PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

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# Appropriate Measures to Be Taken for Pemphigoid Due to Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

"Pemphigoid" is known as an adverse drug reaction of dipeptidyl peptidase-4 (DPP-4) inhibitors and their combination drugs (hereinafter referred to as "DPP-4 inhibitors"), which are antidiabetic drugs, and precaution has been in place in the Japanese package inserts, etc.

However, cases have been reported where pemphigoid, which occurred after the administration* of DPP-4 inhibitors, was exacerbated and led to patient's hospitalization as a result of continuing administration of DPP-4 inhibitors even after skin abnormalities, the initial symptoms of pemphigoid, were observed.

*Diverse periods of administration until onset of pemphigoid have been reported, ranging from early after initiation to several years.

If oedematous erythema accompanied by itching, blister, erosion, etc. are observed, and pemphigoid is suspected during the use of DPP-4 inhibitors, healthcare professionals should consult a dermatologist immediately and take appropriate measures, such as discontinuation of administration.

**[Typical case]**

Male in his 70s.
After 3 to 4 months of the initiation of sitagliptin phosphate hydrate, a blister appeared and resolved by itself repeatedly. Multiple blisters appeared and spread to the entire body 7 months after administration. The patient consulted a clinic 8 months after the administration. He was treated with oral drugs and topical drugs. However, his condition did not improve, and he consulted a hospital dermatologist. He was diagnosed with bullous pemphigoid, and he was admitted to the hospital. The symptoms improved with drug treatment. After the dose of prednisolone was tapered, he was temporarily discharged from the hospital 9 months after the administration. However, blisters recurred, and he was readmitted to the hospital with the confirmation of exacerbated blister formation. The dose of prednisolone was increased, but his condition did not improve. Plasma exchange therapy was conducted. Drug-induced bullous pemphigoid was suspected; therefore, administration of sitagliptin phosphate hydrate was discontinued. After the dose of prednisolone was tapered, he recovered from bullous pemphigoid, and he was discharged from the hospital 11 days after discontinuation of sitagliptin phosphate hydrate.

(Partially modified from Pharmaceuticals and Medical Devices Safety Information No.333)

**[Reference: Number of adverse drug reaction reports of pemphigoid due to DPP-4 inhibitors*1 and number of payments/non-payments in the Relief System*2 by FY]**

| FY | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|
| Number of adverse drug reaction reports (reports by companies) | 25 | 341 | 264 | 351 | 266 | 164 | 138 | 130 |
| Number of adverse drug reaction reports (reports by medical institutions) | 1 | 8 | 6 | 14 | 12 | 19 | 17 | 19 |
| Number of payments/non-payments in the Relief System | 0 | 1 | 3 | 3 | 6 | 5 | 12 | 6 |

*1: Adverse drug reactions reported to the PMDA as “pemphigoid” by MedDRA PT from marketing authorization holders or healthcare professionals (as of April 18, 2023)
*2: Cases for which eligibility for relief benefit under the adverse drug reaction term “bullous pemphigoid” was judged in the relevant FY

**[DPP-4 inhibitors marketed in Japan]**

| DPP-4 inhibitors | Brand name (marketing authorization holder) | DPP-4 inhibitors | Brand name (marketing authorization holder) |
|---|---|---|---|
| Preparations containing anagliptin | Suiny Tablets 100 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)<br>Metoana Combination Tablets LD, HD (Sanwa Kagaku Kenkyusho Co., Ltd.) | Preparations containing teneligliptin hydrobromide hydrate | Tenelia Tablets 20 mg, 40 mg, Tenelia OD Tablets 20 mg, 40 mg (Mitsubishi Tanabe Pharma Corporation)<br>Canalia Combination Tablets (Mitsubishi Tanabe Pharma Corporation) |
| Preparations containing alogliptin benzoate | Nesina Tablets 6.25 mg, 12.5 mg, 25 mg (Takeda Pharmaceutical Company Limited.)<br>Inisync Combination Tablets (Teijin Pharma Limited.)<br>Liovel Combination Tablets LD, HD (Teijin Pharma Limited.) | Trelagliptin succinate | Zafatek Tablets 25 mg, 50 mg, 100 mg (Takeda Pharmaceutical Company Limited) |
| Omarigliptin | Marizev Tablets 12.5 mg, 25 mg (MSD K.K.) | Preparations containing vildagliptin | Equa Tablets 50 mg (Novartis Pharma K.K.)<br>EquMet Combination Tablets LD, HD (Novartis Pharma K.K.) |
| Saxagliptin hydrate | Onglyza Tablets 2.5 mg, 5mg (Kyowa Kirin Co., Ltd.) | Preparations containing linagliptin | Trazenta Tablets 5 mg (Nippon Boehringer Ingelheim Co., Ltd.)<br>Tradiance Combination Tablets AP, BP (Nippon Boehringer Ingelheim Co., Ltd.) |
| Preparations containing sitagliptin phosphate hydrate | Glactiv Tablets 12.5 mg, 25 mg, 50 mg, 100 mg (Ono Pharmaceutical Co., Ltd.)<br>Januvia Tablets 12.5 mg, 25 mg, 50 mg, 100 mg (MSD K.K)<br>Sujanu Combination Tablets (MSD K.K) | | |

**About this information**

- PMDA Alert for Proper Use of Drugs communicates to healthcare providers 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.


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