



# Summary of Investigation Results

## Lomitapide mesilate, istradefylline

September 7, 2021

### Non-proprietary name

- a. Lomitapide mesilate
- b. Istradefylline

### Brand name (Marketing authorization holder)

- a. Juxtapid Capsules 5, 10, 20 mg (Recordati Rare Diseases Japan KK)
- b. Nouriasst Tablets 20 mg (Kyowa Kirin Co., Ltd.)

### Indications

- a. Homozygous familial hypercholesterolemia
- b. Improvement of wearing-off phenomenon in patients with Parkinson's disease being treated with preparations containing levodopa

### Summary of revisions

- a.
  1. "Istradefylline" should be removed from "Moderate CYP3A inhibitors" in the Contraindications for Co-administration section.
  2. "Istradefylline" should be added to "Weak CYP3A inhibitors" in the Precautions for Co-administration section.
- b.
  1. "CYP3A4" as well as "CYP3A5" in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section and INTERACTIONS section should be revised to "CYP3A."
  2. "Lomitapide mesilate" should be added to "Drugs that act as CYP3A substrates" in the Precautions for Co-administration section.

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### **Investigation results and background of the revision**

MHLW/PMDA, for the reasons as follows, considered that it was appropriate for istradefylline to be listed as a weak CYP3A inhibitor and concluded in consultation with expert advisors that revision of Precautions in the package inserts of lomitapide mesilate and istradefylline was necessary to list the co-administration of lomitapide mesilate and istradefylline under the Precautions for Co-administration section.

- The drug interaction guidelines of the U.S. FDA (Drug Development and Drug Interactions) list istradefylline as “Weak inhibitors” of CYP3A4.
- The AUC of atorvastatin when co-administered with istradefylline increased 1.54 fold in a drug interaction study of istradefylline 40 mg and atorvastatin, which is a CYP3A substrate.
- The AUC of midazolam when co-administered with istradefylline increased 1.67 fold in a PBPK modeling study that investigated the effects of istradefylline 40 mg on the pharmacokinetics of midazolam, which is a CYP3A substrate.

In addition, in view of the statement that istradefylline is metabolized by CYP3A4 and CYP3A5, together with the related description for lomitapide mesilate in the Precautions of their respective package inserts, MHLW/PMDA also considered it appropriate to revise “CYP3A4” as well as “CYP3A5” to “CYP3A” and concluded in consultation with expert advisors that revision of the package insert was necessary.

### **Number of cases and patient mortalities reported in Japan during the previous 3 fiscal years**

Cases of co-administration of lomitapide mesilate and istradefylline

No cases have been reported to date.

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).