Revised: July 2010 (13th version)

Standard Commodity Classification No. of Japan
87219

- Oral prostaglandin E_1 derivative preparation -

OPALMON® Tablets 5 μg

< Limaprost alfadex tablets >

Prescription drug

Storage
Store in a tight container with desiccant at room temperature.

Expiration date
The expiration date is indicated on the outer package (3 years).

Approval No.	21700AMZ00066
Date of listing in the NHI reimbursement price	June 2005
Date of initial marketing in Japan	July 2005
Date of latest reexamination	December 2009
Date of latest approval of indications	April 2001 (Opalmon® Tablets)

Caution - Use only pursuant to the prescription of a physician, etc

CONTRAINDICATIONS (OPALMON® is contraindicated in the following patients.)
Pregnant women or women who may possibly be pregnant. (See "Use during Pregnancy, Delivery or Lactation".)

DESCRIPTION

1. Composition

Brand name	OPALMON® Tablets 5 μg
Ingredient/content (Content per tablet)	limaprost 5 μg of limaprost alfadex
Inactive ingredient	Dextran 40, Dextrin , Corn starch, Light anhydrous silicic acid, Stearic acid, Lactose hydrate
Dosage form	White plain tablets

2. Product description

Appearance	**Face**	
	Back	
	Edge	
Diameter (mm)		6.5
Thickness (mm)		2.8
Weight (mg)		about 100
Identification code		ono 201

INDICATIONS

1. Improvement of various ischemic symptoms such as ulcer, pain and feeling of coldness associated with thromboangiitis obliterans
2. Improvement of subjective symptoms (pain and numbness of lower legs) and gait ability associated with acquired lumbar spinal canal stenosis (in patients with bilateral intermittent claudication showing normal SLR test result)

DOSAGE AND ADMINISTRATION

1. Improvement of various ischemic symptoms such as ulcer, pain and feeling of coldness associated with thromboangiitis obliterans

The usual adult dosage for oral use is 30 μg of limaprost daily in three divided doses.

2. Improvement of subjective symptoms (pain and numbness of lower legs) and gait ability associated with acquired lumbar spinal canal stenosis (in patients with bilateral intermittent claudication showing normal SLR test result)

The usual adult dosage for oral use is 15 μg of limaprost daily in three divided doses.

PRECAUTIONS

1. Careful Administration (OPALMON® should be administered with care in the following patients.)

(1) Patients with bleeding tendency [Bleeding may be accelerated.]
(2) Patients under treatment with antiplatelet agent, thrombolytic agent or anticoagulant (See "Drug Interactions")

2. Important Precautions

(1) The administration with OPALMON® should not be continued aimlessly in patients with lumbar spinal canal stenosis. The progress of symptoms should be observed.
(2) The efficacy of this product has not been established in patients with severe lumbar spinal canal stenosis where operation is judged to be adequate.

3. Drug Interactions

Precautions for coadministration (OPALMON® should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Antiplatelet agents Aspirin Ticlopidine Cilostazole **Thrombolytic agents** Urokinase **Anticoagulants** Heparin Warfarin	Co-administration with these drugs may accelerate bleeding tendency. The patient should be carefully monitored and measures such as adjusting the dose should be taken.	This drug inhibits the platelet aggregation, and may enhance the effect by co-administering the drugs having similar effects.

4. Adverse Reactions

<Improvement of various ischemic symptoms such as ulcer, pain and feeling of coldness associated with thromboangiitis obliterans>

Two hundred and forty nine adverse reactions to OPALMON®, including abnormal laboratory test values, were observed in 184 (4.0%) of 4,582 patients evaluated in the investigation conducted up to the time of approval and in the post-marketing survey. The major adverse reactions were diarrhea in 49 patients (1.1%), retching·nausea·vomiting in 22 patients (0.5%), flushing·hot flushes in 22 patients (0.5%), rash in 17 patients (0.4%), abdominal discomfort·epigastric discomfort in 18 patients (0.4%), abdominal pain·epigastric pain in 15 patients (0.3%), headache·heaviness of head in 14 patients (0.3%), hepatic function abnormalities such as increases in AST(GOT)·ALT(GPT) in 12 patients (0.3%), anorexia in 10 patients (0.2%), etc. (At the end of the re-examination period)

<Improvement of subjective symptoms (pain and numbness of lower legs) and gait ability associated with acquired lumbar spinal canal stenosis (in patients with bilateral intermittent claudication showing normal SLR test result)>

Fifty four adverse reactions to OPALMON®, including abnormal laboratory test values, were observed in 34 (9.1%) of 373 patients evaluated in the investigation conducted up to the time of approval. The major adverse reactions were stomach discomfort in 8 patients (2.1%), rash in 6 patients (1.6%), headache·heaviness of head in 4 patients (1.1%), diarrhea in 4 patients (1.1%), anemia in 3 patients (0.8%), etc. (At the time of approval)

One hundred sixty nine (169) adverse reactions to this product, including abnormal laboratory test values, were observed in 136 (5.8%) of the 2,327 patients evaluated in the post-marketing Drug Use Investigation. The major adverse reactions were stomach·abdominal discomfort in 34 patients (1.5%), abdominal pain in 13 patients (0.6%), diarrhea in 10 patients (0.4%), headache in 10 patients (0.4%), nausea in 7 patients (0.3%) and heartburn in 7 patients (0.3%), etc. (At the end of the re-examination)

(1) Clinically significant adverse reactions

1) Hepatic function disorder or jaundice

Hepatic function disorder or jaundice (both incidences unknown) accompanied by remarkably increased AST(GOT)·ALT(GPT) may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate therapeutic measures such as discontinuing the administration should be taken.

(2) Other adverse reactions

	1%> ≥0.1%	<0.1%	Incidence Unknown
Hypersensitivity Note 1)	Rash, pruritus, etc.	Urticaria	Photosensitivity
Bleeding tendency Note 2)		Hemorrhage	
Hematologic		Anemia, thrombocytopenia	
Gastrointestinal	Diarrhea, nausea, Abdominal discomfort, abdominal pain, anorexia, heartburn	Vomiting, abdominal distension, thirst, stomatitis	Numbness of tongue
Hepatic	Hepatic function abnormalities such as increases in AST(GOT) ·ALT(GPT)		
Cardiovascular	Palpitation	Tachycardia, hypotension, cyanosis in the extremities, hypertension	
Psychoneurologic	Headache, dizziness	Numbness, sleepiness, insomnia	
Others	Flushing, hot flushes,	Malaise, chest pain, chest discomfort, pain in extremities, edema, breast swelling, shivering, hypertrichosis in the lower extremities, taste abnormality	

The ADR classified into “Incidence Unknown” is the one collected from spontaneous reports.

Note

1) If such symptoms are observed, appropriate therapeutic measures such as discontinuing administration should be taken.
2) The patient should be carefully monitored. If any abnormality is observed, administration should be discontinued.

5. Use during Pregnancy, Delivery or Lactation

This product should not be administered in pregnant women or in women who may possibly be pregnant. [In animal studies (intravenous administration of this drug in pregnant monkeys and rats), an uterine contractile effect has been reported[1)] and the safety of this product for use during pregnancy in human has not been established.]

6. Pediatric Use

The safety of this product in low birth weight infants, neonates, nursing infants, infants or children has not been established (no clinical experience).

7. Overdosage

This product has been recognized to cause a transient decrease in blood pressure at large doses (30 - 40 μg/dose) in healthy adults.[2)]

8. Precautions concerning Use

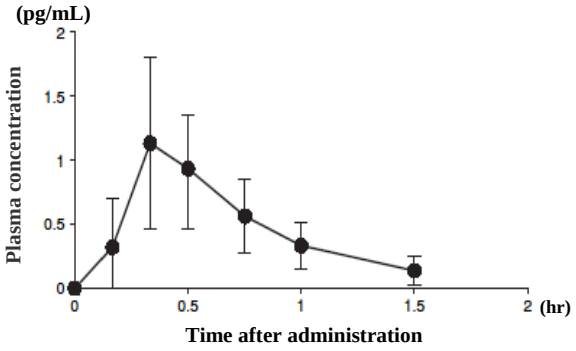
Precautions regarding dispensing:

For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the product from the package prior to use. (It has been reported that if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa resulting in severe complications such as mediastinitis.)

PHARMACOKINETICS

(1) Blood concentration

When limaprost was orally administered to 116 healthy adults in fasting condition at a single dose of 5 μg, the plasma concentration reached a maximum of 1.26 pg/mL 0.42 hours after administration and decreased with a half-life of 0.45 hours. [3)]



T_{max} (hr)	C_{max} (pg/mL)	$AUC_{0-\infty}$ (pg·hr/mL)	$T_{1/2}$ (hr)
0.42 ± 0.12	1.26 ± 0.63	0.880± 0.373	0.45 ± 0.18

Data presented are means ± S.D., n=115 for AUC and T1/2

(2) Metabolism

Limaprost was metabolized by undergoing β-oxidation at α-chain, oxidation at the terminal of ω-chain, isomerization of a cyclopentene ring or reduction of a carbonyl group at C-9. [4)]

Limaprost did not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (*in vitro*) .[5)]

(3) Protein binding

The protein binding rate to human plasma at the concentration of 0.023 mM was 95.8% (*in vitro*, ultrafiltration method). [4)]

(4) (Reference) Absorption and excretion in animals (rats)

When [11β-^{3}H] limaprost alfadex was orally given to rats, 90 to 95% of the drug was absorbed, and 75 to 80% of the dose was excreted into bile. About 30% of the dose was excreted into urine and about 70% into feces within 72 hours, after circulating enterohepatically.[6)]

CLINICAL STUDIES

1. Improvement of various ischemic symptoms such as ulcer, pain and feeling of coldness associated with thromboangiitis obliterans

1) The usefulness of OPALMON® in patients with thromboangiitis obliterans was demonstrated in a double-blind comparative study.[7)]

2) OPALMON® has been shown to improve various ischemic symptoms such as ulcer, pain and feeling of coldness associated with thromboangiitis obliterans, with an overall improvement rate of 56% (77/138 patients in clinical studies including double-blind comparative studies.[8)]

2. Improvement of subjective symptoms (pain and numbness of lower legs) and gait ability associated with acquired lumbar spinal canal stenosis (in patients with bilateral intermittent claudication showing normal SLR test result)

(1) The usefulness of OPALMON® in patients with lumbar spinal canal stenosis was demonstrated in double-blind comparative studies.[9)]

(2) The improvements o the subjective symptoms (pain and numbness of lower legs) and gait ability associated with acquired lumbar spinal canal stenosis (in patients with bilateral intermittent claudication showing normal SLR test result) were demonstrated in patients treated for six weeks in clinical studies including double-blind comparative studies, and an overall improvement rate was 56% (94/168 patients).[10)]

PHARMACOLOGY

1. Pharmacological effects

(1) Improving effect on peripheral circulatory disorder

In the experimental models with peripheral (hind limbs) circulatory disorder induced by injection of lauric acid to the femoral artery and with peripheral (tail) circulatory disorder induced by subcutaneous injection of adrenaline and ergotamine tartrate, limaprost alfadex inhibits the development of ischemic lesion (in rats).[11)]

(2) Increasing effects on blood flow and cutaneous temperature

1) Limaprost alfadex increases femoral arterial blood flow and cutaneous blood flow in the hind limbs and elevates cutaneous temperature in the hind limbs. The effect of increasing blood flow is not affected by lumbar sympathectomy (in dogs).[12)]

2) OPALMON®, when orally administered in patients with thromboangiitis obliterans, increases cutaneous temperature in the extremities (the dorsum and planta of the foot).[13)]

(3) Effect on platelets

1) Inhibitory effect on platelet adhesiveness

a) OPALMON®, when orally administered in patients with thrombotic diseases, decreases platelet adhesiveness.[14)]

b) Limaprost alfadex inhibited platelet adhesiveness with the 50% inhibitory concentration of 0.186

ng/mL of limaprost (in guinea-pigs, *in vitro*). Oral administration of limaprost alfadex also inhibits platelet adhesiveness (in guinea-pigs, *ex vivo*).[15)]

2) Inhibitory effect on platelet aggregation
   a) OPALMON®, when orally administered in patients with thrombotic diseases, inhibits platelet aggregation. The activity is equipotent with that of prostaglandin I_2 (*in vitro*).[14)]
   b) Limaprost alfadex inhibits platelet aggregation induced by various aggregating agents and dissociates ADP-induced platelet aggregation (in guinea-pigs, *in vitro*).[16)] Oral administration of limaprost alfadex also inhibits platelet aggregation (in guinea-pigs, *ex vivo*).[15)]
   c) Limaprost alfadex remarkably elevates platelet cyclic AMP levels and inhibits thromboxane A_2 production (in guinea-pigs, *in vitro*).[16, 176)]

(4) Antithrombotic effect

In the experimental models with thrombosis formation in the mesenteric artery induced by electric stimulation, limaprost alfadex dose-dependently increases threshold voltage of thrombosis formation (in guinea-pigs).[18)]

(5) Increasing effect on blood flow in the nerve tissue

1) Limaprost alfadex improves blood flow in the cauda equina nerve tissue in a model where the cauda equina nerve was compressed by inserting a balloon into the dura mater of the 6th lumbar vertebra (in dogs).[19)]
2) Limaprost alfadex improves blood flow in the cauda equina nerve tissue in a model where the cauda equina nerve was compressed by inserting a silicone rubber into the 4th and 6th lumbar vertebral canals (in rats).[20)]
3) Limaprost alfadex improves blood flow in the sciatic nerve tissue in the midst of two ligatures in a model where the sciatic nerve of the right hind limb was ligated at two sites (in rats).[21)]

(6) Improving effect on nerve function

1) Limaprost alfadex inhibits the decrease in nerve conduction velocity in a model where the cauda equina nerve was compressed by inserting a balloon into the dura mater of the 7th lumbar vertebra (in dogs).[22)]
2) Limaprost alfadex inhibits the prolongation in time duration of thermal stimulation-induced discharge in the muscle on the ligated femur in a model where the sciatic nerve of the right hind limb was ligated at four sites (in rats).[23)]

(7) Improving effect on hyperalgesia

Limaprost alfadex improves hyperalgesia at the ligated side in a model where the sciatic nerve of the right hind limb was ligated at two sites (in rats).[21)]

(8) Improving effect on gait disturbance

Limaprost alfadex improves decreased walking distance in a model where the cauda equina nerve was compressed by inserting a silicone rubber into the 4th and 6th lumbar vertebral canals (in rats).[20)]

2. Mechanism of action

Limaprost alfadex exerts potent effects on vasodilation, increase of blood flow and inhibition of platelet aggregation, and thereby has proven clinical effects on various ischemic symptoms such as ulcer, pain and feeling of coldness associated with thromboangiitis obliterans, as well as those on subjective symptoms (pain and numbness of lower legs) and gait ability associated with acquired lumbar spinal canal stenosis (in patients with bilateral intermittent claudication showing normal SLR test result).

PHYSICOCHEMISTRY

Nonproprietary name:

Limaprost alfadex (JAN), Limaprost (INN)

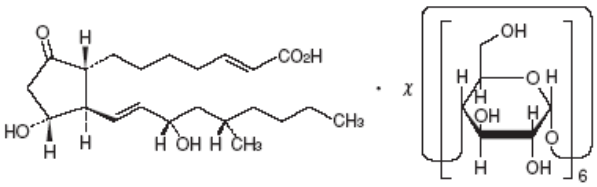
Chemical name:

(2*E*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(1E,3*S*,5*S*)-(*E*)-3-hydroxy-5-methylnon-1-en-1-yl]-5-oxocyclopentyl} hept-2-enoic acid-α- cyclodextrin

Molecular formula: $C_{22}H_{36}O_5 \cdot \chi C_{36}H_{60}O_{30}$

Molecular weight: 380.52 (as limaprost)

Structural formula:



Description:

Limaprost alfadex occurs as a white powder. It is freely soluble in water, slightly soluble in methanol, very slightly soluble in ethanol (99.5) and practically insoluble in ethyl acetate. It is hygroscopic.

PRECAUTIONS FOR HANDLING

Since this product is hygroscopic, the tablets should be kept in the PTP blister package after unsealing the inner package and removed from the PTP blister at the time of the ingestion. [Quality of this product is preserved using the aluminum-foil inner package including a desiccant and the damp-proof PTP blister.]

PACKAGING

OPALMON® Tablets 5 μg:

Boxes of 210 and 1,050 tablets in press-through package

REFERENCES

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17) Fujitani B. et al.: Inhibitory effect of limaprost alfadex on thromboxane A_2 production. Internal data of Ono Pharmaceutical Co., Ltd.
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23) Fujitani B. et al.: Clinical Report, **30**: 245, 1996.

REQUEST FOR LITERATURE SHOULD BE MADE TO:
Copies of the company's internal data that are cited in the list of references above can also be requested at the following address:

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