**Prostaglandin E<sub>1</sub> Preparation**

**PALUX® Injection 5 µg**

**PALUX® Injection 10 µg**

(Alprostadil Injection, JP*)

**Regulatory classification:** Powerful drug, prescription drug  
(Caution: Use only as directed by a physician)

**Storage:** Store in a light-resistant container at 5 °C or below. Do not freeze.

**Expiration date:** Indicated on the package (14 months)

**WARNING**

The administration of PALUX to neonates with ductus arteriosus-dependent congenital heart disease may result in apnea attack; therefore, PALUX should be used where, and only where, adequate ventilatory support is provided.

**CONTRAINDICATIONS**

PALUX is contraindicated in the following patients.  
- Patients with serious heart failure: Exacerbation of heart failure has been reported to be associated with alprostadil.  
- Patients with hemorrhage (intracranial hemorrhage, digestive tract hemorrhage, hemoptysis, etc.): Pre-existing hemorrhage may be aggravated by alprostadil.  
- Women known or suspected to be pregnant. (See PRECAUTIONS, 6. Use during Pregnancy, Delivery, or Lactation)  
- Patients with known hypersensitivity to alprostadil or any other component of the product.

**INDICATIONS, DOSAGE, AND ADMINISTRATION**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of ulcers of the extremities and pain at rest associated with chronic arterial occlusion (Buerger’s disease and atherosclerosis obliterans)</td>
<td>The usual adult dosage of PALUX is 1 to 2 mL (5 to 10 µg of alprostadil) once a day. This product may be administered either by continuous intravenous infusion after dilution or by slow intravenous bolus injection (without dilution or after dilution with a small volume of infusion fluid). The dosage may be adjusted depending on the patient’s symptoms.</td>
</tr>
<tr>
<td>Improvement of skin ulcers associated with progressive systemic sclerosis or systemic lupus erythematosus</td>
<td></td>
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<tr>
<td>Improvement of skin ulcers in diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Improvement of subjective symptoms caused by peripheral blood flow disturbances in vibration disease</td>
<td></td>
</tr>
<tr>
<td>Recovery from peripheral circulatory disorders and/or peripheral nerve/motor dysfunction in vibration disease</td>
<td></td>
</tr>
<tr>
<td>For keeping the ductus arteriosus patent in ductus-dependent congenital heart disease</td>
<td>PALUX should be diluted with infusion fluid and administered by continuous intravenous infusion. An initial dose of 5 ng/kg/min of alprostadil is recommended. Subsequent doses may be adjusted depending on the patient’s symptoms: use the lowest effective dose.</td>
</tr>
<tr>
<td>Enhancement of contrast in superior mesenteric arterial portography</td>
<td>For adults, usually 1 mL of PALUX (5 µg of alprostadil) is diluted to 10 mL with physiological saline and injected into the superior mesenteric artery over 3 to 5 seconds through a catheter, 30 seconds before injection of a contrast medium.</td>
</tr>
</tbody>
</table>

**FORMULATIONS**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>PALUX Injection 5 µg</th>
<th>PALUX Injection 10 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume per ampoule</td>
<td>1 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>Active ingredient</td>
<td>Alprostadil</td>
<td>5 µg</td>
</tr>
<tr>
<td>Inactive ingredients</td>
<td>Purified soybean oil</td>
<td>100 mg</td>
</tr>
<tr>
<td></td>
<td>Highly purified egg yolk lecithin</td>
<td>18 mg</td>
</tr>
<tr>
<td></td>
<td>Oleic acid</td>
<td>2.4 mg</td>
</tr>
<tr>
<td></td>
<td>Concentrated glycerin</td>
<td>22.1 mg</td>
</tr>
<tr>
<td></td>
<td>Sodium hydroxide</td>
<td>As needed</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Lipid microspheres</td>
<td>Injectable suspension (in ampoule form)</td>
</tr>
<tr>
<td>Description</td>
<td>Slightly viscous, white, milky suspension with characteristic odor</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>4.5–6.0</td>
<td></td>
</tr>
<tr>
<td>Osmotic pressure ratio</td>
<td>Approximately 1 (to physiological saline)</td>
<td></td>
</tr>
</tbody>
</table>

* JP: The Japanese Pharmacopoeia

**Standard Commodity Classification No. of Japan**

87219

**Current approval No.**

21300AMZ00688000 (September 2001)

21300AMZ00687000 (September 2001)

**Marketed in Japan**

October 1988

October 1988

**Expiration date:** Indicated on the package

**Second reexamination approved**

December 2008

**NHI: National Health Insurance**
Special Precautions for Dosage and Administration

- PALUX should not be mixed with other therapeutic agents (except infusion fluid) before and during injection or infusion. Avoid dilution with plasma expanders (dextran, gelatin, etc.). When PALUX is administered concomitantly with other drug(s) by continuous infusion, a separate infusion line for sole use with this product must be provided to prevent any possible aggregation (drug incompatibility) within the line.
- To avoid any possible aggregation or creaming, do not mix PALUX directly with contrast medium for superior mesenteric arterial portography. If a single line is used for sequential infusions of PALUX and a contrast medium, the line should be flushed out with physiological saline between infusions of this product and the contrast medium.

PRECAUTIONS

1. Special Precautions for Use

PALUX should be administered with caution in the following patients.

(1) Patients with heart failure: A tendency toward exacerbation of heart failure may develop.
(2) Patients with glaucoma or ocular hypertension: A further increase in intraocular pressure is possible.
(3) Patients with a current or past history of gastric ulcer: Gastric hemorrhage may occur with the use of this product.
(4) Patients with interstitial pneumonia: Pre-existing interstitial pneumonia may be exacerbated by alprostadil therapy.
(5) Patients with renal failure: Renal failure may worsen with the use of this product.
(6) Patients with bleeding tendencies: The risk of bleeding may be increased with the use of this product.
(7) Patients receiving treatment with anticoagulants (e.g., warfarin), platelet function inhibitors (e.g., aspirin, ticlopidine, cilostazol), or thrombolytics (e.g., urokinase).
(8) Patients with severe esophageal varices when this product is used in superior mesenteric arterial portography: Portal hypertension may occur.

2. Important Precautions

(1) When PALUX is used for the treatment of chronic arterial occlusion (Buerger’s disease and atherosclerosis obliterans), progressive systemic sclerosis, systemic lupus erythematosus, vibration disease, or skin ulcers in diabetes mellitus, the following should be taken into consideration:
   - It is important to note that treatment with this product is a symptomatic therapy and its discontinuation may result in relapse of the symptoms.
   - Since heart failure, pulmonary edema, and/or pleurisy effusion may occur, cardiovascular parameters (blood pressure, heart rate, etc.) should be closely monitored. If any abnormalities (palpitations, chest distress, dyspnea, edema, etc.) are observed, PALUX should be discontinued and appropriate therapeutic action taken. Because elderly patients are more likely to have decreased cardiovascular and other physiological functions, caution should be exercised in the administration of this product, while maintaining close observation of the patient.
(2) When PALUX is used for the treatment of skin ulcers in diabetes mellitus, the following should be taken into consideration:
   - This product is not recommended as the first choice for treatment. Treat the patient with standard antidiabetic therapy (e.g., diet, exercise, oral hypoglycemic agents, insulin) before treatment with this product.
   - Treatment with this product should be considered in patients in whom a satisfactory clinical response to external (topical) application of anti-diabetic-ulcer drug is not to be expected.
   - Clinical course should be monitored closely during therapy; if a 28-consecutive-day treatment with this product fails to elicit a response, the medication should be discontinued and another treatment strategy implemented.

(3) When PALUX is used for superior mesenteric arterial portography, the following should be taken into consideration:
   - In the presence of cirrhosis, sufficient contrast may not be obtained.

(4) When PALUX is used in neonates with ductus-dependent congenital heart disease, the following should be taken into consideration:
   - Because the recipients of this product are newborn babies with serious medical problems, careful administration is necessary under close supervision. If any abnormalities are observed, take appropriate measures, such as withdrawal of the product, reduction of infusion rate, and/or the like.
   - Overdosage may result in an increased incidence of adverse reactions. Maintain the lowest effective dose.
   - Cortical proliferation of the long bones has been reported following long-term infusions of alprostadil in neonates. The patient should be carefully monitored and treatment with the product should be limited to the minimum period necessary to achieve the desired results.

3. Drug Interactions

Precautions for co-administration:
Caution should be exercised when considering the concomitant use of PALUX with the following drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Signs, symptoms, and treatment</th>
<th>Mechanism and risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants (Warfarin etc.)</td>
<td>Bleeding tendency may be increased.</td>
<td>Since alprostadil inhibits platelet aggregation, concomitant use may enhance antiplatelet effects.</td>
</tr>
<tr>
<td>Platelet function inhibitors (Aspirin, ticlopidine, cilostazol, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolytics (Urokinase etc.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Adverse Reactions

When administered to adults

(1) Chronic arterial occlusion (Buerger’s disease and atherosclerosis obliterans), progressive systemic sclerosis, systemic lupus erythematosus, vibration disease, and skin ulcers in diabetes mellitus

Results from pre-approval and post-marketing clinical trials
A total of 143 adverse drug reactions (ADRs) were encountered in 103 (12.03%) of 856 patients treated with the product. The most common ADRs included vascular pain in 33 cases (3.86%), abnormal hepatic function in 16 cases (1.87%), injection site redness in 11 cases (1.29%), and vasculitis in 9 cases (1.05%). [Data submitted for extension of the range of indications]
Results from post-marketing clinical experience studies
A total of 460 ADRs were encountered in 269 (4.00%) of 6,730 patients treated with the product. The most common ADRs included nausea in 5 cases (0.53%), abdominal pain in 7 cases (0.52%), and diarrhea in 14 cases (0.21%). [Data submitted for the first reexamination]

(2) Superior mesenteric arterial portography
Results from post-marketing clinical trials
A total of 18 ADRs were encountered in 14 (3.26%) of 429 patients treated with the product. The most common ADRs included apnea attack in 11 cases (12.36%), diarrhea in 7 cases (8.13%), and abdominal pain in 5 cases (6.00%). [Data submitted for approval]

Results from post-marketing clinical experience studies
A total of 180 ADRs were encountered in 122 (23.64%) of 516 patients treated with the product. The most common ADRs included nausea in 12 cases (2.36%), abdominal pain in 18 cases (3.53%), and pyrexia in 36 cases (7.07%). [Data submitted for the second reexamination]

When administered to neonates
Results from pre-approval clinical trials
A total of 34 ADRs were encountered in 26 (4.00%) of 673 patients treated with the product. The most common ADRs included apnea attack in 11 cases (13.65%), diarrhea in 7 cases (9.23%), pyrexia in 5 cases (6.25%), and hyponatremia in 5 cases (6.25%). [Data submitted for approval]

Results from post-marketing clinical experience studies
A total of 180 ADRs were encountered in 122 (23.64%) of 516 patients treated with the product. The most common ADRs included nausea in 12 cases (2.36%), abdominal pain in 18 cases (3.53%), and pyrexia in 36 cases (7.07%). [Data submitted for the first reexamination]

(1) Clinically significant adverse reactions
1) Shock, anaphylactoid reaction (incidence unknown): Since shock or anaphylactoid reaction may occur, patients should be closely monitored. If any abnormalities (urticaria, laryngeal edema, dyspnea, cyanosis, decreased blood pressure, etc.) are observed, PALUX should be discontinued and appropriate therapeutic action taken.

2) Loss of consciousness (incidence unknown): Since transient loss of consciousness may occur associated with a decrease in blood pressure, patients should be closely monitored. If any abnormalities are observed, PALUX should be discontinued and appropriate therapeutic action taken.

3) Heart failure, pulmonary edema (incidence unknown): Heart failure (including its aggravation), pulmonary edema, and/or pleural effusion may occur. If any abnormalities (palpitations, chest distress, dyspnea, edema, etc.) are observed, PALUX should be discontinued and appropriate therapeutic action taken. (See 2. Important Precautions)

4) Interstitial pneumonia (incidence unknown): Interstitial pneumonia (including its aggravation) may occur. If any abnormalities (pyrexia, cough, dyspnea, abnormal chest X-ray, etc.) are observed, PALUX should be discontinued and appropriate measures (e.g., corticosteroid therapy) instituted.

5) Myocardial infarction (incidence unknown): Since myocardial infarction may occur, patients should be closely monitored. If any abnormalities (chest pain, chest pressure sensation, abnormal electrocardiogram, etc.) are observed, PALUX should be discontinued and appropriate therapeutic action taken.

6) Cerebral hemorrhage, digestive tract hemorrhage (incidence unknown): Since cerebral hemorrhage and/or digestive tract hemorrhage may occur, patients should be closely monitored. If any abnormalities are observed, PALUX should be discontinued and appropriate therapeutic action taken.

7) Agranulocytosis, leukopenia, thrombocytopenia (incidence unknown): Since agranulocytosis, leukopenia, and/or thrombocytopenia may occur, patients should be closely monitored. If any abnormalities are observed, PALUX should be discontinued and appropriate therapeutic action taken.

8) Hepatic dysfunction, jaundice (incidence unknown): Since hepatic function disorders with elevated liver enzyme levels etc. and/or jaundice may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as withdrawal of PALUX should be taken.

9) Apnea attack (12.23%): Since apnea attack may occur in neonates treated with PALUX, patients should be closely monitored. If apnea does occur, take appropriate measures, such as reduction of the dosage, reduction of the infusion rate, withdrawal of the product, and/or the like.

(2) Other adverse reactions
1) The following ADRs may occur. If any abnormalities related to these ADRs are observed, appropriate measures, such as reduction of the dosage, withdrawal of PALUX, and/or the like, should be instituted.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Incidence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>≥ 0.1%</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>Nausea, abdominal pain, vomiting, diarrhea, abdominal distension/discomfort</td>
<td>Anorexia, constipation, feeling of swollen mouth</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Decreased blood pressure*, vasculitis, flushed face, chest tightness*</td>
<td>Flushing, chest pain*, palpitations, tachycardia</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Cough, dyspnea, asthma*</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuro-psychiatric</td>
<td>Pyrexia, headache</td>
<td>Dizziness, malaise, numbness</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Rash, itching</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>Vascular pain, redness</td>
<td>Stiffness, itching</td>
</tr>
<tr>
<td>Incidence</td>
<td>Incidence</td>
<td>Incidence</td>
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<tr>
<td>-----------</td>
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<td>-----------</td>
</tr>
<tr>
<td>1% &gt;</td>
<td>≥ 0.1%</td>
<td>&lt; 0.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding tendencies</th>
<th>Hemorrhage* (epistaxis, bleeding of ocular fundus, conjunctival hemorrhage, subcutaneous hemorrhage, hematuria, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Others</td>
<td>Feeling hot, Pain in extremity (including its aggravation), feeling bad, edema, reduced visual acuity, alopecia, Hyponatremia, swelling of limbs</td>
</tr>
</tbody>
</table>

* If any of these symptoms develop, PALUX should be discontinued.

2) When PALUX is administered to a neonate, the patient should be carefully monitored: not only ADRs described above in subsection 1) but also hypochloremia (1.32%), hypocalcemia (0.50%), and/or hyperlipidemia (0.17%) may occur.

5. Geriatric Use
Because elderly patients are more likely to have decreased physiological functions, caution should be exercised in the administration of this product (e.g., reduction of dosage).

6. Use during Pregnancy, Delivery, or Lactation
PALUX is contraindicated in women known or suspected to be pregnant; PGE1® has been reported to exhibit uterotonic activity in vivo (rats) and in vitro, and the safety of this product in pregnant women has not been established.

7. Pediatric Use
The safety of PALUX in pediatric patients except babies with duc tus-dependent congenital heart disease has not been established.

8. Precautions concerning Use
(1) Administration directions
1) If any adverse reactions occur, take appropriate measures, such as withdrawal of the product, adjustment of the infusion rate, and/or the like.
2) When Lipo-PGE1® (0.1–1.0 µg/kg as PGE1) was injected into the anterior mesenteric artery in dogs, intestinal movements were enhanced 1 minute after dosing. Since the enhanced intestinal movements may possibly interfere with angiography, PALUX should be injected 30 seconds before injection of a contrast medium when used in superior mesenteric arterial portography.

9. Other Precautions
Cerebral infarction has been reported in patients receiving PALUX.

PHARMACOKINETICS

1. Pharmacokinetics in humans (healthy adults)
Healthy adults were infused intravenously with PALUX, and the PGE1 levels in their blood were measured using the RIA2 antibody method. However, reliable values could not be obtained because the PGE1 levels were too low, presumably due in part to rapid metabolic breakdown.

2. Pharmacokinetics in animals (rats, dogs)

(1) Blood levels
Following intravenous administration of 3H-Lipo-PGE1® (5 µg/kg as PGE1) to rats, the whole-blood and plasma radioactivity levels were 24.74 and 39.82 ng-eq PGE1/mL, respectively, at 30 seconds after the injection. They subsequently decreased in 4-phase fashion. The radioactivity levels at 8 hours were less than 1% of those at 30 seconds. Similar time courses of decrease in the whole-blood and plasma radioactivity levels were observed in dogs.

* PGE1: Prostaglandin E1; synonym for alprostadil, the active ingredient of PALUX
Lipo-PGE1: PGE1 incorporated in lipid microspheres; the same formulation as PALUX
3H-Lipo-PGE1: 3H-PGE1 incorporated in lipid microspheres
PGE1-CD: PGE1 clathrated in alpha-cyclodextrin (alpha-CD); also known as alprostadil alfadex
3H-PGE1-CD: 3H-PGE1 clathrated in alpha-CD
PHARMACOLOGY

1. Vasodilating effect

The vasodilatory activity was measured and compared between Lipo-PGE1 and PGE1-CD (see footnote on Page 4).

(1) In normal rats and streptozotocin-induced diabetic rats, Lipo-PGE1 increased blood flow more potently than did PGE1-CD. The blood flow-enhancing activity of Lipo-PGE1 was more potent in diabetic rats than in normal rats.

(2) In dogs, Lipo-PGE1 increased blood flow more potently and efficaciously than did PGE1-CD, at doses where no marked hypotensive response was induced.

(3) In streptozotocin-induced diabetic rats and spontaneously hypertensive rats (SHRs), Lipo-PGE1 showed a more potent hypotensive action than did PGE1-CD. This difference in potency between Lipo-PGE1 and PGE1-CD increased with the progress of pathological conditions in diabetic rats and the chronicity of hypertension in SHRs.

(4) In newborn rats, Lipo-PGE1 exerted more potent and longer lasting vasodilatory effects on the ductus arteriosus than did PGE1-CD.

2. Inhibitory effect on platelet aggregation

(1) Lipo-PGE1 was more active and longer acting than PGE1 in terms of inhibitory effects on ADP-induced thrombus formation in intact and electrically damaged microvessels of hamster cheek pouch.

(2) Lipo-PGE1 was more potent than PGE1-CD in terms of inhibitory effects on the progression of lesions in laurate-induced peripheral arterial occlusive disease in rats.

(3) In ex vivo experiments in rats, Lipo-PGE1 increased the platelet cyclic AMP content and thereby inhibited platelet aggregation more potently than did PGE1-CD.

3. Mechanism of action

(1) The active ingredient of PALUX is PGE1, which is incorporated in lipid microspheres. The lipid microspheres act as drug carriers, presumably contributing to the following characteristic/favorable effects of Lipo-PGE1.

1) In experiments in which ADP-induced thrombus formation was evaluated in electrically damaged arterioles of hamster cheek pouch, Lipo-PGE1 demonstrated more potent and longer lasting inhibitory effects on thrombus formation when administered after, rather than before, vascular damage to the microcirculation.

2) Following intravenous administration of Lipo-PGE1, electron microscopy showed that the lipid microspheres adhered to the endothelial cell surface and were taken up into the cells by endocytosis in the mesenteric arteriole and capillary vessels of normal and diabetic rats and, interestingly, in the lesioned, but not normal, areas of the thoracic aorta of SHRs.

3) The radioactivity distributed in the affected blood vessels (thoracic aorta) was significantly higher in the ²H-Lipo-PGE1-injected SHRs than in the ³H-PGE1-injected SHRs.

4) When rats were administered intravenously with ⁴H-Lipo-PGE1 or ⁴H-PGE1-CD, the ratio of unchanged ⁴H-PGE1 to the total radioactivity in the plasma was significantly higher in the ⁴H-Lipo-PGE1-injected rats than in the ⁶H-PGE1-CD-injected rats.
The following effects on superior mesenteric arterial portography have been observed.

1) Following injection of Lipo-PGE1 into the anterior mesenteric artery in dogs, portal blood flow increased in a dose-dependent manner.

2) The intra-mesenteric arterial injection of Lipo-PGE1 to dogs also resulted in:
   - a decrease in the amount of leakage (reflux) of the contrast medium into the aorta,
   - a shorter period of time needed for the contrast medium to reach the main portal vein,
   - an increase in the maximum diameter of the portal vein in the portogram, and
   - a higher resolution for detecting the portal branches in the portogram.

**DESCRIPTION**

Generic name: Alprostadil

Chemical name:

\[ 7-\{(1R, 2R, 3R)-3-Hydroxy-2-\{(1E, 3S)-3-hydroxyoct-1-en-1-yl\}-5-oxocyclopentyl\} heptanoic acid \]

Structural formula:

![Structural formula of Alprostadil](image)

Molecular formula: \( C_{20}H_{34}O_5 \)
Molecular weight: 354.48

Physicochemical properties:

- Alprostadil occurs as white crystals or a crystalline powder. It is freely soluble in 99.5% ethanol and tetrahydrofuran, slightly soluble in acetonitrile, and practically insoluble in water.
- Melting point: 114–118 °C

**PACKAGING**

<table>
<thead>
<tr>
<th>Product</th>
<th>Package Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALUX Injection 5 µg</td>
<td>Pack with 1, 5, or 10 ampoules (1 mL/ampoule)</td>
</tr>
<tr>
<td>PALUX Injection 10 µg</td>
<td>Pack with 1, 5, or 10 ampoules (2 mL/ampoule)</td>
</tr>
</tbody>
</table>

**REFERENCES**

1) Nakura K et al.: *Kiso to Rinshou*, 20(10), 5195 (1986)
2) Ezumi Y et al.: *Kiso to Rinshou*, 20(9), 4399 (1986)
5) Toyota R et al.: *Igaku no Ayumi*, 155(11-12), 749 (1990)
8) Monma K et al.: *Shounika Rinshou*, 39(10), 2441 (1986)

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Revised in June 2009: No changes to the WARNING, CONTRAINDICATIONS, or PRECAUTIONS sections