Pharmaceuticals and Medical Devices Safety Information

No. 416 January 2025

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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) web page (https://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0002.html) and on the MHLW website (https://www.mhlw.go.jp/, only in Japanese).

Available information is listed here

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

The PMDA Medi-navi is an e-mail mailing list service that serves to provide essential safety information released by the MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.
This service is available only in Japanese.

Register here

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1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Pharmaceuticals and Medical Devices Safety Information

No. 416 January 2025

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

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communications, *R:* Distribution of Dear Healthcare Professional Letters of Rapid Communications, *P*: Revision of PRECAUTIONS, *C*: Case Reports

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

If healthcare professionals such as physicians, dentists, and pharmacists detect adverse reactions, infections, or malfunctions associated with drugs, medical devices, or regenerative medical products, please report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As healthcare professionals, drugstore and pharmacy personnel are also required to report adverse reactions, etc.

Please utilize the Report Reception Site for reporting.
(This service is available only in Japanese.)

https://www.pmda.go.jp/safety/reports/hcp/0002.html

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

Abbreviations

ADR	Adverse Drug Reaction
CSII	Continuous Subcutaneous Insulin Infusion
DIC	Disseminated Intravascular Coagulation
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
POCT	Point-of-Care Testing
PS	Performance Status
PSL	Prednisolone
RMP	Risk Management Plan
SMQ	Standardised MedDRA Queries
SGLT2	Sodium Glucose Linked Transporter 2
TEN	Toxic Epidermal Necrolysis

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Revision of PRECAUTIONS for Oral Antivirals Against COVID-19 (Xocova Tablets 125 mg and Lagevrio Capsules 200 mg)

1. Introduction

On December 17, 2024, the MHLW issued a notification instructing the marketing authorization holders (MAHs) of ensitrelvir fumaric acid (Xocova Tablets 125 mg, hereinafter referred to as “Xocova”) and molnupiravir (Lagevrio Capsules 200 mg, hereinafter referred to as “Lagevrio”) to add cautionary statements including the following: The necessity of administering the drug to women of childbearing potential should be carefully considered; the absence of pregnancy and the absence of the possibility of pregnancy should be confirmed through sufficient patient interviews prior to administering the drug, even when administration is deemed necessary. This section will introduce the details of the revision and other relevant information.

2. Background

The administration of Xocova and Lagevrio, which are antivirals for patients with COVID-19, to pregnant women or women who may be pregnant is contraindicated since the drugs have a risk of teratogenicity.

A risk of teratogenicity for Xocova and Lagevrio is listed as an important potential risk in the risk management plan (RMP). In addition to the cautionary statements in the 2. CONTRAINDICATIONS section and 9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section, materials for healthcare professionals/materials for patients have been prepared and they are provided as additional risk minimization activities.

On the basis of the fact that multiple cases have been reported by the MAHs in which pregnancy was detected after administering Xocova or Lagevrio, requests for utilization of materials for healthcare professionals/materials for patients prepared based on RMP have been disseminated repeatedly. However, cases have been intermittently reported until now in which pregnancy was detected after administration of each drug (the table below).

Table. Number of cases reported by the MAH in which pregnancy was detected after administering these drugs (by fiscal year and cumulative data)

(Xocova)
Cumulative number of the cases: 54
(receipt of information: From November 22, 2022 to October 31, 2024)

Fiscal Year (receipt of information)	FY 2021	FY 2022	FY 2023	FY 2024
Number of cases		3	34	17

(Lagevrio)
Cumulative number of the cases: 19
(receipt of information: From December 24, 2021 to October 31, 2024)

Fiscal Year (receipt of information)	FY 2021	FY 2022	FY 2023	FY 2024
Number of cases	1	2	14	2

Taking these situations into account, the MHLW considered it necessary to add cautionary statements in the 8. IMPORTANT PRECAUTIONS section in the package inserts of Xocova and Lagevrio including the following: “The necessity of administering this drug to women of childbearing potential should be carefully considered,” “the absence of pregnancy and the absence of the possibility of pregnancy should be confirmed through sufficient patient interviews prior to administering this drug even when administration is deemed necessary,” and the MHLW instructed the MAHs to revise PRECAUTIONS on December 17, 2024.

3. Precautions for administration to women of childbearing potential

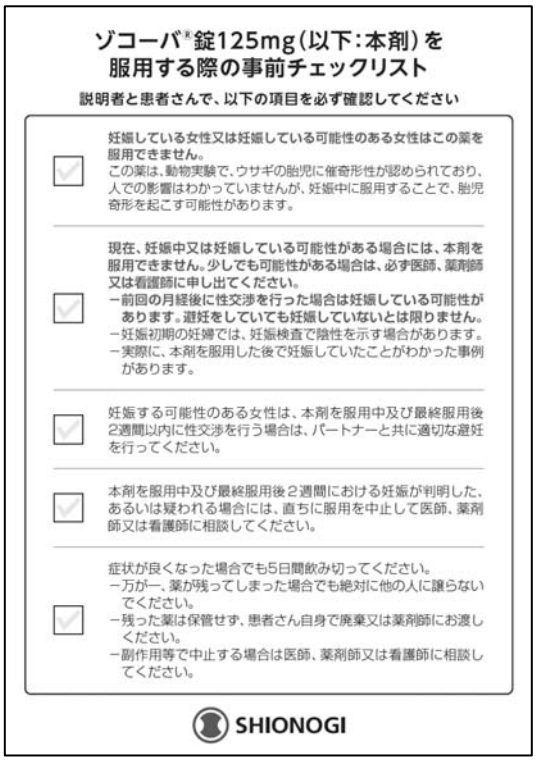
For this revision of PRECAUTIONS, the following statement was added as precautions prior to administering Xocova or Lagevrio to women of childbearing potential. (Please refer also to “Revision of PRECAUTIONS (No.356)” on pages 25 to 33 of this issue of PMDSI.)

The necessity of administering this drug to women of childbearing potential should be carefully considered. If administration is deemed necessary, attention should be paid to the following points.

- Prior to administering this drug, the absence of pregnancy and the absence of the possibility of pregnancy should be confirmed through sufficient patient interviews.
- The following should be explained to patients before starting administration of this drug:
  - This drug can cause foetal harm when administered to a pregnant woman.
  - If pregnancy is detected or suspected during administration of this drug, this drug should be discontinued immediately.
  - If pregnancy is detected or suspected during administration of this drug or within 2 weeks for Xocova or within 4 days for Lagevrio after the last administration of this drug, a physician, pharmacist, etc. should be consulted promptly.

4. Utilization of materials prepared based on RMP

If administration of Xocova or Lagevrio to women of childbearing potential is considered necessary, healthcare professionals are requested to utilize RMP materials such as “Preliminary Checklist for Administering the Drug” and to ensure that an explanation is provided to the patients before the start of administration and that the absence of pregnancy and the absence of the possibility of pregnancy are confirmed. In association with the revision of PRECAUTIONS this time, the RMP materials were revised. Healthcare professionals are encouraged to utilize the latest version of the materials.

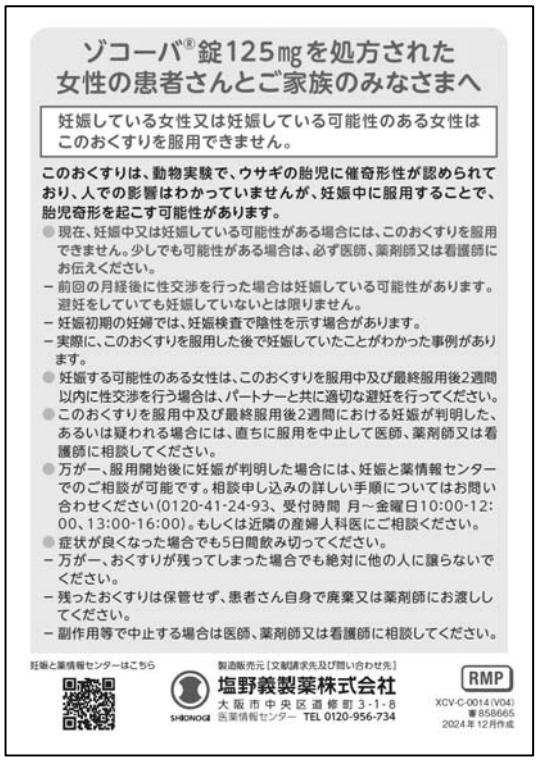


ゾコーバ®錠125mg(以下:本剤)を
服用する際の事前チェックリスト

説明者と患者さんで、以下の項目を必ず確認してください

- 妊娠している女性又は妊娠している可能性のある女性はこの薬を服用できません。
  この薬は、動物実験で、ウサギの胎児に催奇形性が認められており、人での影響はわかっていませんが、妊娠中に服用することで、胎児奇形を起こす可能性があります。
- 現在、妊娠中又は妊娠している可能性がある場合には、本剤を服用できません。少しでも可能性がある場合は、必ず医師、薬剤師又は看護師に申し出てください。
  −前回の月経後に性交渉を行った場合は妊娠している可能性があります。避妊をしていても妊娠していないとは限りません。
  −妊娠初期の妊婦では、妊娠検査で陰性を示す場合があります。
  −実際に、本剤を服用した後で妊娠していたことがわかった事例があります。
- 妊娠する可能性のある女性は、本剤を服用中及び最終服用後2週間以内に性交渉を行う場合は、パートナーと共に適切な避妊を行ってください。
- 本剤を服用中及び最終服用後2週間における妊娠が判明した、あるいは疑われる場合には、直ちに服用を中止して医師、薬剤師又は看護師に相談してください。
- 症状が良くなった場合でも5日間飲み切ってください。
  −万が一、薬が残ってしまった場合でも絶対に他の人に譲らないでください。
  −残った薬は保管せず、患者さん自身で廃棄又は薬剤師にお渡しください。
  −副作用等で中止する場合は医師、薬剤師又は看護師に相談してください。

SHIONOGI



ゾコーバ®錠125mgを処方された
女性の患者さんとご家族のみなさまへ

妊娠している女性又は妊娠している可能性のある女性はこのおくすりを服用できません。

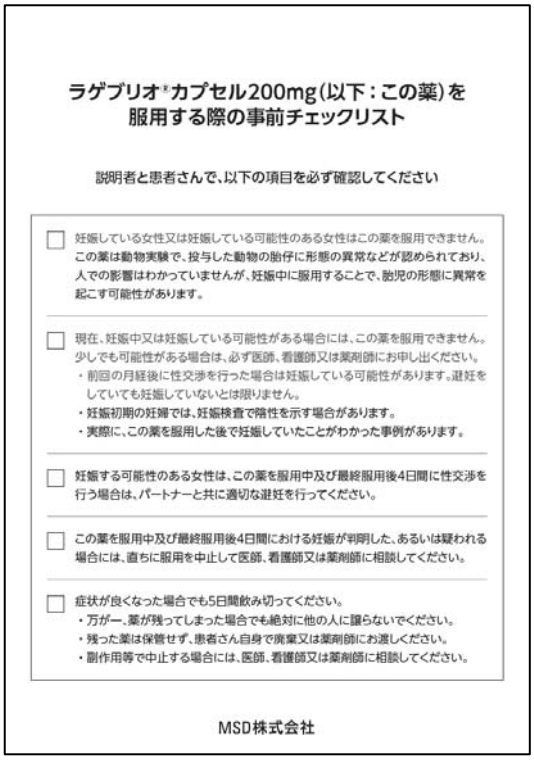
このおくすりは、動物実験で、ウサギの胎児に催奇形性が認められており、人での影響はわかっていませんが、妊娠中に服用することで、胎児奇形を起こす可能性があります。

- 現在、妊娠中又は妊娠している可能性がある場合には、このおくすりを服用できません。少しでも可能性がある場合は、必ず医師、薬剤師又は看護師にお伝えください。
- 前回の月経後に性交渉を行った場合は妊娠している可能性があります。避妊をしていても妊娠していないとは限りません。
- 妊娠初期の妊婦では、妊娠検査で陰性を示す場合があります。
- 実際に、このおくすりを服用した後で妊娠していたことがわかった事例があります。
- 妊娠する可能性のある女性は、このおくすりを服用中及び最終服用後2週間以内に性交渉を行う場合は、パートナーと共に適切な避妊を行ってください。
- このおくすりを服用中及び最終服用後2週間における妊娠が判明した、あるいは疑われる場合には、直ちに服用を中止して医師、薬剤師又は看護師に相談してください。
- 万が一、服用開始後に妊娠が判明した場合には、妊娠と薬情報センターでのご相談が可能です。相談申し込みの詳しい手順についてはお問い合わせください(0120-41-24-93、受付時間 月～金曜日10:00-12:00、13:00-16:00)。もしくは近隣の産婦人科医にご相談ください。
- 症状が良くなった場合でも5日間飲み切ってください。
- 万が一、おくすりが残ってしまった場合でも絶対に他の人に譲らないでください。
- 残ったおくすりは保管せず、患者さん自身で廃棄又は薬剤師にお渡ししてください。
- 副作用等で中止する場合は医師、薬剤師又は看護師に相談してください。

妊娠と薬情報センターはこちら

製造販売元[文献請求先及び問い合わせ先]
塩野義製薬株式会社
大阪市中央区道修町3-1-8
医薬情報センター TEL 0120-956-734

RMP
XCV-C-0014(V04)
審858665
2024年12月作成



ラゲブリオ®カプセル200mg(以下:この薬)を
服用する際の事前チェックリスト

説明者と患者さんで、以下の項目を必ず確認してください

- 妊娠している女性又は妊娠している可能性のある女性はこの薬を服用できません。
  この薬は動物実験で、投与した動物の胎仔に形態の異常などが認められており、人での影響はわかっていませんが、妊娠中に服用することで、胎児の形態に異常を起こす可能性があります。
- 現在、妊娠中又は妊娠している可能性がある場合には、この薬を服用できません。少しでも可能性がある場合は、必ず医師、看護師又は薬剤師にお申し出ください。
  ・前回の月経後に性交渉を行った場合は妊娠している可能性があります。避妊をしていても妊娠していないとは限りません。
  ・妊娠初期の妊婦では、妊娠検査で陰性を示す場合があります。
  ・実際に、この薬を服用した後で妊娠していたことがわかった事例があります。
- 妊娠する可能性のある女性は、この薬を服用中及び最終服用後4日間に性交渉を行う場合は、パートナーと共に適切な避妊を行ってください。
- この薬を服用中及び最終服用後4日間における妊娠が判明した、あるいは疑われる場合には、直ちに服用を中止して医師、看護師又は薬剤師に相談してください。
- 症状が良くなった場合でも5日間飲み切ってください。
  ・万が一、薬が残ってしまった場合でも絶対に他の人に譲らないでください。
  ・残った薬は保管せず、患者さん自身で廃棄又は薬剤師にお渡しください。
  ・副作用等で中止する場合には、医師、看護師又は薬剤師に相談してください。

MSD株式会社

ラゲブリオ®カプセル200mgを処方された
妊娠する可能性のある女性と
ご家族のみなさまへ

妊娠している女性又は妊娠している可能性のある女性はこの薬を服用できません。

この薬は動物実験で、投与した動物の胎仔に形態の異常などが認められており、人での影響はわかっていませんが、妊娠中に服用することで、胎児の形態に異常を起こす可能性があります。

- 現在、妊娠中又は妊娠している可能性がある場合には、この薬を服用できません。少しでも可能性がある場合は、必ず担当の医師、看護師又は薬剤師にお伝えください。
- 前回の月経後に性交渉を行った場合は妊娠している可能性があります。避妊をしていても妊娠していないとは限りません。
- 妊娠初期の妊婦では、妊娠検査で陰性を示す場合があります。
- 実際に、この薬を服用した後で妊娠していたことがわかった事例があります。
- 妊娠する可能性のある女性は、この薬を服用中及び服用終了後4日間に性交渉を行う場合は、パートナーと共に適切な避妊を行ってください。
- この薬を服用中及び最終服用後4日間における妊娠が判明した、あるいは疑われる場合には、直ちに服用を中止して担当の医師、看護師又は薬剤師に相談してください。
- 万が一、服用開始後に妊娠が判明した場合には、妊娠と薬情報センターでのご相談が可能です。相談申し込みの詳しい手順についてはお問い合わせください(0120-41-24-93、受付時間 月～金曜日10:00-12:00、13:00-16:00)。もしくは近隣の産婦人科医にご相談ください。
- 症状が良くなった場合でも5日間飲み切ってください。
- 万が一、薬が残ってしまった場合でも絶対に他の人に譲らないでください。
- 残った薬は保管せず、患者さん自身で廃棄又は薬剤師にお渡ししてください。
- 副作用等で中止する場合には、担当の医師、看護師又は薬剤師に相談してください。

妊娠と薬情報センター
HPはこちら

MSD株式会社

RMP
2024年12月作成

Contact information when requesting materials as of January 22, 2025

- Xocova (MAH: Shionogi & Co., Ltd.)

Mail: opt_otoiawase@shionogi.co.jp
Telephone number: Pharmaceutical Information Center in Shionogi & Co., Ltd.
0120-956-734
Office hours: 9:00-17:00 (excluding Saturdays, Sundays and national holidays)

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

● Lagevrio (MAH: MSD K.K.)
Telephone number: MSD Customer Support Center
0120-024-961
Office hours: 9:00-17:30 (excluding Saturdays, Sundays and national holidays)
In addition, requests via the following Lagevrio Tool Order System will be available from January 27, 2025. Please contact MSD K.K. for the details including the date from when the system can be used to request the materials.
Lagevrio Tool Order System:
https://www.msdconnect.jp/products/lagevrio/materials/toolorder/ (only in Japanese)
Telephone number: Dedicated phone number for the Tool Order System (0120-024-262)
Office hours: 9:00-17:30 (excluding Saturdays, Sundays and national holidays)

5. Closing remarks

In line with the issuance of the notification instructing revision of PRECAUTIONS this time, the PMDA published "PMDA Alert for Proper Use of Drugs" on its website.
https://www.pmda.go.jp/files/000272643.pdf (in Japanese)
https://www.pmda.go.jp/files/000272692.pdf (in English)
Healthcare professionals are encouraged to refer to "PMDA Alert for Proper Use of Drugs" and to pay attention to the above points so that administering Xocova or Lagevrio to pregnant women or women who may be pregnant is avoided in cases of considering administration of Xocova or Lagevrio to women of childbearing potential. Cooperation by healthcare professionals for proper use of drugs would be appreciated.

[Reference information]
•Revisions of PRECAUTIONS (PSB/PSD Notification No.1217-1 dated December 17, 2024)
https://www.mhlw.go.jp/content/11125000/001355867.pdf (in Japanese)
English translation by the PMDA (December 17, 2024)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0012.html

•Provision of Information Regarding Administration of Oral Antivirals Against COVID-19 (Xocova Tablets 125 mg and Lagevrio Capsules 200 mg) to Women of Childbearing Potentials (Revision of Electronic Package Inserts, Ensuring Utilization of Materials, etc.) (Administrative Notice dated December 17, 2024)
https://www.mhlw.go.jp/content/11120000/001357762.pdf (only in Japanese)

•2024 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Council (9th meeting)
Material 2-1 Revision of PRECAUTIONS for Oral Antivirals Against COVID-19 (Xocova Tablets 125 mg and Lagevrio Capsules 200 mg)
https://www.mhlw.go.jp/stf/newpage_45738.html (only in Japanese)

•A Cautionary Statement Regarding the Use of Antivirals for COVID-19 (Xocova Tablets 125 mg) (Administrative Notice dated January 20, 2023)
https://www.mhlw.go.jp/content/001041553.pdf (only in Japanese)

•Additional Provision of Information Regarding a Precaution for the Use of Oral Antivirals for COVID-19 (Xocova Tablets 125 mg) (Administrative Notice dated February 24, 2023)
https://www.mhlw.go.jp/content/001063224.pdf (only in Japanese)

•Additional Provision of Information Regarding a Precaution for the Use of Oral Antivirals for COVID-19 (Xocova Tablets 125 mg) (Request for Utilization of New Materials, etc.) (Administrative Notice dated March 17, 2023)
https://www.mhlw.go.jp/content/001074688.pdf (only in Japanese)

•Additional Provision of Information Regarding a Precaution for the Use of Oral Antivirals for COVID-19 (Xocova Tablets 125 mg) (Ensuring Utilization of Materials) (Administrative Notice dated June 29, 2023)

https://www.mhlw.go.jp/content/001115615.pdf (only in Japanese)

- Additional Provision of Information Regarding a Precaution for the Use of Oral Antivirals for COVID-19 (Xocova Tablets 125 mg) (Ensuring Utilization of Materials and Consultation Service) (Administrative Notice dated August 30, 2023)
  https://www.mhlw.go.jp/content/001140571.pdf (only in Japanese)
- Publication of a Joint Statement, etc. Regarding Prescription and Dispensing of Treatment Drugs for COVID-19 That Are Contraindicated in Pregnant Women (Request for Information Dissemination) (Administrative Notice dated November 14, 2023)
  https://www.mhlw.go.jp/content/001166958.pdf (only in Japanese)

PMDA Alert for Proper Use of Drugs
Pharmaceuticals and Medical Devices Agency
No.16 December 2024

Administration of Treatment Drugs for COVID-19 (Xocova Tablets and Lagevrio Capsules) to Women of Childbearing Potential

- The administration of treatment drugs for COVID-19, "ensitrelvir fumaric acid" (Xocova Tablets) and "molnupiravir" (Lagevrio Capsules) to pregnant women or women who may be pregnant is contraindicated since the drugs have a risk of teratogenicity.
- However, cases have been intermittently reported in which pregnancy was detected after administration of each drug.
- When administering Xocova Tablets or Lagevrio Capsules, the following precautions should be checked. In addition, healthcare professionals are encouraged to use the "Preliminary Checklist for Administering the Drug" (Risk Management Plan (RMP) materials for healthcare professionals) and "Materials for Female Patients Prescribed the Drug and Their Family Members" (RMP materials for patients), which are disseminated by the marketing authorization holders (MAHs).

Precautions prior to administering the drugs to women of childbearing potential

The necessity of administering the drugs to women of childbearing potential should be carefully considered. If administration is deemed necessary, attention should be paid to the following points:

- Prior to administering these drugs, the absence of pregnancy and the absence of the possibility of pregnancy should be confirmed through sufficient patient interviews.
- The following should be explained to patients before starting administration of these drugs:
  - These drugs can cause foetal harm when administered to a pregnant woman.
  - If pregnancy is detected or suspected during administration of these drugs, these drugs should be discontinued immediately.
  - If pregnancy is detected or suspected during administration of these drugs or within 2 weeks for Xocova Tablets or within 4 days for Lagevrio Capsules after the last administration of these drugs, a physician, pharmacist, etc. should be consulted promptly.

● Reports of cases

The MAHs have reported the following number of cases in which pregnancy was detected after administering these drugs (by fiscal year and cumulative data).

<Xocova Tablets>

Cumulative number of the cases: 54 (receipt of information: From November 22, 2022 to October 31, 2024)

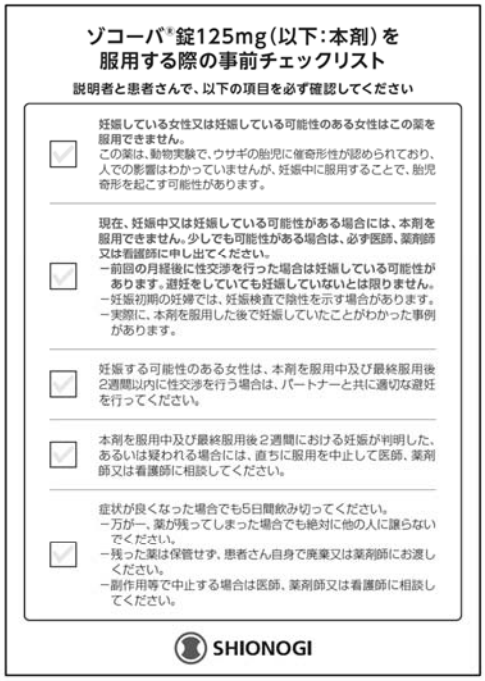
Fiscal Year (receipt of information)	FY 2021	FY 2022	FY 2023	FY 2024
Number of cases		3	34	17

<Lagevrio Capsules>

Cumulative number of the cases: 19 (receipt of information: From December 24, 2021 to October 31, 2024)

Fiscal Year (receipt of information)	FY 2021	FY 2022	FY 2023	FY 2024
Number of cases	1	2	14	2

Please refer to the information search page of prescription drugs in the PMDA website (https://www.pmda.go.jp/PmdaSearch/iyakuSearch/ (only in Japanese)) for the "Preliminary Checklist for Administering the Drug" and "Materials for Female Patients Prescribed the Drug and Their Family Members."



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  この薬は、動物実験で、ウサギの胎児に催奇形性が認められており、人での影響はわかっていませんが、妊娠中に服用することで、胎児奇形を起こす可能性があります。
- 現在、妊娠中又は妊娠している可能性がある場合には、本剤を服用できません。少しでも可能性がある場合は、必ず医師、薬剤師又は看護師に申し出てください。
  −前回の月経後に性交渉を行った場合は妊娠している可能性があります。避妊をしていても妊娠していないとは限りません。
  −妊娠初期の妊婦では、妊娠検査で陰性を示す場合があります。
  −実際に、本剤を服用した後で妊娠していたことがわかった事例があります。
- 妊娠する可能性のある女性は、本剤を服用中及び最終服用後2週間以内に性交渉を行う場合は、パートナーと共に適切な避妊を行ってください。
- 本剤を服用中及び最終服用後2週間における妊娠が判明した、あるいは疑われる場合には、直ちに服用を中止して医師、薬剤師又は看護師に相談してください。
- 症状が良くなった場合でも5日間飲み切ってください。
  −万が一、薬が残ってしまった場合でも絶対に他の人に譲らないでください。
  −残った薬は保管せず、患者さん自身で廃棄又は薬剤師にお渡しください。
  −副作用等で中止する場合は医師、薬剤師又は看護師に相談してください。

SHIONOGI

ラゲブリオ®カプセル200mgを処方された
妊娠する可能性のある女性と
ご家族のみなさまへ

妊娠している女性又は妊娠している可能性のある女性はこの薬を服用できません。

この薬は動物実験で、投与した動物の胎仔に形態の異常などが認められており、人での影響はわかっていませんが、妊娠中に服用することで、胎児の形態に異常を起こす可能性があります。

- 現在、妊娠中又は妊娠している可能性がある場合には、この薬を服用できません。少しでも可能性がある場合は、必ず担当の医師、看護師又は薬剤師にお伝えください。
- −前回の月経後に性交渉を行った場合は妊娠している可能性があります。避妊をしていても妊娠していないとは限りません。
- −妊娠初期の妊婦では、妊娠検査で陰性を示す場合があります。
- −実際に、この薬を服用した後で妊娠していたことがわかった事例があります。
- 妊娠する可能性のある女性は、この薬を服用中及び服用終了後4日間に性交渉を行う場合は、パートナーと共に適切な避妊を行ってください。
- この薬を服用中及び最終服用後4日間における妊娠が判明した、あるいは疑われる場合には、直ちに服用を中止して担当の医師、看護師又は薬剤師に相談してください。
- 万が一、服用開始後に妊娠が判明した場合には、妊娠と薬情報センターでのご相談が可能です。相談申し込みの詳しい手順についてはお問い合わせください(0120-41-24-93、受付時間 月～金曜日10:00-12:00、13:00-16:00)。もしくは近隣の産婦人科医にご相談ください。
- 症状が良くなった場合でも5日間飲み切ってください。
- −万が一、薬が残ってしまった場合でも絶対に他の人に譲らないでください。
- −残った薬は保管せず、患者さん自身で廃棄又は薬剤師にお渡ししてください。
- −副作用等で中止する場合には、担当の医師、看護師又は薬剤師に相談してください。

妊娠と薬情報センター HPはこちら

MSD株式会社

RMP

2024年12月作成

About this information

*PMDA Alert for Proper Use of Drugs communicates to healthcare professionals with clear information from the perspective of promoting the proper use of drugs. The information presented here includes such cases where the reporting frequencies of similar reports have not decreased despite relevant alerts provided in package inserts, among adverse drug reaction/infection cases reported in accordance with the PMD Act.

*We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future

*This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibility on them, but is provided to promote the proper use of the drugs.

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

Access to the most up-to-date safety information is available via the PMDA medi-navi. (only in Japanese)

Published and translated by the Pharmaceuticals and Medical Devices Agency

Contact: Office of Pharmacovigilance II

E-mail: safety.info@pmda.go.jp

2

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated December 17, 2024, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 [1] Ipragliflozin L-proline
[2] Sitagliptin phosphate hydrate/ipragliflozin L-proline
[3] Empagliflozin
[4] Empagliflozin/linagliptin
[5] Canagliflozin hydrate
[6] Teneligliptin hydrobromide hydrate/canagliflozin hydrate
[7] Dapagliflozin propylene glycolate hydrate
[8] Tofogliflozin hydrate
[9] Luseogliflozin hydrate

Brand name (name of company)	[1] Suglat Tablets 25 mg, 50 mg (Astellas Pharma Inc.) [2] Sujanu Combination Tablets (MSD K.K.) [3] Jardiance Tablets 10 mg, 25 mg (Boehringer Ingelheim Japan, Inc.) [4] Tradiance Combination Tablets AP, BP (Boehringer Ingelheim Japan, Inc.) [5] Canaglu Tablets 100 mg, Canaglu OD Tablets 100 mg (Mitsubishi Tanabe Pharma Corporation) [6] Canalia Combination Tablets (Mitsubishi Tanabe Pharma Corporation) [7] Forxiga tablets 5 mg, 10 mg (AstraZeneca K.K.) [8] Deberza Tablets 20 mg (Kowa Company, Ltd.) [9] Lusefi tablets 2.5 mg, 5 mg, Lusefi OD film 2.5 mg (Taisho Pharmaceutical Co., Ltd.)
Therapeutic category	Other cardiovascular agents, antidiabetic agents, agents affecting metabolism, n.e.c. (not elsewhere classified)
Indications	[1] •Type 2 diabetes mellitus •Type 1 diabetes mellitus [2] Type 2 diabetes mellitus (only when a concomitant use of sitagliptin phosphate hydrate with ipragliflozin L-proline is deemed appropriate) [3] <Jardiance Tablets 10 mg, 25 mg> •Type 2 diabetes mellitus <Jardiance Tablets 10 mg> •Chronic cardiac failure (for use only in patients receiving standard treatment of chronic heart failure) •Chronic kidney disease (excluding patients who have end-stage renal failure or are undergoing dialysis) [4] Type 2 diabetes mellitus (only when a concomitant treatment with empagliflozin and

	linagliptin is deemed appropriate) [5] •Type 2 diabetes mellitus •Chronic kidney disease associated with type 2 diabetes mellitus (excluding patients who have end-stage renal failure or are undergoing dialysis) [6] Type 2 diabetes mellitus (only when a concomitant treatment with teneligliptin hydrobromide hydrate and canagliflozin hydrate is deemed appropriate) [7] •Type 2 diabetes mellitus •Type 1 diabetes mellitus •Chronic cardiac failure (for use only in patients receiving standard treatment of chronic heart failure) •Chronic kidney disease (excluding patients who have end-stage renal failure or are undergoing dialysis) [8] Type 2 diabetes mellitus [9] Type 2 diabetes mellitus

PRECAUTIONS (Revised language is underlined.)

•Ipragliflozin L-proline
•Empagliflozin
•Canagliflozin hydrate
•Dapagliflozin propylene glycolate hydrate
•Tofogliflozin hydrate
•Luseogliflozin hydrate

8. IMPORTANT PRECAUTIONS	Fatty acid metabolism may be elevated and ketosis may occur leading to ketoacidosis, even in cases with well-controlled blood glucose levels. This is due to the urinary glucose excretion-enhancing activity, which is the mechanism of action of this drug. <u>Cases have been reported in which urinary glucose excretion and ketoacidosis persisted longer than expected from plasma half-lives of the drugs, after discontinuing administration of SGLT2 inhibitors including this drug. Patients should be carefully monitored, with as-needed urinary glucose measurements, etc.</u>

•Empagliflozin/linagliptin

8. IMPORTANT PRECAUTIONS	Fatty acid metabolism may be elevated and ketosis may occur leading to ketoacidosis, even in cases with well-controlled blood glucose levels. This is due to the urinary glucose excretion-enhancing activity, which is the mechanism of action of empagliflozin. <u>Cases have been reported in which urinary glucose excretion and ketoacidosis persisted longer than expected from the plasma half-lives of the drugs, after discontinuing administration of SGLT2 inhibitors including empagliflozin. Patients should be carefully monitored, with as-needed urinary glucose measurements, etc.</u>

•Sitagliptin phosphate hydrate/ipragliflozin L-proline

8. IMPORTANT PRECAUTIONS	Fatty acid metabolism may be elevated and ketosis may occur leading to ketoacidosis, even in cases with well-controlled blood glucose levels. This is due to the urinary glucose excretion-enhancing activity, which is the mechanism of action of ipragliflozin. <u>Cases have been reported in which urinary glucose excretion and ketoacidosis persisted longer than expected from the plasma half-</u>

lives of the drugs, after discontinuing administration of SGLT2 inhibitors including ipragliflozin. Patients should be carefully monitored, with as-needed urinary glucose measurements, etc.

•Teneligliptin hydrobromide hydrate/canagliflozin hydrate

8. IMPORTANT PRECAUTIONS

Fatty acid metabolism may be elevated and ketosis may occur leading to ketoacidosis, even in cases with well-controlled blood glucose levels. This is due to the urinary glucose excretion-enhancing activity, which is the mechanism of action of canagliflozin, the active ingredient of this drug.

Cases have been reported in which urinary glucose excretion and ketoacidosis persisted longer than expected from the plasma half-life of the drug, after discontinuing administration of SGLT2 inhibitors including canagliflozin. Patients should be carefully monitored, with as-needed urinary glucose measurements, etc.

Reference information

Number of cases† (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports

[1] 30 cases (No patient mortalities)
[2] No cases
[3] 44 cases (1 patient mortality)
[4] 3 cases (No patient mortalities)
[5] 21cases (No patient mortalities)
[6] 5 cases (No patient mortalities)
[7] 64 cases (No patient mortalities)
[8] 7 cases (No patient mortalities)
[9] 21 cases (No patient mortalities)

† Cases retrieved by the MAHs based on the criteria of each MAH as those involving ketoacidosis persisting for 3 days or more after discontinuing administration. Of note, the possibility of a causal relationship between the drugs and the events was not evaluated.

Number of patients using the drug as estimated by the MAH during the previous 1-year period:

[1] Approximately 425,502
[2] Approximately 254,200
[3] Approximately 1,130,000
[4] Approximately 380,000
[5] Approximately 288,000
[6] Approximately 228,000
[7] Approximately 1,377,000
[8] Approximately 240,000
[9] Approximately 248,900

Japanese market launch:

[1] April 2014
[2] May 2018
[3] February 2015
[4] November 2018
[5] Tablets 100 mg: September 2014, OD Tablets 100 mg: May 2024
[6] September 2017
[7] May 2014
[8] May 2014
[9] tablets 2.5 mg, 5 mg: May 2014, OD film 2.5 mg: June 2022

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female 40s	Type 2 diabetes mellitus (hyperlipidaemia, depression, gastroenteritis)	100 mg for 262 days	**Euglycaemic diabetic ketoacidosis**	
				Day 1 of administration	Administration of canagliflozin hydrate was initiated to treat type 2 diabetes mellitus.
				Day 261 of administration:	The patient had gastrointestinal symptoms with nausea and vomiting as primary complaints, resulting in difficulty eating.
				Day 262 of administration (day of discontinuation)	The patient presented to a hospital, where goreisan extract and a sanactase combination drug were prescribed. Hyperpnoea developed at night, and she visited another hospital. Administration of canagliflozin hydrate was discontinued. Lactic acidosis was suspected and she was hospitalized.
				1 day after discontinuation	The lactic acid level was within the normal range. The patient was diagnosed with euglycaemic diabetic ketoacidosis due to the continued administration of an SGLT2 inhibitor while experiencing difficulty eating. Treatment of dehydration and carbohydrate supplementation by fluid infusion as well as administration of insulin were initiated.
				2 days after discontinuation	Dehydration findings and prolonged acidosis were noted. Physiological saline solution was added.
				3 days after discontinuation	Dehydration and acidosis were resolving. The patient resumed eating.
				5 days after discontinuation	Acidosis improved.
				15 days after discontinuation	Well-controlled blood glucose levels were achieved by adjusting medication, and the patient was discharged.

Laboratory test value

Test item (Unit)	Day 217 of administration	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	5 days after discontinuation	8 days after discontinuation	15 days after discontinuation
Blood glucose (mg/dL)	128	133	−	169	173	153	112
Blood creatinine (mg/dL)	0.45	0.59	0.48	0.42	0.44	0.39	0.52
Hematocrit (%)	43.1	50.0	47.5	41.1	38.6	37.9	42.8
Blood ketone body	−	3+	−	−	−	1+	−
Urinary glucose	−	4+	4+	4+	4+	4+	−
Urine ketone body	−	3+	3+	3+	2+	1+	−
Blood pH	−	7.038	7.004	7.204	7.390	−	−

Concomitant drugs: Biperiden hydrochloride, magnesium oxide, alprazolam, aripiprazole, acarbose, suvorexant, clomipramine hydrochloride, ezetimibe, vildagliptin/metformin hydrochloride, metformin hydrochloride

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td>2</td><td>Female
30s</td><td>Type 1
diabetesmellitus
(obesity)</td><td>5 mg
approximately
6 to 7 months</td><td colspan="2">Diabetic ketoacidosis
History of diabetic ketoacidosis, carbohydrate restriction, sick day, dehydration: Present
Surgery, excessive alcohol drinking, excessive exercise, recent cardiovascular episode, pancreatic disorder, dementia, presence/absence of discontinuation of insulin on self-judgment, insulin pump trouble: None
Insufficient administration of insulin: Unknown</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Day 1 of administration</td><td>The patient received oral administration of dapagliflozin propylene glycolate hydrate and carbohydrate-restricted diet concomitantly, with her HbA1c ranging between 7% and 7.9%.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Approximately 6 to 7 months after the start of administration
(day of discontinuation)</td><td>The patient complained of hypoglycaemia, but it was unknown whether her blood sugar levels had been measured.
She independently discontinued taking dapagliflozin propylene glycolate hydrate.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>2 days after discontinuation</td><td>Nausea persisted, and the patient experienced inappetence.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>3 days after discontinuation</td><td>In the morning, the patient vomited and called an ambulance. Upon admission, she presented with euglycaemic ketosis. Continuous subcutaneous insulin infusion (CSII) was maintained, and fluid replacement (23 units of bolus insulin) was administered.
At night, she vomited again. As her condition progressed to diabetic ketoacidosis, CSII was changed to continuous intravenous insulin infusion.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>11 days after discontinuation</td><td>Point-of-Care Testing (POCT) confirmed a decrease in ketone bodies, and the treatment was changed back to CSII.
Although blood glucose levels sometimes decreased to 200 mg/dL, urinary glucose and urine ketone bodies remained positive.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>12 days after discontinuation</td><td>The event resolved.</td></tr>
<tr><td></td><td colspan="5">Laboratory test value
<table>
<tr><th>Test item (unit)</th><th>Day 1 of adminis-tration</th><th>3 days after discontinuation</th><th>4 days after dis-continuation</th><th>5 days after dis-continuation</th><th>6 days after dis-continuation</th><th>7 days after dis-continuation</th><th>11 days after dis-continuation</th></tr>
<tr><td>HbA1c (%)</td><td>7.0 to 7.9</td><td>—</td><td>—</td><td>—</td><td>—</td><td>—</td><td>—</td></tr>
<tr><td>pH</td><td>—</td><td>7.39 (morning)
7.13 (night)</td><td>7.26</td><td>—</td><td>—</td><td>7.39</td><td>—</td></tr>
<tr><td>Urine ketone body</td><td>—</td><td>++ (morning)</td><td>—</td><td>+++</td><td>—</td><td>++</td><td>+</td></tr>
<tr><td>Urinary glucose</td><td>—</td><td>++ (morning)</td><td>—</td><td>++++</td><td>—</td><td>++++</td><td>++++</td></tr>
<tr><td>Blood glucose (mg/dL)</td><td>—</td><td>106 (morning)
255 (afternoon)
394 (night)</td><td>—</td><td>—</td><td>—</td><td>200 to 300</td><td>200</td></tr>
<tr><td>Acetoacetate (μmol/L)</td><td>—</td><td>675</td><td>—</td><td>870</td><td>—</td><td>608</td><td>240</td></tr>
<tr><td>3-hydroxybutyric acid (μmol/L)</td><td>—</td><td>1,144</td><td>—</td><td>2,310</td><td>—</td><td>1,906</td><td>639</td></tr>
<tr><td>HCO_3^- (mEq/L)</td><td>—</td><td>15.2 (night)</td><td>—</td><td>—</td><td>—</td><td>—</td><td>—</td></tr>
<tr><td>AG</td><td>—</td><td>25.6 (night)</td><td>18.2</td><td>—</td><td>—</td><td>—</td><td>—</td></tr>
<tr><td>Ketone bodies on POCT (mM)</td><td>—</td><td>3.4 (night)</td><td>—</td><td>—</td><td>1.9</td><td>—</td><td>0.4</td></tr>
</table></td></tr>
<tr><td></td><td colspan="5">Concomitant drugs: Insulin</td></tr>
</table>

2 Sorafenib tosilate

Brand name (name of company)	Nexavar tablets 200 mg (Bayer Yakuhin, Ltd.)
Therapeutic category	Other antitumor agents
Indications	•Radically unresectable or metastatic renal cell carcinoma •Unresectable hepatocellular carcinoma •Radically unresectable thyroid cancer

PRECAUTIONS (Revised language is underlined.)

8. IMPORTANT PRECAUTIONS <Common to all indications> (newly added)	Tumour lysis syndrome may occur. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Tumour lysis syndrome If any abnormalities are observed, administration of this drug should be discontinued, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.
Reference information	Number of cases† (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving tumour lysis syndrome reported in Japan: 2 (No patient mortalities) Cases involving tumour lysis syndrome reported overseas: 3 cases including 1 case in which the drug was administered outside the approved dosage and administration (No patient mortalities) † Cases with information on laboratory test values (uric acid, potassium, phosphorus, or calcium) related to the diagnostic criteria for tumour lysis syndrome, as documented in the case report form Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 1,547 Japanese market launch: April 2008

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 80s	Hepatocellular carcinoma (hypertension, congestive cardiac failure, dementia)	400 mg for 3 days	**Tumour lysis syndrome**	
				Day 1 of administration	Administration of sorafenib tosilate was initiated to treat hepatocellular carcinoma.
				Day 3 of administration (day of discontinuation)	Tumour lysis syndrome occurred. The following increased test values were observed: Potassium: 6.3 mEq/L, urea nitrogen: 58 mg/dL, phosphorus: 5.4 mg/dL, uric acid: 11.2 mg/dL. Sorafenib tosilate was discontinued, and treatment with allopurinol 100 mg, fluid loading 2000 mL/day, and furosemide 40/mg/day was initiated.
				1 day after discontinuation	Acute pancreatitis occurred. Administration of nafamostat mesilate 30 mg/day was initiated. CT examinations (from chest to pelvis (plain)): No major changes were found in the hepatocellular carcinoma in the right lobe of the liver.
				2 days after discontinuation	The dose of nafamostat mesilate was increased to 60 mg/day. Sodium bicarbonate 40 mL was additionally administered.
				7 days after discontinuation	Abdominal ultrasonography (liver): The liver margin was dull, and the surface was smooth. There was little impression of coarseness inside. Masses with a diameter of 70 mm, consisting of both hyperechoic and hypoechoic components, were found in the right lobe of the liver. No remarkable changes in size were observed compared to CT examination results, but the hypoechoic lesions were suspected to be necrotic.
				8 days after discontinuation	Tumour lysis syndrome resolved, and fluid loading was completed.
				15 days after discontinuation	Acute pancreatitis was resolving.

Laboratory test value

Tests item (Unit)	1 day before administration	Day 3 of administration (day of onset, day of discontinuation)	1 day after discontinuation	8 days after discontinuation
Urea nitrogen (mg/dL)	39	58	58	17
Creatinine (mg/dL)	1.46	1.87	1.75	1.44
Uric acid (mg/dL)	9.2	11.2	11.2	5.5
Sodium (mEq/L)	139	139	132	122
Potassium (mEq/L)	5.4	6.3	5.1	4.5
Calcium (mg/dL)	8.9	9.0	8.6	−
Phosphorus (mg/dL)	3.9	5.4	4.8	−
Amylase (IU/L)	118	225	1541	360
P-type amylase (IU/L)	41	167	1526	−
Lipase (IU/L)	56	446	4190	−

Concomitant drugs: Brotizolam, donepezil hydrochloride, acetylsalicylic acid, valsartan/hydrochlorothiazide, amlodipine besilate, metildigoxin, pitavastatin calcium, isosorbide dinitrate, furosemide, lansoprazole, rebamipide, ethyl icosapentate

3 Vedolizumab (genetical recombination)

Brand name (name of company)	Entyvio for I.V. Infusion 300 mg, Entyvio Pens for S.C. Injection 108 mg, Entyvio Syringes for S.C. Injection 108 mg (Takeda Pharmaceutical Company Limited)
Therapeutic category	Other agents affecting digestive organs
Indications	<Entyvio for I.V. Infusion 300 mg> •Treatment and maintenance therapy for moderate to severe ulcerative colitis (for use only in patients who have not sufficiently responded to conventional treatments) •Treatment and maintenance therapy for moderate to severe active Crohn's disease (for use only in patients who have not sufficiently responded to conventional treatments) <Entyvio Pens for S.C. Injection 108 mg, Entyvio Syringes for S.C. Injection 108 mg> •Maintenance therapy for moderate to severe ulcerative colitis (for use only in patients who have not sufficiently responded to conventional treatments) •Maintenance therapy for moderate to severe active Crohn's disease (for use only in patients who have not sufficiently responded to conventional treatments)

PRECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	<u>Interstitial lung disease</u> <u>Interstitial lung disease (interstitial pneumonia, eosinophilic pneumonia, etc.) has been reported. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations), etc. are observed, examinations such as chest X-ray, chest CT scan, and serum marker test should be promptly performed. If interstitial lung disease is suspected, administration of this drug should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.</u>
Reference information	Number of cases† (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving interstitial lung disease reported in Japan: 6 (No patient mortalities) †:Cases retrieved by the following conditions •Retrieved by MedDRA ver.27.1 SMQ “interstitial lung disease (broad)” •Cases for which the diagnostic basis for interstitial lung disease (chest x-ray, chest CT scan, KL-6 level, bronchoalveolar lavage, etc.) is mentioned Number of patients using the drug as estimated by the MAH during the previous 1-year period: Entyvio for I.V. Infusion 300 mg: Approximately 10,183 Entyvio Pens for S.C. Injection 108 mg: Approximately 126 Entyvio Syringes for S.C. Injection 108 mg: Approximately 14 Japanese market launch: Entyvio for I.V. Infusion: November 2018, Entyvio for S.C. Injection: June 2023

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td rowspan="9">1</td><td rowspan="9">Male
60s</td><td rowspan="9">Ulcerative colitis
(atrial fibrillation, gout, eczema, angina pectoris, hypertension, allergic dermatitis)</td><td rowspan="9">300 mg
Administration at Week 2 and Week 6 after the first dose
↓
Discontinuation</td><td colspan="2">Interstitial lung disease</td></tr>
<tr><td>Day 1 of administration</td><td>The patient started receiving vedolizumab.</td></tr>
<tr><td>42 days after administration (day of termination)</td><td>The patient received the third dose of vedolizumab (last dose).</td></tr>
<tr><td>21 days after termination</td><td>The patient noticed mild exertional dyspnoea and visited the hospital. A chest CT (3 weeks after the third dose) revealed an infiltrative shadow and ground-glass opacity in the right lower lobe, and he was referred to the respiratory medicine department. There were no abnormal findings before administration of vedolizumab.
The respiratory rate was 12/min, and SpO_2 was 95%. Blood test findings included WBC 10,400/μL and CRP 1.37 mg/dL.
Considering the possibility of atypical pneumonia, levofloxacin hydrate was administered.</td></tr>
<tr><td>29 days after termination</td><td>A chest CT revealed an expansion of the infiltrative shadow and ground-glass opacity. KL-6 was high at 2,380 U/mL. Procalcitonin was 0.13 ng/mL, and β-D-glucan was less than 2.26 pg/mL. Candida antigen was negative, aspergillus antigen was 1.6 (positive; considered negative when less than 0.5.), and cryptococcus antigen was negative. Lung infection was unlikely based on the CT findings, blood test results, and poor response to new quinolone drugs. The patient was diagnosed with drug-induced interstitial lung disorder. He received an intravenous injection of methylprednisolone sodium succinate 125 mg for 3 days. Thereafter, he started receiving oral prednisolone (PSL) 40 mg.</td></tr>
<tr><td>36 days after termination</td><td>The dose of PSL was reduced to 30 mg.</td></tr>
<tr><td>Date unknown</td><td>A chest CT performed 1 month later revealed that the infiltrative shadow and ground-glass opacity had almost completely disappeared, and KL-6 also decreased to 923 U/mL. Therefore, PSL was tapered.</td></tr>
<tr><td>Approximately 4.5 months after termination</td><td>The subjective symptoms of ulcerative colitis also went into remission with the oral administration of PSL 10 mg. Drug-induced lymphocyte stimulation tests were negative for both mesalazine and colchicine. The event was resolving.</td></tr>
<tr><td colspan="6">Laboratory test value
<table>
<tr><th>Test item (unit)</th><th>Before administration of vedolizumab</th><th>29 days after termination</th><th>Date unknown</th><th>Date unknown</th><th>Approximately 4.5 months after termination</th></tr>
<tr><td>KL-6 (U/mL)</td><td>470</td><td>2,380</td><td>923</td><td>572</td><td>346</td></tr>
</table></td></tr>
<tr><td colspan="6">Suspected concomitant drugs: Mesalazine, colchicine
Concomitant drugs: Amlodipine besilate, candesartan cilexetil, digoxin, rivaroxaban, rupatadine fumarate</td></tr>
</table>

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Female 40s	Ulcerative colitis (thyroid disorder, Basedow's disease, allergy to animal)	300 mg Administration at Week 2 and Week 6 after the first dose ↓ Discontinuation	**Eosinophilic pneumonia**	
				Day 1 of administration	The patient started receiving the first dose of vedolizumab for remission induction of ulcerative colitis.
				2 weeks after administration	The patient received the second dose of vedolizumab.
				6 weeks after administration	The patient received the third dose of vedolizumab (last dose).
				Date unknown	The patient presented with dry cough and exertional dyspnoea after the third dose of vedolizumab.
				70 days after administration (day of discontinuation)	Due to dry cough and exertional dyspnoea, the patient visited the respiratory medicine department. A chest CT showed peripherally predominant ground-glass opacities, mainly in the bilateral upper lobes. Drug-induced eosinophilic pneumonia caused by vedolizumab was suspected based on the clinical course, with an increased peripheral blood eosinophil count (6,000/μL: 35.9%). She declined to undergo a bronchoscopy examination. Vedolizumab was discontinued (last dose: 6 weeks after administration), and administration of prednisolone 25 mg (0.5 mg/kg) and garenoxacin mesilate hydrate 200 mg was initiated.
				3 days after discontinuation	Dry cough improved. Eosinophils normalized to 2%. The dose of prednisolone was reduced to 20 mg.
				12 days after discontinuation	The clinical course was favorable. The dose of prednisolone was reduced to 17.5 mg.
				26 days after discontinuation	The clinical course was favorable. The dose of prednisolone was reduced to 15 mg.
				40 days after discontinuation	The clinical course was favorable. The dose of prednisolone was reduced to 12.5 mg.
				Date unknown	Imaging findings and respiratory symptoms also improved on a weekly basis. Vedolizumab was not re-administered. Prednisolone was tapered and discontinued over 6 months after the start of treatment, and no relapse was observed thereafter.
	Suspected concomitant drugs: None Concomitant drugs: Mesalazine, thiamazole, levothyroxine sodium hydrate				

4 Gemcitabine hydrochloride

Brand name (name of company)	Gemzar Injection 200 mg, 1 g (Eli Lilly Japan K.K.), and the others
Therapeutic category	Antimetabolic agents
Indications	•Non-small cell lung cancer •Pancreatic carcinoma •Biliary carcinoma •Urothelial carcinoma •Inoperable or recurrent breast cancer •Ovarian cancer that has progressed after cancer chemotherapy •Relapsed or refractory malignant lymphoma

PRECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Severe skin disorders Severe skin disorders such as toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema, blister, or desquamation may occur.
Reference information	Number of cases† (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving toxic epidermal necrolysis reported in Japan: 1 (No patient mortalities) Cases involving toxic epidermal necrolysis reported overseas: 2 (No patient mortalities) Cases involving oculomucocutaneous syndrome reported in Japan: 1 (No patient mortalities) Cases involving oculomucocutaneous syndrome reported overseas: 3 (including 1 case in which the drug was administered outside the approved indications) (No patient mortalities) † Cases with information related to the diagnostic criteria (skin eruption, pyrexia, skin biopsy), as documented in the case report form Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 494,000 Japanese market launch: August 1999

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 50s	Lung squamous cell carcinoma stage IV (metastasis to right pleura, metastases to bone)	1,500 mg (1 course)	**Toxic epidermal necrolysis (TEN)** Smoking history: Present (20 cigarettes per day, years of smoking unknown) Performance status (PS) before administration of gemcitabine hydrochloride: 0 Allergy history: Drug eruption (erythema due to ceftriaxone sodium and cefozopran hydrochloride, time of onset: Approximately 3 months before administration of gemcitabine hydrochloride)	
				11 days before administration	After 3 courses of administration of cisplatin 80 mg/m^2 and docetaxel 80 mg/m^2, pericardial fluid that had been noted from before rapidly increased. The patient was admitted to the hospital with the condition of cardiac tamponade due to carcinomatous pericarditis.
				Day 1 of administration	After the patient's general condition recovered, administration of gemcitabine hydrochloride was initiated for lung squamous cell carcinoma (last administration).
				5 days after administration	Nikolsky's sign was observed, resulting in erosion in approximately 30% of the entire body. Blisters and ulcers were noted. Skin color of the area of skin eruption was normal. Numerous rashes were noted (diameter: 20 cm or longer). Healthy skin was present. The sites of onset were the trunk, upper extremities, and face. Subjective symptoms were spontaneous pain and tenderness. The dermatology department was consulted, and the patient was diagnosed with TEN type drug eruption.
				6 days after administration	An intravenous drip infusion of methylprednisolone sodium succinate 500 mg was administered. Treatment with ointments (alprostadil alfadex 10 mg, white petrolatum 100 g) was initiated (until 11 days after administration).
				7 days after administration	After administering the infusion of methylprednisolone sodium succinate 500 mg for the second day, the patient was transferred to the dermatology department of another hospital. However, he developed seizures of loss of consciousness due to cardiac tamponade at the transferred department.
				8 days after administration	The patient was hospitalized to the internal medicine department at this hospital again. A pericardium drainage tube was reinserted.
				Date unknown	Skin conditions gradually tended to improve with various ointments and treatments. However, respiratory, cardiac, hepatic, and renal functions deteriorated. The patient had a complication of disseminated intravascular coagulation (DIC).
				12 days after administration	The patient died. Cause of death: DIC, lung cancer No autopsy was performed. At the time of death, TEN type drug eruption had not resolved.

Laboratory test value

Test item (unit)	11 days before administration	3 days after administration	7 days after administration	8 days after administration	11 days after administration	12 days after administration
AST (IU/L)	17	60	-	-	-	-
ALT (IU/L)	21	118	-	-	-	-
BUN (mg/dL)	12	14	32	-	-	98
Cr (mg/dL)	0.89	0.73	1.56	-	-	5.14
eGFR (mL/min/m^2)	71	88	38	-	-	10
White blood cell count (/μL)	10,770	18,420	14,780	-	-	7,600
Red blood cell count (10^4/μL)	277	287	265	-	-	238
Hb (g/dL)	8.0	8.9	8.3	-	-	7.3
Ht (%)	25.4	28.0	26.3	-	-	22.9
PLT (10^4/μL)	23.2	22.8	9.2	-	-	3.6
ALB (g/dL)	2.0	-	-	2.7	3.1	-
CRP (mg/dL)	-	11.90	32.53	-	-	-
PT (seconds)	-	-	-	16.5	13.1	-
PT (%)	-	-	-	38	63	-
PT-INR	-	-	-	1.98	1.35	-
APTT (seconds)	-	-	-	32.3	36.5	-
AT III (%)	-	-	-	55	93	-
FDP (μg/mL)	-	-	-	15.0	18.3	-
Fib (mg/dL)	-	-	-	477	258	-

Concomitant drugs: Dexamethasone sodium phosphate

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>2</td><td>Female
70s</td><td>Pancreatic carcinoma
stage IV
(metastases to liver)</td><td>1,500 mg
(1 course)</td><td>Stevens-Johnson syndrome
PS before administration of gemcitabine hydrochloride: 0
Day 1 of administration: Co-administration of gemcitabine hydrochloride and tegafur/gimeracil/oteracil potassium (120 mg) was initiated (last dose of gemcitabine hydrochloride)
2 days after administration: Skin eruption with itching developed from the precordial region.
4 days after administration: Tegafur/gimeracil/oteracil potassium was administered (last administration).
5 days after administration (day of discontinuation): Red papule/erythema appeared, starting in the cervical region and spreading across the entire body. Suspected drug eruption was diagnosed. Discontinuation of chemotherapy was decided.
5 days after discontinuation: The patient visited a dermatologist.
8 days after discontinuation: Skin biopsy was performed.
Clinical diagnosis: Suspected drug eruption
Histopathological diagnosis: Compatible with drug eruption
Histopathological findings: Quite strong diffuse infiltration of eosinophil and lymphocyte was noted in the upper dermis. It partially spread into the epidermis accompanied by mild intercellular oedema (spongiosis). Hydropic degeneration in the basal cell layer was also noted in some areas, albeit slightly.
The patient had no pyrexia. Haemorrhagic findings in mucosal junctions were noted.
Site of onset: Vulva
Specific lesions: Erosion (less than 10% of body surface area), with no necrotic changes in the pathological findings
Finally, the patient was diagnosed with Stevens-Johnson syndrome.
9 days after discontinuation: Treatment with oral administration of prednisolone 20 mg/day was initiated.
Date unknown: The symptoms remained unresolved, but they were improving with concomitant phototherapy.
The patient complained of slight itching. The administration was continued since the degree of itching was not considered to affect the treatment.</td></tr>
<tr><td></td><td colspan="4">Laboratory test value
<table>
<tr><th>Test item
(unit)</th><th>2 days before
administration</th><th>4 days after
administration</th><th>2 days after
discontinuation</th><th>19 days after
discontinuation</th></tr>
<tr><td>AST (IU/L)</td><td>88</td><td>136</td><td>68</td><td>58</td></tr>
<tr><td>ALT (IU/L)</td><td>120</td><td>202</td><td>111</td><td>80</td></tr>
<tr><td>ALP (IU/L)</td><td>1,071</td><td>1,252</td><td>1,113</td><td>1,082</td></tr>
<tr><td>γ-GTP (IU/L)</td><td>255</td><td>306</td><td>279</td><td>333</td></tr>
<tr><td>BUN (mg/dL)</td><td>15.9</td><td>20.4</td><td>14.9</td><td>16.6</td></tr>
<tr><td>WBC (/μL)</td><td>5,260</td><td>5,740</td><td>1,380</td><td>5,840</td></tr>
<tr><td>CRP (mg/dL)</td><td>-</td><td>2.0</td><td>0.6</td><td>2.3</td></tr>
</table></td></tr>
<tr><td></td><td colspan="4">Concomitant drugs: Tegafur/gimeracil/oteracil potassium</td></tr>
</table>

3

Revisions of PRECAUTIONS (No. 356)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated December 17, 2024.

1 Antihypertensives
Esaxerenone

Brand name

Minnebro Tablets 1.25 mg, 2.5 mg, 5 mg, Minnebro OD Tablets 1.25 mg, 2.5 mg, 5 mg (Daiichi Sankyo Co., Ltd.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)

Patients receiving the following drugs: Potassium-sparing diuretics (spironolactone, triamterene, potassium canrenoate), aldosterone antagonists (eplerenone), potassium preparations (potassium chloride, potassium gluconate, potassium aspartate, potassium iodide (excluding the cases where potassium iodide is used for prevention/reduction of internal exposure of the thyroid gland to radioactive iodide), potassium acetate)

10. INTERACTIONS
10.1 Contraindications for Co-administration (Do not co-administer with the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Potassium preparations Potassium chloride Potassium gluconate Potassium aspartate Potassium iodide (excluding the cases where potassium iodide is used for prevention/reduction of internal exposure of the thyroid gland to radioactive iodide) Potassium acetate	Serum potassium levels may increase.	Potassium retention effect may be enhanced.

10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Angiotensin-converting enzyme inhibitors Imidapril hydrochloride Enalapril maleate, etc. Angiotensin II receptor blockers Olmesartan medoxomil Azilsartan Telmisartan, etc. Aliskiren fumarate Ciclosporin Tacrolimus	Serum potassium levels may increase. Careful attention should be paid such as measuring serum potassium levels more frequently.	Potassium retention effect may be enhanced.

Drospirenone combination drugs Potassium iodide (cases when potassium iodide is used for prevention/ reduction of internal exposure of the thyroid gland to radioactive iodide)		

2 Antihypertensives

Eplerenone

Brand name

Selara Tablets 25 mg, 50 mg, 100 mg (Viatris Pharmaceuticals Japan G.K.), and the others

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)

<Hypertension>
Patients receiving potassium preparations (excluding potassium iodide in cases where it is used for prevention/reduction of internal exposure of the thyroid gland to radioactive iodide)

10. INTERACTIONS
10.1 Contraindications for Co-administration (Do not co-administer with the following.)

<Hypertension>

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Potassium preparations Potassium chloride Potassium gluconate Potassium aspartate Potassium iodide (excluding the cases where potassium iodide is used for prevention/ reduction of internal exposure of the thyroid gland to radioactive iodide) Potassium acetate	Serum potassium levels may increase.	Potassium retention effect may be enhanced.

10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.) (newly added)

<Hypertension>

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Potassium iodide (in cases where potassium iodide is used for prevention/ reduction of internal exposure of the thyroid gland to radioactive iodide)	Serum potassium levels may increase. Careful attention should be paid such as monitoring serum potassium levels periodically.	Potassium retention effect may be enhanced.

3 Other cardiovascular agents, antidiabetic agents, agents affecting metabolism, n.e.c. (not elsewhere classified)

[1] Empagliflozin
[2] Dapagliflozin propylene glycolate hydrate

[3] Ipragliflozin L-proline
[4] Canagliflozin hydrate
[5] Tofogliflozin hydrate
[6] Luseogliflozin hydrate

Brand name	[1] Jardiance Tablets 10 mg, 25 mg (Nippon Boehringer Ingelheim Co., Ltd.) [2] Forxiga 5 mg, 10 mg tablets (AstraZeneca K.K.) [3] Suglat Tablets 25 mg, 50 mg (Astellas Pharma Inc.) [4] Canaglu Tablets 100 mg, Canaglu OD Tablets 100 mg (Mitsubishi Tanabe Pharma Corporation) [5] Deberza Tablets 20 mg (Kowa Company, Ltd.) [6] Lusefi tablets 2.5 mg, 5 mg, Lusefi OD film 2.5mg (Taisho Pharmaceutical Co., Ltd.)
8. IMPORTANT PRECAUTIONS	Fatty acid metabolism may be elevated and ketosis may occur leading to ketoacidosis, even in cases with well-controlled blood glucose levels. This is due to the urinary glucose excretion-enhancing activity, which is the mechanism of action of this drug. Cases have been reported in which urinary glucose excretion and ketoacidosis persisted longer than expected from plasma half-lives of the drugs, after discontinuing administration of SGLT2 inhibitors including this drug. Patients should be carefully monitored, with as-needed urinary glucose measurements, etc.

4 Other agents affecting digestive organs

Vedolizumab (genetical recombination)

Brand name	Entyvio for I.V. Infusion 300 mg, Entyvio Pens for S.C. Injection 108 mg, Entyvio Syringes for S.C. Injection 108 mg (Takeda Pharmaceutical Company Limited)
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Interstitial lung disease Interstitial lung disease (interstitial pneumonia, eosinophilic pneumonia, etc.) has been reported. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations), etc. are observed, examinations such as chest X-ray, chest CT scan, and serum marker test should be promptly performed. If interstitial lung disease is suspected, administration of this drug should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

5 Estrogen and gestagen preparations

Chlormadinone acetate (2 mg, 25 mg)

Brand name	Lutoral tablets 2 mg (Fuji Pharma Co., Ltd.), Prostal Tablets 25 mg (Aska Pharmaceutical Co., Ltd.), and the others
8. IMPORTANT PRECAUTIONS <Common to all indications> (newly added)	Meningioma has been reported following administration of chlormadinone acetate. Attention should be paid to symptoms suggestive of meningioma, such as headache, motor paralysis, visual impairment/visual field disorder, cranial nerve paralysis, seizure, and changes in cognitive function during administration of this drug. Imaging tests should be performed if necessary. If meningioma is diagnosed, discontinuation of this drug should be considered. Cases in which meningioma shrunk after discontinuation of administration have been reported.
9. PRECAUTIONS CONCERNING	Patients with meningioma or a history of the disease The necessity of administration of this drug should be considered taking

PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc. (newly added)**	into account the conditions of meningioma and primary diseases.
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Use**	An overseas epidemiological study reported a higher risk of meningioma in women with cumulative doses of chlormadinone acetate greater than 360 mg over 6 months compared to those with cumulative doses less than or equal to 360 mg (hazard ratio 4.4 (95% confidence interval: 3.4 to 5.8)). The risk increased as the cumulative doses increased. In addition, an increased risk of meningioma was reported in women receiving chlormadinone acetate compared to those not receiving it (odds ratio 3.87 (95% confidence interval: 3.48 to 4.30)).

6 Estrogen and gestagen preparations

Chlormadinone acetate (50 mg)

Brand name	Prostal-L Tablets 50 mg (Aska Pharmaceutical Co., Ltd.)
8. IMPORTANT PRECAUTIONS **<Common to all indications>** **(newly added)**	Meningioma has been reported following administration of chlormadinone acetate. Attention should be paid to symptoms suggestive of meningioma, such as headache, motor paralysis, visual impairment/visual field disorder, cranial nerve paralysis, seizure, and changes in cognitive function during administration of this drug. Imaging tests should be performed if necessary. If meningioma is diagnosed, discontinuation of this drug should be considered. Cases in which meningioma shrunk after discontinuation of administration have been reported.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc. (newly added)**	Patients with meningioma or a history of the disease The necessity of administration of this drug should be considered taking into account the conditions of meningioma and primary diseases.
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Use**	An overseas epidemiological study reported a higher risk of meningioma in women with cumulative doses of chlormadinone acetate greater than 360 mg over 6 months compared to those with cumulative doses less than or equal to 360 mg (hazard ratio 4.4 (95% confidence interval: 3.4 to 5.8)). The risk increased as the cumulative doses increased. In addition, an increased risk of meningioma was reported in women receiving chlormadinone acetate compared to those not receiving it (odds ratio 3.87 (95% confidence interval: 3.48 to 4.30)).

7 Estrogen and gestagen preparations

Medroxyprogesterone acetate (2.5 mg, 5 mg) (preparations with indications such as adjusting the start of controlled ovarian stimulation in assisted reproductive technology)

Brand name	Hysron Tablets 5 (Kyowa Kirin Co., Ltd.) and the others

8. IMPORTANT PRECAUTIONS (newly added)	<Common to all indications> Meningioma has been reported following administration of medroxyprogesterone acetate. Attention should be paid to symptoms suggestive of meningioma, such as headache, motor paralysis, visual impairment/visual field disorder, cranial nerve paralysis, seizure, and changes in cognitive function during administration of this drug. Imaging tests should be performed if necessary. If meningioma is diagnosed, discontinuation of this drug should be considered. Cases in which meningioma shrunk after discontinuation of administration have been reported.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc. (newly added)**	Patients with meningioma or a history of the disease The necessity of administration of this drug should be considered taking into account the conditions of meningioma and primary diseases.
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Use (newly added)**	An overseas epidemiological study reported a higher risk of meningioma in women receiving medroxyprogesterone acetate compared to those not receiving it (odds ratio 5.55 (95% confidence interval: 2.27 to 13.56)).

8 Estrogen and gestagen preparations

Medroxyprogesterone acetate (2.5 mg) (preparations without indications such as adjusting the start of controlled ovarian stimulation in assisted reproductive technology)

Brand name	Provera Tablets 2.5 mg (Pfizer Japan Inc.)
8. IMPORTANT PRECAUTIONS (newly added)	Meningioma has been reported following administration of medroxyprogesterone acetate. Attention should be paid to symptoms suggestive of meningioma, such as headache, motor paralysis, visual impairment/visual field disorder, cranial nerve paralysis, seizure, and changes in cognitive function during administration of this drug. Imaging tests should be performed if necessary. If meningioma is diagnosed, discontinuation of this drug should be considered. Cases in which meningioma shrunk after discontinuation of administration have been reported.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc. (newly added)**	Patients with meningioma or a history of the disease The necessity of administration of this drug should be considered taking into account the conditions of meningioma and primary diseases.
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Use**	An overseas epidemiological study reported a higher risk of meningioma in women receiving medroxyprogesterone acetate compared to those not receiving it (odds ratio 5.55 (95% confidence interval: 2.27 to 13.56)).

(newly added)

9 Estrogen and gestagen preparations

Medroxyprogesterone acetate (200 mg)

Brand name	Hysron-H Tablets 200 mg (Kyowa Kirin Co., Ltd.) and the others
8. IMPORTANT PRECAUTIONS (newly added)	Meningioma has been reported following administration of medroxyprogesterone acetate. Attention should be paid to symptoms suggestive of meningioma, such as headache, motor paralysis, visual impairment/visual field disorder, cranial nerve paralysis, seizure, and changes in cognitive function during administration of this drug. Imaging tests should be performed if necessary. If meningioma is diagnosed, discontinuation of this drug should be considered. Cases in which meningioma shrunk after discontinuation of administration have been reported.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS	Patients with meningioma or a history of the disease The necessity of administration of this drug should be considered taking into account the conditions of meningioma and primary diseases.
9.1 Patients with Complication or History of Diseases, etc. (newly added)	
15. OTHER PRECAUTIONS	An overseas epidemiological study reported a higher risk of meningioma in women receiving medroxyprogesterone acetate compared to those not receiving it (odds ratio 5.55 (95% confidence interval: 2.27 to 13.56)).
15.1 Information Based on Clinical Use (newly added)	

10 Mineral preparations

Potassium iodide (powders, pills) (preparations indicated for prevention/reduction of internal exposure of the thyroid gland to radioactive iodine)

Brand name	Potassium Iodide “Nichi-iko” (Nichi-Iko Pharmaceutical Co., Ltd.), Potassium Iodide “Hoei” (Viatris Healthcare G.K.), Potassium Iodide Pills 50 mg “Nichi-iko” (Nichi-Iko Pharmaceutical Co., Ltd.)
2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)	<Indications other than prevention/reduction of internal exposure of the thyroid gland to radioactive iodine> Patients receiving eplerenone (for hypertension) or esaxerenone
10. INTERACTIONS **10.1 Contraindications for Co-administration (Do not co-administer with the following.)**	<Indications other than prevention/reduction of internal exposure of the thyroid gland to radioactive iodine>

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Eplerenone (for hypertension) Esaxerenone	Serum potassium levels may increase.	Potassium retention effect may be enhanced due to co-administration.

10.2 Precautions for Co-Administration (This drug should be administered with	<Common to all indications>

caution when co-administered with the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Eplerenone (for chronic cardiac failure) Finerenone	Serum potassium levels may increase. Careful attention should be paid such as monitoring serum potassium levels periodically.	Potassium retention effect may be enhanced.

<Prevention/reduction of internal exposure of the thyroid gland to radioactive iodine>

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Eplerenone (hypertension) Esaxerenone	Serum potassium levels may increase.	Potassium retention effect may be enhanced.

11 Mineral preparations
Potassium iodide (jellies) (preparations indicated for prevention/reduction of internal exposure of the thyroid gland to radioactive iodine)

Brand name Potassium Iodide Oral Jelly 16.3 mg, 32.5 mg “Nichi-iko” (Nichi-Iko Pharmaceutical Co., Ltd.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) (deleted)

10. INTERACTIONS (deleted)

10.1 Contraindications for Co-administration (Do not co-administer with the following.)

10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Eplerenone Esaxerenone Finerenone	Serum potassium levels may increase. Careful attention should be paid such as monitoring serum potassium levels periodically.	Potassium retention effect may be enhanced.

12 Antidiabetic agents
Empagliflozin/linagliptin

Brand name Tradiance Combination Tablets AP, BP (Nippon Boehringer Ingelheim Co., Ltd.)

8. IMPORTANT PRECAUTIONS Fatty acid metabolism may be elevated and ketosis may occur leading to ketoacidosis, even in cases with well-controlled blood glucose levels. This is due to the urinary glucose excretion-enhancing activity, which is the mechanism of action of empagliflozin.

Cases have been reported in which urinary glucose excretion and

	ketoacidosis persisted longer than expected from the plasma half-lives of the drugs, after discontinuing administration of SGLT2 inhibitors including empagliflozin. Patients should be carefully monitored, with as-needed urinary glucose measurements, etc.

13 Antidiabetic agents

Sitagliptin phosphate hydrate/ipragliflozin L-proline

Brand name	Sujanu Combination Tablets (MSD K.K.)
8. IMPORTANT PRECAUTIONS	Fatty acid metabolism may be elevated and ketosis may occur leading to ketoacidosis, even in cases with well-controlled blood glucose levels. This is due to the urinary glucose excretion-enhancing activity, which is the mechanism of action of ipragliflozin. Cases have been reported in which urinary glucose excretion and ketoacidosis persisted longer than expected from the plasma half-lives of the drugs, after discontinuing administration of SGLT2 inhibitors including ipragliflozin. Patients should be carefully monitored, with as-needed urinary glucose measurements, etc.

14 Antidiabetic agents

Teneligliptin hydrobromide hydrate/canagliflozin hydrate

Brand name	Canalia Combination Tablets (Mitsubishi Tanabe Pharma Corporation)
8. IMPORTANT PRECAUTIONS	Fatty acid metabolism may be elevated and ketosis may occur leading to ketoacidosis, even in cases with well-controlled blood glucose levels. This is due to the urinary glucose excretion-enhancing activity, which is the mechanism of action of canagliflozin, the active ingredient of this drug. Cases have been reported in which urinary glucose excretion and ketoacidosis persisted longer than expected from the plasma half-life of the drug, after discontinuing administration of SGLT2 inhibitors including canagliflozin. Patients should be carefully monitored, with as-needed urinary glucose measurements, etc.

15 Antimetabolic agents

Gemcitabine hydrochloride

Brand name	Gemzar Injection 200 mg, 1 g (Eli Lilly Japan K.K.), and the others
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Severe skin disorders Severe skin disorders such as toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema, blister, or desquamation may occur.

16 Other antitumor agents

Sorafenib tosilate

Brand name	Nexavar tablets 200 mg (Bayer Yakuhin, Ltd.)
8. IMPORTANT PRECAUTIONS **<Common to all indications>** **(newly added)**	Tumour lysis syndrome may occur. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
11. ADVERSE REACTIONS **11.1 Clinically**	Tumour lysis syndrome If any abnormalities are observed, administration of this drug should be discontinued, appropriate measures (e.g., administration of

Significant Adverse Reactions (newly added)	physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

17 Anti-virus agents

Ensitrelvir fumaric acid

Brand name	Xocova Tablets 125 mg (Shionogi & Co., Ltd.)
8. IMPORTANT PRECAUTIONS (newly added)	The necessity of administering this drug to women of childbearing potential should be carefully considered. If administration is deemed necessary, attention should be paid to the following points. Prior to administering this drug, the absence of pregnancy and the absence of the possibility of pregnancy should be confirmed through sufficient patient interviews. The following should be explained to patients before starting administration of this drug: •This drug can cause foetal harm when administered to a pregnant woman. •If pregnancy is detected or suspected during administration of this drug, this drug should be discontinued immediately. •If pregnancy is detected or suspected during administration of this drug or within 2 weeks after the last administration of this drug, a physician, pharmacist, etc. should be consulted promptly.

18 Anti-virus agents

Molnupiravir

Brand name	Lagevrio Capsules 200 mg (MSD K.K.)
8. IMPORTANT PRECAUTIONS (newly added)	The necessity of administering this drug to women of childbearing potential should be carefully considered. If administration is deemed necessary, attention should be paid to the following points. Prior to administering this drug, the absence of pregnancy and the absence of the possibility of pregnancy should be confirmed through sufficient patient interviews. The following should be explained to patients before starting administration of this drug: •This drug can cause foetal harm when administered to a pregnant woman. •If pregnancy is detected or suspected during administration of this drug, this drug should be discontinued immediately. •If pregnancy is detected or suspected during administration of this drug or within 4 days after the last administration of this drug, a physician, pharmacist, etc. should be consulted promptly.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect adverse drug reactions (ADRs) 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 November 30, 2024)
◎: Products for which EPPV was initiated after November 1, 2024

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
◎	Donanemab (genetical recombination) kisunla Intravenous Infusion 350 mg	Eli Lilly Japan K.K.	November 26, 2024
◎	Fruquintinib Fruzaqla capsules 1 mg, 5 mg	Takeda Pharmaceutical Company Limited	November 22, 2024
◎	Sacituzumab govitecan (genetical recombination) Trodelvy for Injection 200 mg	Gilead Sciences K.K.	November 20, 2024
◎	Amivantamab (genetical recombination) Rybrevant Intravenous Infusion 350 mg	Janssen Pharmaceutical K.K.	November 20, 2024
◎	Repotrectinib Augtyro capsules 40 mg	Bristol-Myers Squibb K.K.	November 20, 2024
◎	Mecobalamin[*1] Rozebalamin for Injection 25 mg	Eisai Co., Ltd.	November 20, 2024
◎	Teprotumumab (genetical recombination) Tepezza for Intravenous Infusion 500 mg	Amgen K.K.	November 20, 2024
◎	Voclosporin Lupkynis Capsules 7.9 mg	Otsuka Pharmaceutical Co., Ltd.	November 20, 2024
◎	Tasurgratinib succinate Tasfygo Tablets 35 mg	Eisai Co., Ltd.	November 20, 2024
◎	Avibactam sodium/ceftazidime hydrate Zavicefta Combination for Intravenous Infusion 2.5 g	Pfizer Japan Inc.	November 12, 2024
	Tapinarof Vtama cream 1%	Japan Tobacco Inc.	October 29, 2024
	Gumarontinib hydrate Haiyitan tablets 50 mg	Haihe Biopharma K.K.	October 11, 2024
	Live attenuated influenza vaccine Flumist Intranasal Spray	Daiichi Sankyo Co., Ltd.	October 3, 2024
	Coronavirus (SARS-CoV-2) RNA vaccine[*2] Kostaive intramuscular injection	Meiji Seika Pharma Co., Ltd.	September 30, 2024

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

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
Brexpiprazole[*3] Rexulti tablets 1 mg, 2 mg, Rexulti OD tablets 0.5 mg, 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.	September 24, 2024
Treprostinil[*4] Treprost Inhalation Solution 1.74 mg	Mochida Pharmaceutical Co., Ltd.	September 24, 2024
Inactivated tissue culture tick-borne encephalitis vaccine Ticovac suspension liquid for intramuscular injection 0.5 mL, Ticovac Junior suspension liquid for intramuscular injection 0.25 mL	Pfizer Japan Inc.	September 13, 2024
Freeze-dried human protein C concentrate Ceprotin for Intravenous Injection 1000 IU	Takeda Pharmaceutical Company Limited	September 6, 2024
Pneumococcal 20-valent conjugate vaccine adsorbed (mutated diphtheria CRM_{197} conjugate)[*5] Prevenar 20 Suspension Liquid for Injection	Pfizer Japan Inc.	August 30, 2024
Brivaracetam Briviact Tablets 25 mg, 50 mg, Briviact for I.V. injection 25 mg	UCB Japan Co. Ltd.	August 30, 2024
Mepolizumab (genetical recombination)[*6] Nucala solution for s.c. injection 100 mg	GlaxoSmithKline K.K.	August 28, 2024
Maribavir Livtencity tablets 200 mg	Takeda Pharmaceutical Company Limited	August 28, 2024
Vilanterol trifenatate/fluticasone furoate Relvar 50 Ellipta 14 doses for Pediatric, Relvar 50 Ellipta 30 doses for Pediatric	GlaxoSmithKline K.K.	August 23, 2024
Pirtobrutinib Jaypirca Tablets 50 mg, 100 mg	Eli Lilly Japan K.K.	August 21, 2024
Zinc histidine hydrate Zintus Tablets 50 mg	Nobelpharma Co., Ltd.	August 20, 2024
Momelotinib hydrochloride hydrate Omjjara Tablets 100 mg, 150 mg, 200 mg	GlaxoSmithKline K.K.	August 15, 2024
Iptacopan hydrochloride hydrate Fabhalta capsules 200 mg	Novartis Pharma K.K.	August 15, 2024
Favipiravir[*7] Avigan Tablets 200 mg	FUJIFILM Toyama Chemical Co., Ltd.	August 15, 2024
Sargramostim (genetical recombination) Sargmalin for inhalation 250 μg	Nobelpharma Co., Ltd.	July 29, 2024
Fluciclovine (^{18}F) Axumin Injection	Nihon Medi-Physics Co., Ltd.	July 2, 2024
Concizumab (genetical recombination)[*8] Alhemo Subcutaneous Injection 15 mg, 60 mg, 150 mg, 300 mg	Novo Nordisk Pharma Ltd.	June 24, 2024
Vilanterol trifenatate/fluticasone furoate Relvar 100 Ellipta 14 doses, 30 doses	GlaxoSmithKline K.K.	June 24, 2024

Nonproprietary name / Brand name		Name of the MAH	Date of EPPV initiation
	Zolbetuximab (genetical recombination) / Vyloy for I.V. infusion 100 mg	Astellas Pharma Inc.	June 12, 2024
	Nemolizumab (genetical recombination)*9 / Mitchga Vials 30 mg	Maruho Co., Ltd.	June 11, 2024
	Susoctocog alfa (genetical recombination) / Obizur Intravenous Injection 500	Takeda Pharmaceutical Company Limited	June 10, 2024

*1 Slowing the progression of functional impairment in amyotrophic lateral sclerosis (ALS)

*2 Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

*3 Excessive motor activity or physically/verbally aggressive behavior due to rapid changes in mood, irritability, and/or outbursts associated with dementia due to Alzheimer's disease

*4 Pulmonary hypertension associated with interstitial lung disease

*5 Prophylaxis of pneumococcal disease (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V,10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) in the elderly and individuals who are considered to be at high risk of pneumococcal disease

*6 Chronic sinusitis with nasal polyps (for use only in patients who have not sufficiently responded to conventional treatments)

*7 Severe fever with thrombocytopenia syndrome virus infection

*8 Prevention of bleeding tendency in patients with congenital haemophilia who don’t have inhibitors against blood coagulation factor VIII or IX

*9 Addition of a pediatric dosage indicated for the following diseases in patients who have not responded sufficiently to conventional treatments
Pruritus associated with atopic dermatitis
Prurigo nodularis