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Pharmaceuticals and Medical Devices Agency

Revision of Precautions

Istradefylline

September 7, 2021

Therapeutic category

Antiparkinsonism agents

Non-proprietary name

Istradefylline

Safety measure

Precautions should be revised in the package insert.

Pharmaceuticals and Medical Devices Agency

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

Revision in line with the Instructions for Package Inserts of Prescription Drugs, PAB Notification No. 606 by the Director General of Pharmaceutical Affairs Bureau, MHW, dated April 25, 1997 (Old instructions): Revised language is underlined.

<table>
<tr><th>Current</th><th>Revision</th></tr>
<tr><td>
Precautions concerning Dosage and Administration
The blood concentration of this drug may increase in the following patients. The dosage should not exceed 20 mg once daily.

· Patients with moderate liver disorder
· Patients receiving drugs that strongly inhibit CYP3A4

Drug Interactions
This drug is mainly metabolized by CYP1A1, CYP3A4, and CYP3A5. In addition, this drug inhibits CYP3A4/5 and P-glycoprotein.

Precautions for Co-Administration
<table>
<tr><th>Drugs</th><th>Signs, Symptoms, and Treatment</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Drugs that strongly inhibit CYP3A4 (itraconazole, clarithromycin, etc.)</td><td>When co-administered at 40 mg with ketoconazole, the $AUC_{0-\infty}$ of this drug increased 2.47 fold</td><td>Co-administration with CYP3A4 inhibitors may inhibit metabolism and increase the blood concentration of this</td></tr>
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Precautions concerning Dosage and Administration
The blood concentration of this drug may increase in the following patients. The dosage should not exceed 20 mg once daily.

· Patients with moderate liver disorder
· Patients receiving drugs that strongly inhibit CYP3A

Drug Interactions
This drug is mainly metabolized by CYP1A1 and CYP3A (CYP3A4 and CYP3A5). In addition, this drug inhibits CYP3A and P-glycoprotein.

Precautions for Co-Administration
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<tr><th>Drugs</th><th>Signs, Symptoms, and Treatment</th><th>Mechanism and Risk Factors</th></tr>
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	and $t_{1/2}$ extended 1.87 fold. Effects of this drug may be enhanced. When co-administered with drugs that strongly inhibit CYP3A4, the dosage of this drug should not exceed 20 mg once daily.	drug.		fold and t1/2 extended 1.87 fold. Effects of this drug may be enhanced. When co-administered with drugs that strongly inhibit CYP3A, the dosage of this drug should not exceed 20 mg once daily.	drug.
Drugs that inhibit CYP3A4 (erythromycin, fluconazole, etc.)	Effects of this drug may be enhanced.		Drugs that inhibit CYP3A (erythromycin, fluconazole, etc.)	Effects of this drug may be enhanced.	
Drugs that induce CYP3A4 (rifampicin, carbamazepine, etc.) Food containing St. John's Wort	Effects of this drug may be attenuated.	Co-administration with CYP3A4 inducers may promote metabolism and decrease the blood concentration of this drug.	Drugs that induce CYP3A (rifampicin, carbamazepine, etc.) Food containing St. John's Wort	Effects of this drug may be attenuated.	Co-administration with CYP3A inducers may promote metabolism and decrease the blood concentration of this drug.
Drugs that act as	Effects of the drugs	Co-administration	Drugs that act as	Effects of the drugs	Co-administration

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CYP3A4 substrates (midazolam, atorvastatin, etc.)	listed on the left may be enhanced.	with this drug may inhibit metabolism and increase the blood concentration of the drugs that act as CYP3A4 substrates.	CYP3A substrates (midazolam, atorvastatin, lomitapide mesilate, etc.)	listed on the left may be enhanced.	with this drug may inhibit metabolism and increase the blood concentration of the drugs that act as CYP3A substrates.

Revision in line with the Instructions for Electronic Package Inserts of Prescription Drugs, etc. PSEHB Notification No. 0611-1 by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 11, 2021 (New instructions): Revised language is underlined.

Current	Revision
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION 7.2 The blood concentration of this drug may increase in the following patients. The dosage should not exceed 20 mg once daily. · Patients with moderate liver disorder · Patients receiving drugs that strongly inhibit CYP3A4 10. INTERACTIONS This drug is mainly metabolized by CYP1A1, CYP3A4, and CYP3A5. In addition, this drug inhibits CYP3A4/5 and P-	7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION 7.2 The blood concentration of this drug may increase in the following patients. The dosage should not exceed 20 mg once daily. · Patients with moderate liver disorder · Patients receiving drugs that strongly inhibit CYP3A 10. INTERACTIONS This drug is mainly metabolized by CYP1A1 and CYP3A (CYP3A4 and CYP3A5). In addition, this drug inhibits CYP3A and P-

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glycoprotein.

10.2 Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs that strongly inhibit CYP3A4 (itraconazole, clarithromycin, etc.)	Effects of this drug may be enhanced.	Co-administration with CYP3A4 inhibitors may inhibit metabolism and increase the blood concentration of this drug. The $AUC_{0-\infty}$ of this drug increased and $t_{1/2}$ extended when co-administered with ketoconazole.
Drugs that inhibit CYP3A4 (erythromycin, fluconazole, etc.)	Effects of this drug may be enhanced.	Co-administration with CYP3A4 inhibitors may inhibit metabolism and increase the blood concentration of this drug.
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glycoprotein.

10.2 Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs that strongly inhibit CYP3A (itraconazole, clarithromycin, etc.)	Effects of this drug may be enhanced.	Co-administration with CYP3A inhibitors may inhibit metabolism and increase the blood concentration of this drug. The $AUC_{0-\infty}$ of this drug increased and $t_{1/2}$ extended when co-administered with ketoconazole.
Drugs that inhibit CYP3A (erythromycin, fluconazole, etc.)	Effects of this drug may be enhanced.	Co-administration with CYP3A inhibitors may inhibit metabolism and increase the blood concentration of this drug.
Drugs that induce	Effects of this drug	Co-administration

CYP3A4 (rifampicin, carbamazepine, etc.) Food containing St. John's Wort	may be attenuated.	with CYP3A4 inducers may promote metabolism and decrease the blood concentration of this drug.	CYP3A (rifampicin, carbamazepine, etc.) Food containing St. John's Wort	may be attenuated.	with CYP3A inducers may promote metabolism and decrease the blood concentration of this drug.
Drugs that act as CYP3A4 substrates (midazolam, atorvastatin, etc.)	Effects of the drugs listed on the left may be enhanced.	Co-administration with this drug may inhibit metabolism and increase the blood concentration of the drugs that act as CYP3A4 substrates.	Drugs that act as CYP3A substrates (midazolam, atorvastatin, lomitapide mesilate, etc.)	Effects of the drugs listed on the left may be enhanced.	Co-administration with this drug may inhibit metabolism and increase the blood concentration of the drugs that act as CYP3A substrates.

Note: Designated as a drug requiring preparation of a Drug Guide for Patients

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