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# Summary of Investigation Results

## Preparations containing GLP-1 receptor agonists and tirzepatide

February 14, 2023

**Non-proprietary name**

See attachment.

**Brand name (marketing authorization holder)**

See attachment.

**Japanese market launch**

See attachment.

**Indications**

See attachment.

**Summary of revisions**

1. a.-g.

A precautionary statement regarding cholelithiasis, cholecystitis, cholangitis, or cholestatic jaundice should be added to the IMPORTANT PRECAUTIONS section.

2. h.

A precautionary statement regarding acute gallbladder disease in the IMPORTANT PRECAUTIONS section should be revised to a precautionary statement regarding cholelithiasis, cholecystitis, cholangitis, or cholestatic jaundice.

3. a.-h.

“Cholecystitis, cholangitis, cholestatic jaundice” should be added to the Clinically Significant Adverse Reactions section.

**Investigation results and background of the revision**



3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

Cases involving acute gallbladder disease-related events (cholecystitis, cholangitis, cholestatic jaundice) after administration of preparations containing GLP-1 receptor agonists reported in Japan and several published articles discussing the association between GLP-1 receptor agonists and acute gallbladder disease were evaluated. As a result of consultation with expert advisors on the causality assessment of the cases and the necessity of revision of Precautions, MHLW/PMDA concluded that revision for all the GLP-1 receptor agonist-containing preparations was necessary based on the following points.

- Cases involving acute gallbladder disease-related events (cholecystitis, cholangitis, cholestatic jaundice) for which a causal relationship with preparations containing GLP-1 receptor agonists was reasonably possible have been reported in Japan.
- The pharmacological mechanism of GLP-1 receptor agonists, such as inhibition of gallbladder contraction, may promote gallstone formation and cause acute gallbladder disease such as cholecystitis.
- There have been several published articles suggesting an increased risk of acute gallbladder disease with the use of GLP-1 receptor agonists (e.g., JAMA Intern Med 2022; 182: 513-9, JAMA Intern Med 2016; 176: 1474-81).

Although no related cases have been reported for tirzepatide, it has GLP-1 agonist activity, and the possibility of adverse drug reactions similar to those of GLP-1 receptor agonists cannot be ruled out. As a result of consultation with expert advisors, MHLW/PMDA concluded that revision of Precautions was necessary as well.

**Reference: Number of cases* and patient mortalities involving acute gallbladder disease reported in Japan**

a.

A total of 13 cases have been reported to date (including 8 cases for which a causal relationship between the drug and event was reasonably possible).

No patient mortalities have been reported to date.



3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
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b.

A total of 3 cases have been reported to date (including 1 case for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported to date.

c.

A total of 4 cases have been reported to date (including 1 case for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported to date.

d.

A total of 23 cases have been reported to date (including 6 cases for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported to date.

e.

A total of 3 cases have been reported to date (including 1 case for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported to date.

f.

1 case has been reported to date. (A causal relationship between the drug and event could not be established for this case.)
No patient mortalities have been reported to date.

g.

1 case has been reported to date. (A causal relationship between the drug and event could not be established for this case.)
No patient mortalities have been reported to date.

h.

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No cases have been reported to date.

*Cases collected in the PMDA's database for adverse drug reactions, etc. reports

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

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Attachment

| No. | Non-proprietary name | Brand name | Marketing authorization holder | Japanese market launch | Indications |
|---|---|---|---|---|---|
| a. | Liraglutide (genetical recombination) | Victoza Subcutaneous Injection 18 mg | Novo Nordisk Pharma Ltd. | June 2010 | Type 2 diabetes mellitus |
| b. | Exenatide | Byetta Subcutaneous Injection 5 μg Pen 300, 10 μg Pen 300<br>Bydureon Subcutaneous Injection 2 mg Pen | AstraZeneca K.K. | Byetta Subcutaneous Injection: December 2010<br>Bydureon Subcutaneous Injection: May 2015 | ・Byetta Subcutaneous Injection<br>Type 2 diabetes mellitus<br>The use is limited to patients who have not adequately responded to treatment with sulfonylureas (including concomitant use with biguanides or thiazolidines) in addition to diet and exercise therapy.<br>・Bydureon Subcutaneous Injection<br>Type 2 diabetes mellitus<br>The use is limited to patients who have not adequately responded to treatment with sulfonylureas, biguanides, and thiazolidines (including monotherapy or combination therapy |



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| No. | Non-proprietary name | Brand name | Marketing authorization holder | Japanese market launch | Indications |
|---|---|---|---|---|---|
| | | | | | with each drug) in addition to diet and exercise therapy. |
| c. | Lixisenatide | Lyxumia S.C. Injection 300 µg | Sanofi K.K. | September 2013 | Type 2 diabetes mellitus |
| d. | Dulaglutide (genetical recombination) | Trulicity Subcutaneous Injection 0.75 mg Ateos | Eli Lilly Japan K.K. | September 2015 | Type 2 diabetes mellitus |
| e. | Semaglutide (genetical recombination) | Ozempic Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD, Ozempic Subcutaneous Injection 2 mg, Rybelsus tablets 3 mg, 7 mg, 14 mg | Novo Nordisk Pharma Ltd. | Injection 0.25 mg, 0.5 mg, 1.0 mg: June 2020<br>Injection 2 mg: May 2022<br>Tablets: February 2021 | Type 2 diabetes mellitus |
| f. | Insulin degludec (genetical recombination)/liraglutide | Xultophy combination injection FlexTouch | Novo Nordisk Pharma Ltd. | September 2019 | Type 2 diabetes mellitus for which insulin therapy is indicated |



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| No. | Non-proprietary name | Brand name | Marketing authorization holder | Japanese market launch | Indications |
|---|---|---|---|---|---|
| | (genetical recombination) | | | | |
| g. | Insulin glargine (genetical recombination)/lixisenatide | Soliqua Injection SoloStar | Sanofi K.K. | June 2020 | Type 2 diabetes mellitus for which insulin therapy is indicated |
| h. | Tirzepatide | Mounjaro Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos | Eli Lilly Japan K.K. | Not listed in the Japanese National Health Insurance Drug Price List | Type 2 diabetes mellitus |



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