</strong>&lt;br&gt;The patient had a history of appendicitis.</td>
<td><strong>Day 1 of administration</strong>&lt;br&gt;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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>15 days after administration</strong>&lt;br&gt;Large bowel endoscopy revealed many diverticula in the ascending colon, but did not show any lung cancer metastasis foci.</td>
<td><strong>Date unknown</strong>&lt;br&gt;No abnormalities were found by imaging procedure (systematic CT, etc.) or blood test after the first dose of nivolumab.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Date unknown</strong>&lt;br&gt;Abdominal pain, vomiting, and black stools observed every time nivolumab was administered.</td>
<td><strong>57 days after administration (day of discontinuation)</strong>&lt;br&gt;The patient received the 5th dose of nivolumab. CRP results were negative with no abdominal pain, etc.</td>
</tr>
</tbody>
</table>

**[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.
<table>
<thead>
<tr>
<th>Days after discontinuation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 days after discontinuation</td>
<td>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.</td>
</tr>
<tr>
<td>11 days after discontinuation</td>
<td>Hydrocortisone sodium succinate (300 mg/day) was administered for 3 days. Abdominal pain and intestinal obstruction symptoms improved.</td>
</tr>
<tr>
<td>17 days after discontinuation</td>
<td>Liquid food was started.</td>
</tr>
<tr>
<td>24 days after discontinuation</td>
<td>Conservative treatment with corticosteroids was continued, and the patient was followed up with the ileus tube for drainage inserted. The medication was switched to prednisolone (20 mg/day). Lesions at the terminal ileum were suspected. Endoscopy (lower gastrointestinal endoscopy) was performed up to the terminal ileum, but no abnormalities were observed.</td>
</tr>
<tr>
<td>31 days after discontinuation</td>
<td>The diet was resumed, and the dose of prednisolone was titrated down to 5 mg/day. 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.</td>
</tr>
<tr>
<td>38 days after discontinuation</td>
<td>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.</td>
</tr>
<tr>
<td>41 days after discontinuation</td>
<td>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-intestinal regions were observed.</td>
</tr>
<tr>
<td>Date unknown</td>
<td>Concomitant medications: Edoxaban tosilate hydrate</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>52 days after discontinuation</td>
<td>[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. 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. Perforative peritonitis improved.</td>
</tr>
</tbody>
</table>
### Palbociclib

<table>
<thead>
<tr>
<th>Branded name (name of company)</th>
<th>Ibrance Capsules 25 mg, 125 mg (Pfizer Japan Inc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic category</td>
<td>Antineoplastics-miscellaneous</td>
</tr>
<tr>
<td>Indications</td>
<td>Inoperable or recurrent breast cancer</td>
</tr>
</tbody>
</table>

#### PRECAUTIONS (revised language is underlined)

**Warnings**

(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**

(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**

(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)
<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Daily dose</th>
<th>Adverse reactions</th>
<th>Clinical course and Therapeutic measures</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| 1   | Female 60s | Breast cancer | Interstitial lung disease | Bronchiectasis  
Breast cancer recurrent (metastasis to lungs, liver, bones, and lymph nodes)  
10 days before administration  
3 days before administration  | Improved |
|     |         | 125 mg for 21 days |  | Chest X ray did not show any significant findings.  
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  
Day 35 of administration  
Day 63 of administration  
Day 91 of administration  
Day 119 of administration  
Day 147 of administration  
Day 175 of administration  
Day 203 of administration  
Day 238 of administration  
Day 267 of administration  
Day 287 of administration  |  |
|     |         | 100 mg for 21 days | | Treatment with palbociclib 125 mg/day and fulvestrant 500 mg/month was started.  
The dose of palbociclib was reduced to 100 mg/day.  
Treatment with palbociclib was started at a dose of 100 mg/day.  
Treatment with palbociclib was started at a dose of 100 mg/day.  
Treatment with palbociclib was started at a dose of 100 mg/day.  
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Treatment with palbociclib was started at a dose of 100 mg/day.  
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. Chest X ray revealed ground-glass opacity in the left lower lung.

CT scan did not show improvement or aggravation in the pulmonary interstitial shadow. Treatment with prednisolone 20 mg was started. As a reduced KL-6 level was observed, prednisolone was reduced to 15 mg. Chest X ray did not show aggravation and prednisolone was reduced to 10 mg.

CT scan showed an improvement trend on pulmonary interstitial shadow. The dose of prednisolone was reduced to 7.5 mg. The dose of prednisolone was reduced to 5 mg. 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. Treatment with prednisolone at 2.5 mg was to be continued.

Laboratory Examination:

<table>
<thead>
<tr>
<th></th>
<th>176 days before administration</th>
<th>0 days before administration</th>
<th>Day of discontinuation</th>
<th>6 days after discontinuation</th>
<th>27 days after discontinuation</th>
<th>97 days after discontinuation</th>
<th>111 days after discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-D-glucan (pg/ml)</td>
<td>&lt;5.0</td>
<td>-</td>
<td>&lt;5.0</td>
<td>-</td>
<td>&lt;5.0</td>
<td>&lt;5.0</td>
<td>-</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>93</td>
<td>-</td>
<td>-</td>
<td>96</td>
<td>96</td>
<td>95</td>
<td>-</td>
</tr>
<tr>
<td>KL-6 (IU/mL)</td>
<td>272</td>
<td>1100</td>
<td>-</td>
<td>948</td>
<td>624</td>
<td>953</td>
<td>-</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>-</td>
<td>225</td>
<td>225</td>
<td>220</td>
<td>254</td>
<td>238</td>
<td>-</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>-</td>
<td>0.38</td>
<td>0.38</td>
<td>0.08</td>
<td>0.11</td>
<td>0.23</td>
<td>-</td>
</tr>
<tr>
<td>WBC (mm³)</td>
<td>8290</td>
<td>11400</td>
<td>11400</td>
<td>11400</td>
<td>11400</td>
<td>11400</td>
<td>11400</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>-</td>
<td>46.0</td>
<td>20.1</td>
<td>35.3</td>
<td>27.0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Concomitant medications: Fulvestrant
### Case summary 2

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Daily dose</th>
<th>Adverse reactions</th>
</tr>
</thead>
</table>
| 1   | Female 80s | Breast cancer metastatic | Lung disorder  
Breast cancer multiple bone metastasis, recurrence of advanced breast cancer  
84 days before administration  
Day 1 of administration  
Day 43 of administration (day of discontinuation)  
(Date unknown)  
25 days after discontinuation  
35 days after discontinuation  
36 days after discontinuation  
(Date unknown)  
41 days after discontinuation  
43 days after discontinuation |

#### Clinical course and Therapeutic measures

- **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. The dose of prednisolone was down-titrated. The patient experienced pyrexia (above 38°C) and then gradually had dyspnoea. 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.
- **Since her respiratory failure symptom further aggravated, non-invasive positive pressure ventilation (NIPPV) was introduced. Tests for several infections were negative.** The patient was diagnosed with drug-induced lung disorder.
- **The ground-glass opacity in the right upper lobe improved to some extent, but other parts slightly worsened and pleural effusion occurred.** 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.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Discontinued</th>
</tr>
</thead>
</table>
| 1 | Female 80s | Breast cancer metastatic | Lung disorder  
Breast cancer multiple bone metastasis, recurrence of advanced breast cancer  
84 days before administration  
Day 1 of administration  
Day 43 of administration (day of discontinuation)  
(Date unknown)  
25 days after discontinuation  
35 days after discontinuation  
36 days after discontinuation  
(Date unknown)  
41 days after discontinuation  
43 days after discontinuation |

#### Outcome

- **Fatal**
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. The dose of prednisolone was reduced to 30 mg/day.

56 days after discontinuation

70 days after discontinuation

84 days after discontinuation

87 days after discontinuation

88 days after discontinuation

107 days after discontinuation

Dyspnoea developed again.

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.

Laboratory Examination:

<table>
<thead>
<tr>
<th></th>
<th>25 days after discontinuation</th>
<th>35 days after discontinuation</th>
<th>37 days after discontinuation</th>
<th>44 days after discontinuation</th>
<th>55 days after discontinuation</th>
<th>90 days after discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-D-glucan (ng/ml)</td>
<td>-</td>
<td>7.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt;5.0</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>38</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>KL-6 (IU/mL)</td>
<td>-</td>
<td>9000&lt;</td>
<td>-</td>
<td>9000&lt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urinary Legionella antigen</td>
<td>-</td>
<td>(+)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mycoplasma antibody</td>
<td>-</td>
<td>(+)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carinii diagnosis</td>
<td>-</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SP-D (ng/mL)</td>
<td>-</td>
<td>-</td>
<td>895</td>
<td>-</td>
<td>154</td>
<td>340</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>1</th>
<th>Circulatory organ agents-miscellaneous</th>
<th>Epoprostenol sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branded name</td>
<td>Flolan for Injection 0.5 mg, 1.5 mg, (GlaxoSmithKline K.K.) and the others</td>
<td></td>
</tr>
<tr>
<td>[Under Old instructions] Adverse Reactions (Clinically Significant Adverse Reactions) (Newly added)</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>[Under New instructions] 8. IMPORTANT PRECAUTIONS (newly added) 11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)</td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>Antineoplastics-miscellaneous</th>
<th>Nivolumab (genetical recombination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branded name</td>
<td>Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceuticals Co., Ltd.)</td>
<td></td>
</tr>
<tr>
<td>[Under Old instructions] Adverse Reactions (Clinically Significant Adverse Reactions)</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>[Under New instructions] 11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3</th>
<th>Antineoplastics-miscellaneous</th>
<th>Palbociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branded name</td>
<td>Ibrance Capsules 25 mg, 125 mg (Pfizer Japan Inc.)</td>
<td></td>
</tr>
<tr>
<td>[Under Old instructions] Warnings</td>
<td>Cases of interstitial lung disease resulting in mortality have been reported. Patients should be carefully monitored for initial symptoms</td>
<td></td>
</tr>
</tbody>
</table>
Pharmaceuticals and Medical Devices
Safety Information No. 365 - 34 - August 2019

(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**

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**

**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.)

**Adverse Reactions**

**Colitis, enteritis, severe diarrhea:** Colitis, enteritis, and severe diarrhoea may occur, and cases of enterocolitis that resulted in perforation or ileus have been reported. Patients should be carefully monitored. If symptoms such as persistent 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 farinae 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.)
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

[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
Children younger than 12 years old

[Under New instructions]
Contraindications (newly added)
Use in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy

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.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.7 Pediatric use

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.
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
(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
[Under New instructions]
2. 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 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)

Branded name
[2] Lightgen Combination Syrup (Teijin Pharma Limited.) and the others
[3] Coughcode-N Combination Tablets (Pfizer Japan Inc.)

[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.
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)

<table>
<thead>
<tr>
<th>Nonproprietary name</th>
<th>Name of the MAH</th>
<th>Date of EPPV initiate</th>
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<tbody>
<tr>
<td>Ceftolozane sulfate/tazobactam sodium</td>
<td>MSD K.K.</td>
<td>June 25, 2019</td>
</tr>
<tr>
<td>Zerbaxa Combination for Intravenous Drip Infusion</td>
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<tr>
<td>Romiplostim (genetical recombination)</td>
<td>Kyowa Hakko Kirin Co., Inc</td>
<td>June 18, 2019</td>
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<tr>
<td>Romiplate for s.c. injection 250 μg</td>
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<td>Tocilizumab (genetical recombination)</td>
<td>Chugai Pharmaceutical Co., Ltd.</td>
<td>June 12, 2019</td>
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<td>Actemra Intravenous Infusion 80 mg, 200 mg, 400 mg</td>
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<tr>
<td>Sodium selenite</td>
<td>Fujimoto Pharmaceutical Corporation</td>
<td>June 6, 2019</td>
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<tr>
<td>Aselend Injection 100 μg</td>
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<tr>
<td>Apalutamide</td>
<td>Janssen Pharmaceutical K.K.</td>
<td>May 30, 2019</td>
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<tr>
<td>Erleada Tablets 60 mg</td>
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<td>Thiotepa</td>
<td>Sumitomo Dainippon Pharma Co., Ltd.</td>
<td>May 28, 2019</td>
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<td>Rethio Intravenous Infusion 100 mg</td>
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<td>Risankizumab (genetical recombination)</td>
<td>AbbVie GK</td>
<td>May 24, 2019</td>
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<td>Skyrizi Subcutaneous Injection 75 mg Syringe 0.83 mL</td>
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<tr>
<td>Fluticasone furoate/vilanterol trifenatate/umecclidinium bromide</td>
<td>Glaxo Smith Kline K.K.</td>
<td>May 22, 2019</td>
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<td>Trelegy 100 Ellipta 14 doses, 30 doses</td>
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<td>Esaxerenone</td>
<td>Daiichi Sankyo Co., Ltd.</td>
<td>May 13, 2019</td>
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<tr>
<td>Minnebro Tablets 1.25mg, 2.5mg, 5mg</td>
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<tr>
<td>Bicitgravir sodium/emuclidine/tenofovir alafenamide fumarate</td>
<td>Gilead Sciences Inc.</td>
<td>April 8, 2019</td>
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<tr>
<td>Biktarvy Combination Tablets</td>
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<tr>
<td>Tafamidis meglumine*3</td>
<td>Pfizer Japan Inc.</td>
<td>March 26, 2019</td>
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<tr>
<td>Vyndagel capsules 20 mg</td>
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<tr>
<td>Landiol hydrochloride*4</td>
<td>Ono Pharmaceutical Co., Ltd.</td>
<td>March 26, 2019</td>
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<tr>
<td>Onoact for Intravenous Infusion 50 mg, 150 mg</td>
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<tr>
<td>Dupilumab (genetical recombination)</td>
<td>Sanofi K.K.</td>
<td>March 26, 2019</td>
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<td>Branded name on</td>
<td>Name of the MAH</td>
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<td>Dupixent Subcutaneous Injection 300 mg Syringe</td>
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<tr>
<td>Dapagliflozin propylene glycolate hydrate*6</td>
<td>Forxiga Tablets 5 mg, 10 mg</td>
<td>AstraZeneca K.K.</td>
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<td>Nalmefene hydrochloride hydrate</td>
<td>Selincro tablets 10 mg</td>
<td>Otsuka Pharmaceutical Co., Ltd</td>
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<tr>
<td>Romosozumab (genetical recombination)</td>
<td>Evenity subcutaneous injection 105 mg syringe</td>
<td>Amgen Astellas Bi-Pharma K.K.</td>
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<td>Dacomitinib Hydrate</td>
<td>Vizipro Tablets 15 mg, 45 mg</td>
<td>Pfizer Japan Inc.</td>
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<td>Relugolix</td>
<td>Relumina Tablets 40 mg</td>
<td>Takeda Pharmaceutical Company Limited.</td>
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<td>Lora-pita Intravenous Injection 2mg</td>
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<tr>
<td>Binimetinib</td>
<td>Mektovi Tablets 15 mg</td>
<td>Ono Pharmaceutical Co., Ltd</td>
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<td>Encorafenib</td>
<td>Braftovi Capsules 50 mg</td>
<td>Ono Pharmaceutical Co., Ltd</td>
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<td>Epclusa Combination Tablets</td>
<td>Gilead Sciences Inc.</td>
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<td>Metirosine</td>
<td>Demser Capsules 250 mg</td>
<td>Ono Pharmaceutical Co., Ltd</td>
</tr>
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<td>Damoctocog alfa pegol (genetical recombination)</td>
<td>Jivi for i.v. injection 250, 500, 1000, 2000, 3000</td>
<td>Bayer Yakuhin Ltd</td>
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<tr>
<td>Refixia I.V. Injection 500, 1000, 2000</td>
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</tbody>
</table>

*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