



Summary of Investigation Results

Antidepressants (escitalopram oxalate, sertraline hydrochloride, duloxetine hydrochloride, milnacipran hydrochloride, vortioxetine hydrobromide)

January 10, 2024

Non-proprietary name

- a. Escitalopram oxalate
- b. Sertraline hydrochloride
- c. Duloxetine hydrochloride
- d. Milnacipran hydrochloride
- e. Vortioxetine hydrobromide

Brand name (marketing authorization holder)

- a. Lexapro Tablets 10mg, 20 mg (Mochida Pharmaceutical Co., Ltd.), and the others
- b. Jzoloft Tablets 25 mg, 50 mg, 100 mg, Jzoloft OD Tablets 25 mg, 50 mg, 100 mg (Viatris Pharmaceuticals Japan Inc.), and the others
- c. Cymbalta Capsules 20 mg, 30 mg (Shionogi & Co., Ltd.), and the others
- d. Toledomin Tablets 12.5 mg, 15 mg, 25 mg, 50 mg (Asahi Kasei Pharma Corporation), and the others
- e. Trintellix tablets 10mg, 20 mg (Takeda Pharmaceutical Company Limited.)

Japanese market launch

- a. Tablets 10 mg: August 2011
Tablets 20 mg; June 2019
- b. Tablets 25 mg, 50 mg: July 2006
Tablets 100 mg: August 2014

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- OD tablets 25 mg, 50 mg, 100 mg: December 2014
- c. April 2010
- d. Tablets 15 mg, 25 mg: October 2000
Tablets 12.5 mg, 50 mg: November 2008
- e. November 2019

Indications

- a. Depression/depressed state, social anxiety disorder
- b. • Depression/depressed state
 - Panic disorder
 - Post-traumatic stress disorder
- c. • Depression/depressed state
 - Pain accompanying the following diseases
Diabetic neuropathy
Fibromyalgia
Chronic lumbago
Osteoarthritis
- d., e. Depression/depressed state

Summary of revisions

- b.
 1. Precautions concerning blood tests should be added to the IMPORTANT PRECAUTIONS section.
 2. "Thrombocytopenia" should be added to the Clinically Significant Adverse Reactions section in ADVERSE REACTIONS.

Investigation results and background of the revision

Based on the Summary of the MID-NET® study on the risk of decreased platelet count of antidepressants* (appendix) and the post-marketing cases involving thrombocytopenia, the PMDA determined that sertraline hydrochloride has this risk.

The PMDA consulted with expert advisors regarding the appropriateness of the above-

mentioned PMDA's opinion, the causality assessment of the reported cases involving thrombocytopenia, and the necessity of taking safety measures regarding thrombocytopenia for the drugs noted above. As a result, taking into account the results of the MID-NET[®] study and the reported cases for which a causal relationship between sertraline hydrochloride and thrombocytopenia was reasonably possible, the MHLW/PMDA concluded that the PRECAUTIONS should be revised for sertraline hydrochloride, and that no measures were deemed necessary at this time for escitalopram oxalate, duloxetine hydrochloride, milnacipran hydrochloride and vortioxetine hydrobromide. Since no results have been obtained from the MID-NET[®] study which can completely rule out the risk of thrombocytopenia for the drugs noted above, for which taking safety measures are deemed unnecessary, it was determined appropriate to continue to carefully monitor the information that is being further accumulated.

Reference: Number of cases^{†‡} and patient mortalities involving thrombocytopenia reported in Japan and overseas

- a. One case has been reported in Japan to date. (A causal relationship between the drug and event could not be established for this case.)
No patient mortalities have been reported in Japan to date.
A total of 8 cases have been reported overseas to date. (A causal relationship between the drug and event could not be established for these cases.)
No patient mortalities have been reported overseas to date.
- b. A total of 4 cases have been reported in Japan to date (including 3 cases for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported in Japan to date.
A total of 3 cases have been reported overseas to date (including 1 case for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported overseas to date.
- c. No cases have been reported in Japan to date.
A total of 4 cases have been reported overseas to date (including 1 case for which a causal relationship between the drug and event was reasonably possible).
No patient mortalities have been reported overseas to date.



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d. No cases have been reported in Japan to date.

A total of 2 cases have been reported overseas to date. (A causal relationship between the drug and event could not be established for these cases.)

No patient mortalities have been reported overseas to date.

e. No cases have been reported in Japan to date.

No cases have been reported overseas to date.

*: Drugs for which no precaution for thrombocytopenia is included in the Clinically Significant Adverse Reactions section in ADVERSE REACTIONS of the electronic package inserts (escitalopram oxalate, sertraline hydrochloride, duloxetine hydrochloride, milnacipran hydrochloride, and vortioxetine hydrobromide) were investigated.

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

‡: Cases retrieved by the following conditions.

- Cases were retrieved by MedDRA ver.26.1 SMQ “haematopoietic thrombocytopenia (broad),” PT “immune thrombocytopenia,” PT “thrombotic thrombocytopenic purpura,” PT “vascular purpura,” PT “thrombocytopenic purpura,” and PT “purpura.”
- Cases that had both a platelet count greater than or equal to 75 000/mm³ (equivalent of grade 1 or lower by the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0) either before initiation of administration or prior to the onset of adverse reactions after initiation of administration and that had a platelet count less than 50 000/mm³ after initiation of administration (equivalent of grade 3 or higher by the CTCAE Version 5.0) were retrieved.

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).