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Limaprost

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Contents

Abstract

▲ Limaprost, an alprostadil (prostaglandin E_1) analogue, is a vasodilator that increases blood flow and inhibits platelet aggregation.

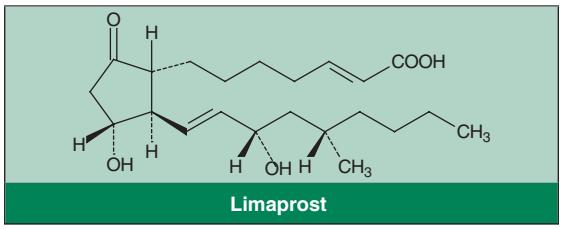
▲ The efficacy of oral limaprost was evaluated in adult Japanese patients in three randomised, double-blind, 6-week trials. One study included patients with thromboangiitis obliterans and two trials included patients with lumbar spinal canal stenosis. Limaprost was generally well tolerated and serious adverse events were uncommon.

▲ **Thromboangiitis Obliterans:** In a randomised, double-blind trial in Japanese patients primarily with thromboangiitis obliterans (n = 136), there was no significant difference between patients receiving limaprost 30 μg/day and those receiving oral ticlopidine 500 μg/day in the improvement of ischaemic symptoms.

▲ **Lumbar Spinal Canal Stenosis:** Limaprost 15 μg/day was superior to limaprost 3 μg/day for overall drug usefulness and overall improvement from baseline to study end in a phase III trial in 146 patients with lumbar spinal canal stenosis. Assessment of overall improvement considered various objective symptoms (e.g. muscle strength, walking ability) and subjective symptoms (e.g. pain or numbness in extremities), while overall usefulness also considered safety issues.

▲ The efficacy of limaprost 15 μg/day was not significantly different from that of 30 μg/day, but tended to be better than that of 6 μg/day in a phase II trial in patients with lumbar spinal canal stenosis and normal straight leg raise test results. The optimal dosage of limaprost for this indication was therefore deemed to be 15 μg/day.

Features and properties of limaprost (Opalmon®)	
Featured indications	
Thromboangiitis obliterans (TAO) [Buerger's disease]	
Lumbar spinal canal stenosis (LSCS) [in patients with bilateral intermittent claudication and a normal straight leg raise test result]	
Mechanism of action	
Vasodilation, increased blood flow and inhibition of platelet aggregation	
Dosage and administration in adults	
Route of administration	Oral
Frequency of administration	Daily in three divided doses
Dose TAO	30 μg/day
Dose LSCS	15 μg/day
Single-dose pharmacokinetic properties of oral limaprost in adult healthy volunteers (n = 12)	
Mean maximum plasma concentration	5μg: 1.18 pg/mL 10μg: 2.06 pg/mL
Median time to maximum plasma concentration	5μg: 0.75h 10μg: 0.5h
Mean area under the concentration-time curve from time 0 to infinity	5μg: 1.97 pg • h/mL 10μg: 3.43 pg • h/mL
Mean elimination half-life	5μg: ≈1h 10μg: ≈1h
Adverse events	
Gastrointestinal-related, rash, hot flushes/flushing, headaches and anaemia	



Limaprost

Limaprost is an alprostadil (prostaglandin E_1) analogue that was developed in Japan to treat numerous ischaemic symptoms of thromboangiitis obliterans (TAO) and lumbar spinal canal stenosis (LSCS)[1] because of the well known vasodilatory, antiplatelet and cytoprotective properties of prostaglandins.[2]

TAO (Buerger's disease) is a nonatherosclerotic, occlusive, inflammatory disease of distal, small- and medium-size arteries and veins of the arms and legs.[2,3] Signs and symptoms are pain at rest, ischaemic ulcers (in the arms, legs or both), thrombophlebitis, Raynaud's phenomenon, an abnormal Allen-test result, sensory findings and intermittent claudication.[2,3] This disease is more prevalent in Japan and Korea than in Western Europe (16–66% vs 0.5–5.6% of patients with peripheral arterial disease) and occurs mainly in young, male smokers.[3] Patients experience alternating periods of acute exacerbation and remission.[2] The only proven treatment of TAO is cessation of tobacco use; disease progression is prevented and amputations may be successfully avoided.[3] Nevertheless, alleviation of ischaemic pain, improved microcirculation and healing of ulcers may be achieved via pharmacological treatment with prostaglandins or aspirin; however, the latter agent appears less effective than prostaglandins.[2] Iloprost (an analogue of epoprostenol[4]) and alprostadil are available in numerous European countries for the treatment of TAO[2,3] and limaprost is approved only in Japan and South Korea in this indication.[1]

LSCS is a constriction of the spinal canal at the third to fourth (L3/L4) or fourth to fifth (L4/L5) lumbar vertebrae, or at the fifth lumbar vertebra to the sacrum (L5/S1),[5] which is usually caused by bone and ligamentous hypertrophy or intervertebral disc degeneration.[5] This constriction leads to entrapment of the cauda equina (a collection of spinal nerve roots), causing ischaemia, which is a contributing factor in the development of the intermittent neurogenic claudication.[6] Patients also experience pain in the back, buttocks, thighs and legs, a feeling of weakness and numbness in the legs, gait disturbance[5,6] and, in severe cases, bowel or bladder disturbances.[7] The middle-aged and elderly are commonly affected; disease progression is slow and the lower back and leg pain may be incapacitating.[6] Treatment of the symptoms of LSCS depends on disease severity (severity is based on level of leg pain and related disability); discussion of surgical management and conservative treatment options such as bed rest, physical therapy and lumbar bracing are beyond the scope of this review.[8] Pharmacological treatment options include epidural corticosteroids, anaesthetic nerve block or narcotic analgesics, which are used to relieve pain.[8] In Japan, limaprost is approved not only for pain relief, but also for relief of other ischaemic symptoms, such as numbness, and also of walking disturbances.[1]

The pharmacological properties, efficacy and tolerability of limaprost (Opalmon®)[1] in patients with TAO or LSCS are the focus of this review.

1. Pharmacodynamic Profile

- Limaprost has vasodilatory properties and increases blood flow.[9] In an animal model of peripheral circulatory disorder, oral administration of limaprost inhibited the development of ischaemic lesions in limbs and peripheral extremities.[10] The effect of limaprost on ischaemic lesions in patients with TAO or LSCS is reviewed in section 3.
- In animal studies with relevance for TAO, limaprost decreased coronary vessel resistance,[11] increased coronary blood flow[11] and increased femoral arterial and cutaneous blood flow in the hind limbs of dogs.[12]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

• The inhibitory effect of limaprost on platelet aggregation and platelet adhesiveness was 10- to 16-fold and 20-fold more potent than with epoprostenol (prostacyclin or prostaglandin I_2) in an *in vitro* study using guinea-pig platelets.[13] This inhibitory effect on platelet function may result in inhibition of thrombus formation; in an *in vivo* guinea-pig model of electrically induced thrombosis, limaprost significantly ($p < 0.05$) inhibited thrombus formation as assessed by the change of the threshold voltage for formation of a thrombus.[14]

• By contrast, limaprost inhibited platelet aggregation with similar potency to that of epoprostenol in an *in vitro* study with human platelets.[15]

• Oral limaprost 20–40μg produced no significant change in platelet function (either bleeding time or platelet adhesiveness) in a single-dose study in healthy volunteers.[16] However, in patients with thromboembolic disorders (n = 6), a single 30 or 40μg dose inhibited platelet aggregation by ≈3–35% and adhesiveness by ≈13% (30μg) or ≈35% (40μg) in a dose-dependent manner up to 2 hours after administration (values estimated from a graph).[15] Moreover, oral limaprost increased platelet cyclic AMP levels by 10–20% after a single 30 or 40μg dose in patients with thromboembolic disorders.[15]

• Oral limaprost produced transient decreases in blood pressure in healthy volunteers in a single-dose study (n = 12).[16] These decreases were not statistically significant with a 20μg dose. Significant reductions from baseline were reported in systolic blood pressure only at 2 hours post-dose with a 40μg dose, and in both diastolic and mean blood pressure up to 2 hours after a 30μg dose and 1–3 hours after a 40μg dose (all $p < 0.05$). All blood pressure parameters returned to baseline values after 3–6 hours.[16]

• In animal models of ischaemia with relevance for LSCS, limaprost improved blood flow to the cauda equina ($p < 0.05$ vs baseline),[17] sciatic nerve[18] and nerve tissue in the lumbar vertebral canal.[19] Blood flow in the tissue between two ligations around the right sciatic nerve[18] and in the nerve tissue of the fifth lumbar vertebra[19] increased significantly after multiple-dose oral administration of limaprost ($p < 0.001$[18] and $p < 0.01$[19] vs control). Limaprost also increased the diameter of the cauda equina blood capillary (at the seventh lumbar vertebra).[20]

• Additionally, animal models of LSCS have shown that limaprost may improve nerve function[18,21,22] and walking ability.[19,23] For example, intravenous limaprost inhibited an induced reduction in nerve conduction velocity in the cauda equina nerve at the seventh lumbar vertebra ($p < 0.05$ vs control), but had no significant effect on another measure of nerve function (the reduction of muscle action potential area).[21]

• Sciatic nerve function may be affected in LSCS since the stenosis may occur at the fourth and fifth lumbar vertebrae.[5] Sciatic nerve ligation in rats caused prolongation of heat-stimulated myogenic nerve discharges in the femoral muscles ipsilateral to the nerve, but with oral administration of limaprost, this prolongation was inhibited ($p < 0.05$ vs control).[22] In another *in vivo* rat model of disturbed sciatic nerve function, chronic administration of oral limaprost reduced hyperalgesia.[18]

• Oral administration of limaprost in rats significantly ($p < 0.05$) increased walking[23] or running[19] distance compared with a sham control in *in vivo* models of walking dysfunction.[19,23] By contrast, beraprost did not improve walking distance in one trial.[23] Section 3 reviews the efficacy of limaprost in improving walking ability in patients with LSCS.

• There is potential for a pharmacodynamic drug interaction (an increased tendency to bleed) between limaprost and the following agents if coadministered: antiplatelets (aspirin, ticlopidine, cilostazole), thrombolytics (urokinase) and anticoagulants (heparin, warfarin).[9]

2. Pharmacokinetic Profile

The pharmacokinetic properties of oral limaprost 5 and 10μg have been evaluated in a single-dose, crossover study in Japanese adult healthy volunteers (n = 12).[24] Similar results to those reviewed here have been reported in a study of parallel-group design (n = 24), which is not discussed further.[25] Additional data are available from animal[26,27] and *in vitro*[28] studies. The pharmacokinetics of limaprost in the elderly and in paediatric patient

populations, or in patients with renal or hepatic impairment have not been investigated.

Absorption and Distribution

- Limaprost is rapidly absorbed following oral administration; the median time to peak plasma concentration (t_{max}) was under 1 hour after a single dose of 5 or 10μg (0.75 and 0.5 hours).[24] Oral limaprost tablets were taken with water after a meal.[24]
- The mean maximum plasma concentration (C_{max}) of limaprost after a single 5 and 10μg dose was 1.18 and 2.06 pg/mL.[24] Respective mean area under the concentration-time curve from time zero to infinity (AUC_∞) values were 1.97 and 3.43 pg • h/mL.
- Absorption of limaprost appears to be dose-proportional; the ratios for the dose-adjusted mean C_{max} and AUC_∞ values of a single 10μg dose versus a single 5μg dose were 0.971 and 0.935, which was within the 0.90–1.11 range considered by investigators to indicate linear pharmacokinetics.[24]
- In an *in vitro* study,[28] limaprost was highly protein bound in human plasma (95.8%).

Metabolism and Elimination

- According to a study in rats,[26] ≈70% of an orally administered radiolabelled dose of limaprost is excreted in the faeces and ≈30% is eliminated in the urine over a 96-hour post-dose period. Two major metabolites have been identified in rats; both metabolites are excreted primarily in the faeces and bile (5–18% of the administered dose).[28] The extent or site of metabolism, and route of excretion of limaprost has not yet been investigated in humans.
- Limaprost is rapidly eliminated from the body after a single 5 or 10μg dose. The mean elimination half-life was approximately 1 hour with either dose.[24] Thus, oral limaprost is taken daily in three divided doses (section 5).
- Similarly, the apparent clearance of oral limaprost from the plasma was not dose-proportional, and was 3110 L/h for both 5 and 10μg doses.[24]

3. Therapeutic Efficacy

This section reviews data from fully published, randomised, double-blind trials with more than 50 patients. All studies are in adult Japanese patients.

Thromboangiitis Obliterans

The efficacy of oral limaprost 30 μg/day in the treatment of ischaemic symptoms (ulcer, feeling of coldness, pain) associated with TAO was evaluated versus oral ticlopidine 500 μg/day in a randomised, double-blind, multicentre 6-week trial.[29] Patients with occlusive arteriosclerosis were enrolled in this trial (n = 49); however, since limaprost is not approved for use in this indication, these data are not reviewed here. A small number of patients with chronic arterial occlusion or diabetic vascular disease (n = 13) were enrolled in the trial and were grouped together with patients with TAO (n = 136) ['TAO group']. Patients were required to have ulcers on their extremities and were excluded if they had any of the following: prior surgical revascularisation or excision of sympathetic ganglia; a tendency for haemorrhage; granulocytopenia or a history thereof; and severe hepatic or renal impairment. Baseline characteristics were not significantly different between treatment groups.[29]

Study drugs were taken three times daily in divided doses after meals for 6 weeks following a 1-week placebo run-in period.[29] Concomitant use of antibacterial agents or analgesics was permissible, but any agents that may have affected trial results (e.g. antiplatelets, anticoagulants, vasodilators and barbiturates) were not allowed.

Efficacy endpoints were the following: general usefulness, which considered both efficacy and tolerability and was assessed via a 100-point visual analogue scale (VAS) [a score of ≥70 of 100 was considered 'useful']; improvement in ulcer size (an objective symptom); improvement in rest pain (a subjective symptom); and overall improvement, which considered all clinical symptoms taken together and was assessed using a 5-point study-defined categorical scale.[29] All endpoints were investigator-rated except for an evaluation of drug effec-

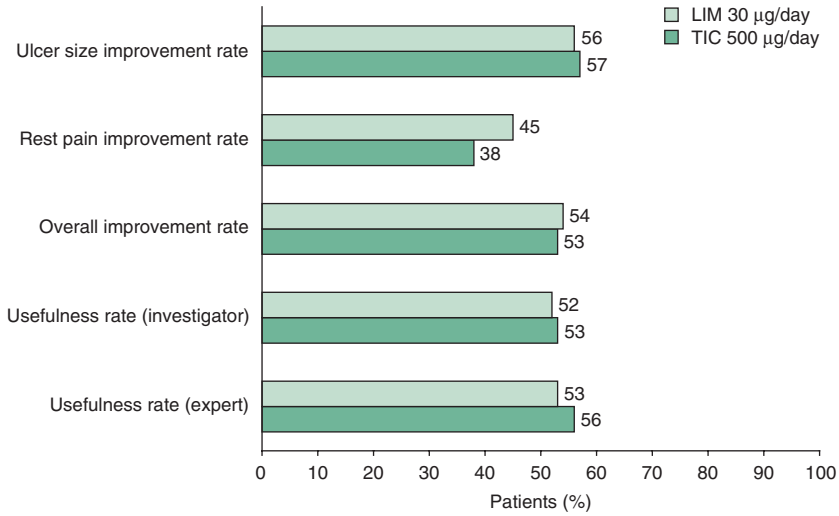


Fig. 1. Efficacy of limaprost (LIM) vs ticlopidine (TIC) in patients (pts) with thromboangiitis obliterans (n = 136), or chronic arterial occlusion or diabetic vascular disease (n = 13).[29] In this randomised, double-blind, multicentre, 6-week trial, pts received LIM 30 μg/day (n = 53–60) or TIC 500 μg/day (n = 64–76) in three divided doses after meals; evaluable patient numbers differed for each endpoint. Efficacy endpoints were assessed via investigator-rated 5-point categorical or 100-point visual analogue scales. Improvement or usefulness rates were the ratio of the number of pts in the two highest ranking categories of improvement/usefulness to the total number of evaluable pts.

tiveness, which was based on changes in ulcer size and reported using a VAS by an expert committee (a score of ≥70 of 100 indicated that the drug was considered 'useful'). Analyses were per-protocol, unless specified otherwise.

- The efficacy of limaprost was not significantly different from that of ticlopidine in the TAO group.[29] Thus, a similar proportion of patients in the two treatment groups had improvement ratings in the top two categories for ulcer size (healed or reduced), rest pain (markedly improved or improved), overall improvement (markedly improved or improved), investigator-rated usefulness (scores of 90–100 or 70–89) and usefulness rated by an expert panel (90–100 or 70–89) [figure 1].
- In addition, the reduction in ulcer size from baseline to study end was significant in both the limaprost (n = 57) and ticlopidine (n = 99) treatment groups (12–8 mm^2 and 13–8 mm^2) [p-value not reported].[29] This analysis included patients presenting with occlusive arteriosclerosis as well as those in the TAO group.

Lumbar Spinal Canal Stenosis

Patients with LSCS and symptoms of degenerative spondylolisthesis and bilateral intermittent claudication,[30] or degenerative, combined, spondylolisthetic, or spondolytic symptoms[31] were enrolled in two randomised, double-blind, multicentre, 6-week trials.[30,31] Patients were excluded from the studies if they met any of the following criteria: had prior surgery or were suitable candidates for surgery;[30,31] had chronic occlusive arterial disease;[30] had concomitant internal organ disease;[30,31] had severe impediment to lower extremity movement;[30] or were pregnant women or nursing mothers.[30] Patients enrolled in the trials were elderly (mean patient age of 66–70 years), the majority of whom had degenerative spinal canal stenosis (75%[30] and 72%[31] of patients) of mild or moderate severity (84%[30] and 90%[31]) and of less than 2 years' duration (66–79%).[30,31]

Nerve blocking treatment was not allowed during the trial; physical therapies (e.g. physiotherapy or corsets) were permissible only where patients had been receiving these treatments prior to the trial.[30,31] Concomitant pharmacological treatment

with vasodilatory, muscle-relaxing or bone metabolism agents and cyanocobalamin preparations was generally excluded.[30,31] In one trial, treatment of concomitant illnesses was permitted[30] and, in the other trial,[31] analgesics and anti-inflammatory agents were allowed but, in either case, only where patients had been receiving these treatments prior to the trial.

Patients received oral limaprost 3[30] or 6[31] μg/day (i.e. control treatment groups; n = 77[30] and 38[31]), or 15 μg/day (n = 69[30] and 47[31]) or 30 μg/day (n = 44)[31] in three divided doses after meals. Patient baseline demographic and disease characteristics were not significantly different between treatment groups in one trial,[30] although in the other study[31] there were more women in the 30 μg/day than in the 6 or 15 μg/day groups (n = 25 vs 13 and 16) and more patients with degenerative spondylolisthetic, combined or spondolytic spinal canal stenosis in the 6 and 15 μg/day than in the 30 μg/day group (n = 15 and 16 vs 5). Where stated, approximately two-thirds of patients showed onset of intermittent claudication within a walking distance of 500m.[30]

Primary efficacy endpoints, which were investigator-rated measurements, were specified only in one trial and were the overall improvement in symptoms at the end of treatment (both subjective and objective symptoms were assessed) and drug usefulness.[30] The third primary endpoint was a tolerability endpoint (see section 4).[30] The straight leg raise (SLR) test score, sensation, muscle strength and, in one trial, walking ability,[30] were assessed objectively, whereas lower extremity or lumbar pain and lower extremity numbness, and walking ability in the other trial,[31] were assessed subjectively. In one trial, baseline assessment of subjective symptoms was made at the time of onset of intermittent claudication; however, further on-treatment assessments of these symptoms were conducted after patients had walked the same distance that they had walked at baseline before intermittent claudication began.[30] By contrast, at least one subjective symptom was assessed at rest in the other trial (lumbar pain).[31] Activities of daily living ('everyday life actions'),[31] 'patient complaints' (at rest)[30] and the distance to onset of intermittent claudication[30] were additional endpoints. With the exception of the SLR test and the distance to onset of intermittent claudication, most assessments were categorical, and values at the end of study were compared with baseline values to assess the degree of improvement shown. The scales used to rate subjective and objective symptoms were different between the two trials, thus results are reported separately. Statistical analyses were generally per-protocol, unless otherwise specified.

- Limaprost 15 μg/day was considered by investigators to provide greater overall improvement and to be a more useful treatment than the control dosage of 3 μg/day (primary endpoints) in the phase III trial in 146 patients with LSCS.[30] When comparing assessment rates, there were more patients in the higher dosage group than in the control dosage group rated as 'improved' or 'markedly improved' (overall improvement rate 50.7% vs 27.3%; $p < 0.01$) at the end of treatment or for whom limaprost was rated as 'useful' or 'extremely useful' (usefulness rate 50.7% vs 27.3%; $p < 0.01$) [figure 2].[30] Assessment of overall improvement considered va-

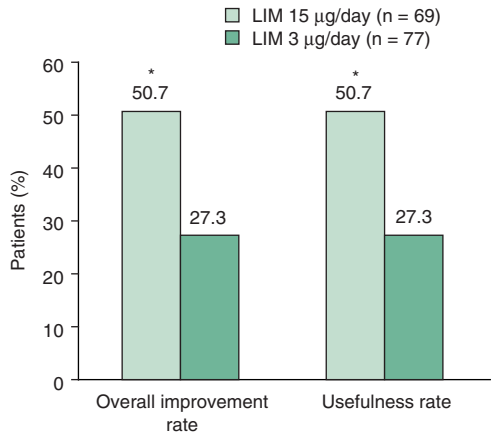


Fig. 2. Efficacy of oral limaprost (LIM) 15 vs 3 μg/day in adult patients (pts) with lumbar spinal canal stenosis in a randomised, double-blind, multicentre, 6-week trial.[30] Investigator-rated categorical global measures of efficacy were the overall improvement at end of treatment and usefulness. Overall improvement rate and usefulness rate were the ratio of the number of pts in the two highest ranking categories of improvement/usefulness to the total number of evaluable pts. * $p < 0.01$ vs comparator.

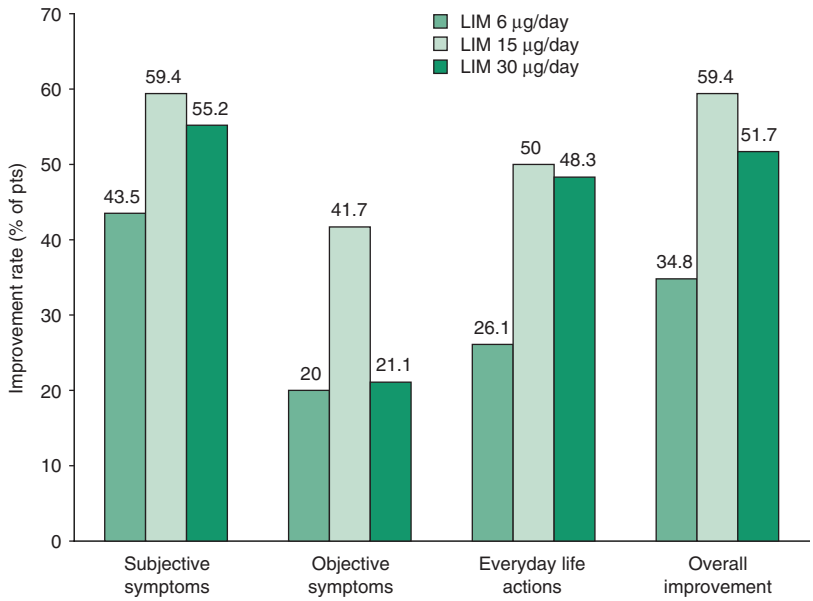


Fig. 3. Improvement rates with oral limaprost (LIM) in patients (pts) with lumbar spinal canal stenosis and normal straight leg raise test results. In this randomised, double-blind, multicentre, 6-week trial, patients received oral LIM in three daily divided doses after meals.[31] Improvement rates are shown for subjective symptoms, objective symptoms, everyday life action and overall improvement, and represent the ratio of the number of pts in the two highest ranking categories (e.g. markedly improved or improved subjective symptoms) to the total number of evaluable pts. The total number of pts varied for each assessment: LIM 6 μg/day (n = 20–23), LIM 15 μg/day (n = 24–32) and LIM 30 μg/day (n = 19–29). There were no statistically significant differences between treatment groups.

rious objective symptoms (e.g. muscle strength, walking ability) and subjective symptoms (e.g. pain or numbness in extremities), while assessment of usefulness also considered safety issues.

- Between-group differences in improvement in most objective symptoms at study end were not significant except for muscular strength and distance walked to onset of intermittent claudication according to Japanese Orthopaedic Association criteria for walking ability in the same trial (secondary efficacy endpoints).[30] More patients in the 15 μg/day than the 3 μg/day dosage group experienced an improvement of at least one grade in muscular strength (59% vs 15% of patients; $p = 0.0025$) or of at least one scale point in the distance walked to onset of intermittent claudication (40% vs 25%; $p = 0.0187$).[30]

- The efficacy of the 15 μg/day dosage was generally superior to that of the 3 μg/day group according to subjective measures of efficacy.[30] At study end, the proportion of patients with improved or markedly improved subjective symptoms (42% vs 26%), patient impressions of 'got better' (39% vs 25%), or with improved or markedly improved overall general improvement (55% vs 35%) was greater in the higher than in the control dosage group (secondary efficacy endpoints) [all $p < 0.05$].

- The optimal dosage of limaprost in LSCS was determined in a phase II trial comparing limaprost 6, 15 and 30 μg/day in a total of 129 patients.[31] A *post-hoc* analysis was conducted in 84 patients with normal SLR test results; patients with abnormal SLR results were excluded because they are typically good surgical candidates, often having concurrent disc hernia or lateral stenosis of the lumbar canal. The efficacy of limaprost 15 μg/day was not significantly different from that of 30 μg/day but tended to be better than that of 6 μg/day when patients with abnormal SLR were excluded (figure 3). For example, improvement rates for subjective symptoms, objective symptoms and overall improvement were approximately 15–20% higher with limaprost 15 μg/

day than with limaprost 6 μg/day, and results with limaprost 30 μg/day were generally similar to or slightly lower than those with limaprost 15 μg/day.

- Efficacy data from a postmarketing surveillance study are available from 1800 patients with LSCS who received limaprost (mean dosage 15.1 μg/day) for a mean duration of 116 days.[32] The overall improvement rate was 49.9%, i.e. approximately half of the patients improved or markedly improved with limaprost therapy. Lower extremity pain, both at rest and after walking, was significantly reduced by limaprost and walking ability was significantly improved. For example, 55.7% of patients could not walk 500m before administration of limaprost, but this decreased to 27.4% of patients following treatment ($p < 0.0001$). Mean walking time almost doubled from 12.98 minutes at baseline to 21.23 minutes with limaprost ($p < 0.0001$).
- A total of 363 patients who were evaluated for efficacy in the postmarketing surveillance study received limaprost treatment for >6 months (including 140 who received limaprost for >1 year).[32] The overall improvement rate was 52.9% among patients treated for >6 months and 60.7% among those treated for >1 year. A comparison of improvement rates among patients treated for >1 year versus those treated for <1 year showed a significantly higher rate in the longer-term treatment group (60.7% vs 47.9%; p-value not stated).

4. Tolerability

Data in this section are primarily from pooled tolerability analyses available in the manufacturer's Japanese prescribing information,[9] postmarketing surveillance data[32] and the 6-week trials discussed in section 3.[29-31] The duration of drug exposure in patients included in the pooled analyses was not reported.

- Oral limaprost 3–30 μg/day was generally well tolerated in adult patients with TAO[9,29] or LSCS.[9,30-32] The overall incidence of treatment-emergent adverse events with limaprost in the latter indication appeared to be dose-related, occurring in 3% or 4% of patients receiving 3[30] or 6[31] μg/day compared with 9%[30] and 6%[31] of those receiving 15 μg/day and 16%[31] of those receiving 30 μg/day. However, between-group differences in the incidence of these adverse events in one trial,[30] or in the number of patients without these adverse events in the other trial,[31] were not significant.
- The most frequent treatment-related adverse effects included gastrointestinal (GI)-related effects, rash, hot flushes/flushing, headaches and anaemia.[9] In patients with TAO, diarrhoea, nausea/vomiting/retching, hot flushes/flushing, rash and abdominal or epigastric discomfort were reported in 1.1%, 0.5%, 0.5%, 0.4% and 0.4% of patients (n = 4582; pooled analysis);[9] in patients with LSCS, there were 25 reports of adverse events affecting the GI tract (e.g. stomach discomfort, diarrhoea, abdominal discomfort) among 397 patients (pooled analysis).[32]
- Other treatment-related adverse events occurring in 0.2–0.3% of patients with TAO were abdominal or gastric pain, headache, hepatic function abnormalities (e.g. increased AST or ALT levels) and anorexia.[9]
- Serious treatment-emergent adverse events described by investigators as occurring in patients for whom treatment was 'not safe' were reported only in one trial, in three patients receiving limaprost 30 μg/day.[29] These adverse events were GI-related in two patients and increased AST or ALT levels in the third patient; all three patients discontinued the study drug.
- Four of 92 patients receiving limaprost and one of 106 patients receiving ticlopidine discontinued treatment because of an adverse event in a 6-week trial (see section 3 for trial design details).[29] Reasons for discontinuation were not reported for all patients; however, two patients stopped treatment because of GI-related adverse events.[29]
- In this trial versus ticlopidine,[29] adverse events were not reported separately for the two indication groups (TAO and occlusive arteriosclerosis). Treatment-emergent adverse events occurred in 12% of patients receiving limaprost versus 8% of patients receiving ticlopidine. Nevertheless, the investigator-rated safety of limaprost 3–30 μg/day was not significantly different from that of ticlopidine in the

TAO group (safety rate of 88% [n = 69] vs 95% [n = 80] of patients).[29]

- In similar investigator-rated assessments of overall safety in the trials in patients with LSCS, safety rates were 94–97% of 38–47 evaluable patients receiving limaprost 3–15 μg/day,[30,31] and 84% of 44 patients receiving 30 μg/day, i.e. twice the recommended dosage (section 5).[31] Between-group differences were not significant.[30,31] The safety rate was the ratio of the number of patients for whom the drug was rated by the investigator as 'fairly safe' or 'safe' to the number of all evaluable patients.
- In addition to elevated AST and ALT levels,[9,29-31] limaprost has been associated with thrombocytopenia[30] and increased blood urea nitrogen levels[31] in a small number of patients. The drug may also be associated with hepatic impairment or jaundice.[9]
- Tolerability data from a postmarketing surveillance study are available from 1930 patients with LSCS who received limaprost (mean dosage 15.1 μg/day) for a mean duration of approximately 4 months.[32] Adverse events occurred in 5.2% of patients. A total of 123 events were reported, almost half of which involved GI disorders, such as stomach discomfort or diarrhoea. One serious adverse event was reported (bleeding duodenal ulcer). Among 397 patients treated for >6 months (including 141 who received limaprost for >1 year), 9.1% experienced an adverse event, in most cases a GI disorder.[32] The incidence of adverse events was significantly lower among patients who received treatment for >1 year than among those who received treatment for <1 year (2.84% vs 12.5%; p = 0.0025).

5. Dosage and Administration

Oral limaprost is approved in Japan for the treatment of ischaemic symptoms (ulcer, feeling of coldness, pain) in adult patients with TAO and for the treatment of pain and numbness in the lower legs and of abnormal gait in adult patients with acquired LSCS who have bilateral intermittent claudication and a normal result on the SLR test.[2] The recommended daily dose is 30μg in patients with TAO and 15μg in patients with LSCS, taken in three divided doses.[9]

Currently no dosage recommendations for special patient populations exist, although the drug should be administered with caution in patients with a tendency to bleed or those receiving treatment with thrombolytic, antiplatelet or anticoagulant agents. Local prescribing information should be consulted for information on precautions, contraindications and drug interactions.[9]

6. Limaprost: Current Status

In Japan, oral limaprost is approved for the treatment of various ischaemic symptoms, such as pain, ulcers and a sensation of coldness in the peripheral extremities, in patients with TAO and of subjective symptoms, such as pain and numbness in the lower legs and reduced walking ability in patients with acquired LSCS. In a randomised, double-blind trial, the efficacy of limaprost 30 μg/day was not significantly different from that of ticlopidine 500 μg/day in patients with TAO. In patients with LSCS who were deemed to be good candidates for medical rather than surgical intervention on the basis of SLR test results, the optimal dose of limaprost was found to be 15 μg/day. Limaprost was generally well tolerated in clinical trials.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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