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Long-Acting Isosorbide Mononitrate

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Contents

Abstract

▲ Elantan® long[1] (EL) is the only long-acting isosorbide mononitrate formulation based on a controlled membrane principle. 30% of the dose is available for immediate release and the remaining 70% is gradually released over time.

▲ After oral administration, isosorbide mononitrate EL has a quick onset of action (30 minutes) and effects are evident for up to 17 hours.

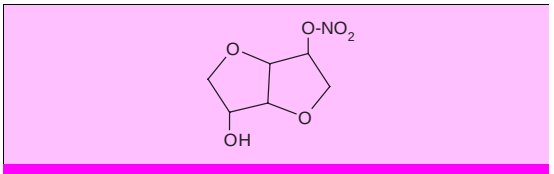
▲ The antianginal effects of once-daily isosorbide mononitrate EL 50 to 100mg were generally similar to those of conventional isosorbide mononitrate or isosorbide dinitrate 10 to 20mg twice or 3 times daily, or sustained-release nifedipine 20mg twice or 3 times daily. Patients tended to show a better response with once-daily isosorbide mononitrate EL 50mg than with bupranolol 100mg.

▲ Patients showed significantly greater improvement in some quality-of-life indices with once-daily isosorbide mononitrate EL than with twice or 3 times daily regimens of conventional isosorbide mononitrate or isosorbide dinitrate.

▲ Tolerance did not develop after 13 months of once-daily administration of isosorbide mononitrate EL. No rebound increase in incidence of ischaemic episodes was observed after discontinuation of the drug.

Features and properties of long-acting isosorbide mononitrate	
Indication	
Chronic stable angina pectoris	
Mechanism of action	
Venous and arterial vasodilator	Improves subendocardial blood flow in the heart by decreasing preload and afterload and causing coronary vasodilation
Dosage and administration	
Usual dosage in clinical trials	50mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile	
Peak plasma concentration	0.488 mg/L
Time to peak plasma concentration	5h
Area under the plasma concentration-time curve	5.029 mg/L • h
Relative bioavailability	84% of the immediate-release tablet formulation
Elimination half-life	5.1h
Adverse events	
Most frequent	Headache (41 to 66.6%)

1 Use of the trade name is for product identification only and does not imply an endorsement.



Isosorbide mononitrate

Anginal symptoms [retrosternal chest pain, feeling of pressure or a strangling sensation (which may radiate to either side of the chest or arms), breathlessness, fatigue and faintness] are regarded as stable when they occur in association with conditions of increased myocardial oxygen consumption (e.g. physical exercise) and have been present for several weeks without major deterioration.[1] The treatment of patients with stable angina pectoris is aimed at improving prognosis by preventing myocardial infarction and death and minimising or abolishing symptoms. Organic nitrates, β-adrenoceptor blockers and calcium antagonists, either alone or in combination, are recommended for controlling anginal symptoms.[1]

Long-acting isosorbide mononitrate (isosorbide-5-mononitrate) is a prodrug, similar to other organic nitrates, which acts as a vasodilator by releasing nitric oxide. It is used for the prevention of stable angina pectoris in patients with coronary artery disease.[2] Elantan® long (EL) is the only long-acting isosorbide mononitrate formulation that is based on a controlled membrane principle where 30% of the drug is available for immediate release and 70% is released slowly over time. This formulation aims to provide a quick onset and prolonged duration of action.

1. Pharmacodynamic Properties

Mechanism of Action

• Organic nitrates are biotransformed by denitration to release nitric oxide. Nitric oxide activates the enzyme guanylate cyclase, which catalyses the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP). Acting through a cGMP-dependent protein kinase, cGMP causes relaxation of vascular smooth muscles (vasodilation) by decreasing intracellular calcium.[3]

• Organic nitrates decrease myocardial oxygen demand by causing vasodilation of the capacitance veins (to decrease preload) and the large conductive arteries (to decrease afterload), and increase myocardial oxygen supply by causing vasodilation of the epicardial coronary arteries.[2]

Haemodynamic Effects

• In a randomised, double-blind, placebo-controlled trial, 16 volunteers received a single oral dose of either isosorbide mononitrate EL 50mg or immediate-release isosorbide mononitrate 20mg.[4] Within 10 minutes of administration, haemodynamic effects, such as the change in heart rate following orthostatic challenge and change in peripheral arterial resistance [reflected as an increase in the ratio of the height of systolic peak (a) to that of the dicrotic wave (b) of the finger pulse curve], were evident.

• Maximum change in a/b ratio (after 0.95 *vs* 2.73 hours, $p = 0.0059$) and decrease in systolic blood pressure following orthostatic challenge (after 10 *vs* 30 minutes, $p < 0.05$) occurred earlier after immediate-release isosorbide mononitrate than after isosorbide mononitrate EL. However, there was no difference in the extent of effects between the formulations.[4]

• On ergometric exercise testing, 30 minutes after oral administration of isosorbide mononitrate EL 50mg, 20 patients showed a significantly longer time to angina and time to moderate angina (necessitating discontinuation of exercise) than after placebo (547 *vs* 443 seconds and 692 *vs* 616 seconds, respectively) in a randomised, double-blind, crossover trial.[5] ST segment depression at comparable load and at the end of exercise was significantly lower after isosorbide mononitrate EL than after placebo (0.02 *vs* 0.07mV and 0.14 *vs* 0.16mV, respectively).[5]

• In clinical trials, patients receiving isosorbide mononitrate EL 50 mg/day experienced no clini-

cally important changes in heart rate or blood pressure.[6-9]

2. Pharmacokinetic Properties

• The frequency of anginal attacks shows marked circadian variation with the peak incidence of ischaemic events (acute myocardial infarction and sudden cardiac death) occurring between 6am and noon. The frequency of ischaemic episodes tends to plateau during the afternoon and reaches a trough during the night.[10]

• Isosorbide mononitrate EL is formulated so that after oral administration in the morning there is a quick onset of action and high plasma isosorbide mononitrate concentrations are maintained until noon. Thereafter, plasma isosorbide mononitrate concentrations decline to about 0.04 to 0.05 mg/L after 24 hours[11] (low plasma concentrations have been proposed to delay the development of nitrate tolerance).[12] This is achieved with 30% of the active drug outside the semipermeable membrane, available for immediate release, and inert pellets coated with 70% of the active drug covered by a semipermeable membrane. (fig. 1).

• At 20 minutes, plasma isosorbide mononitrate concentrations after isosorbide mononitrate EL 50mg (≈0.1 mg/L, approximate value from graph) were >2-fold greater than those after sustained-release tablets containing 40mg or 60mg isosorbide mononitrate in a randomised, crossover trial in 6 volunteers.[13]

• The pharmacokinetic disposition of isosorbide mononitrate EL 50mg once daily for 5 days was compared with that of immediate-release isosorbide mononitrate 20mg twice daily for 5 days in 18 healthy male volunteers in a randomised, crossover trial.[11] On day 4, a plasma isosorbide mononitrate concentration of 0.3 mg/L was attained 1 hour after administration of isosorbide mononitrate EL 50mg. Steady-state peak plasma isosorbide mononitrate concentrations (C_{max}) were similar between the 2 formulations (0.488 *vs* 0.436 mg/L).[11]

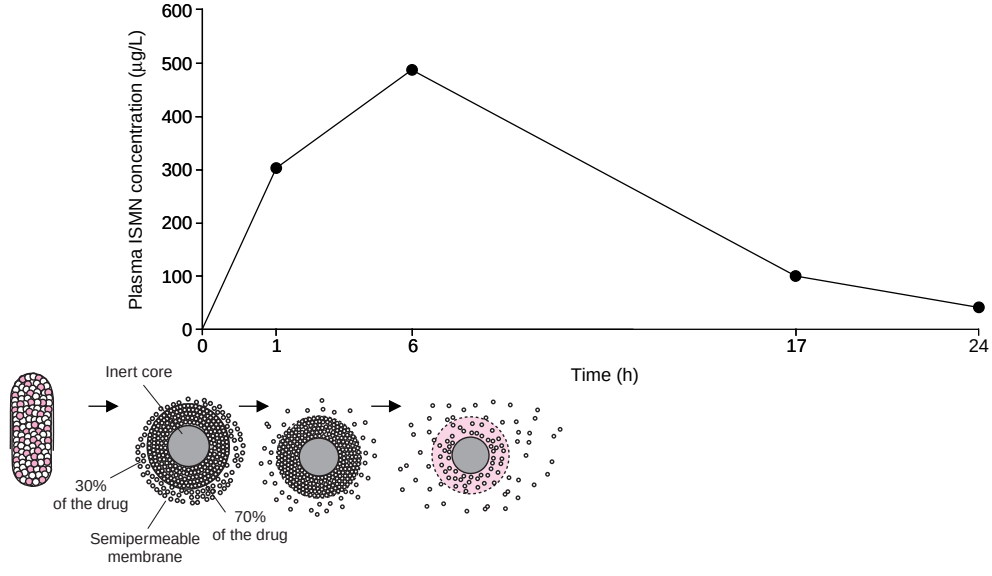


Fig. 1. Hypothetical correlation of the plasma isosorbide mononitrate (ISMN) concentration observed in 18 healthy volunteers given ISMN 50mg (Elantan® long) once daily for 5 days.[11] 30% of the dose, outside the semipermeable membrane, is available for immediate release and 70% of the dose is gradually released through the semipermeable membrane.

• An earlier report of this study indicated that time to peak plasma concentration (t_{max}; 5 *vs* 1 hours), duration while plasma isosorbide mononitrate concentration remained above 100 μg/L (17 *vs* 10 hours), dose-corrected area under the plasma concentration-time curve (AUC; 5.029 *vs* 5.843 mg/L · h) and the relative bioavailability (84 *vs* 100%) were significantly different between the 2 formulations.[14]

• 16 patients with chronic stable angina pectoris showed slightly higher mean C_{max} (216 *vs* 199 μg/L), mean AUC (2.56 *vs* 2.20 mg/L · h) and mean elimination half-life (7.1 *vs* 5.1 hours) values after a single oral dose of isosorbide mononitrate EL 25mg than 12 volunteers.[15]

• The presence of food significantly prolonged the t_{max} of isosorbide mononitrate (4 *vs* 2 to 3 hours), but did not affect the C_{max} and AUC values in 10 healthy volunteers given a single tablet of isosorbide mononitrate EL 50mg after a standard breakfast or in a fasted state in a randomised, crossover trial.[16]

3. Therapeutic Use

Comparisons with Placebo or a Higher Daily Dosage

• After 7 days, 15 patients with stable angina pectoris treated with oral isosorbide mononitrate EL 25, 50 or 100mg showed dose-dependent, significant reductions from baseline values in the extent of ST segment depression (28.6, 46 and 63.5%, respectively) but not with placebo (2.4%) in a randomised, double-blind, crossover trial.[7] A corresponding reduction in the frequency of anginal attacks per week (28.6, 50.6, 70.1%, respectively) and nitroglycerin consumption (33.3, 50 and 70.5%, respectively) was observed with isosorbide mononitrate EL 25, 50 or 100mg but not with placebo.[7]

• In a further randomised, double-blind, crossover study, 10 patients with stable angina pectoris received oral isosorbide mononitrate EL 50 or 100mg once daily or placebo for 3 weeks. At end-point (6 hours after administration of the final dose), there were significantly greater increases in ischaemia-free exercise time (180 and 216 *vs* 99 seconds) and reductions in extent of ST segment depression (1.17 and 0.99 *vs* 2.26mm) at comparable workload with isosorbide mononitrate EL 50 or 100mg than with placebo.[6]

• Patients with stable angina pectoris [severity at baseline graded according to the New York Heart Association (NYHA) angina classification: 7% with class I, 32% with class II, 52% with class III and 10% with class IV] received isosorbide mononitrate EL 50 mg/day (n = 295) or sustained-release isosorbide mononitrate 50 to 60 mg/day (n = 56) once daily for 3 months, followed by isosorbide mononitrate EL 100 mg/day (n = 351) once daily for a further 3-month period in a nonblind, multicentre trial.[17] Isosorbide mononitrate EL 100 mg/day led to significantly ($p < 0.001$) greater improvement in mobility, distress and anginal pain quality-of-life indices than sustained-release isosorbide mononitrate 50 to 60 mg/day: mobility index score of 2.65 *vs* 2.20, psychological distress score of 3.65 *vs* 3.40 and anginal pain index score of 3.60 *vs* 3.16.[17]

• Improvement in patient satisfaction indices (such as pleasure in daily life and satisfaction with current disease stage and with treatment) with isosorbide mononitrate EL 100 mg/day were significantly ($p < 0.001$) greater than those with sustained-release isosorbide mononitrate 50 to 60 mg/day (by 11.2 to 19.6%).[17] After 6 months, 291 of 351 patients preferred isosorbide mononitrate EL 100 mg/day to the lower dosages.

Comparison with Conventional Isosorbide Mononitrate or Isosorbide Dinitrate

• 1350 patients with stable angina pectoris (baseline severity: 20% with NYHA class I, 63% with NYHA class II, 13% with NYHA class III, and 1% with NYHA class IV) were treated with immediate-release isosorbide mononitrate or isosorbide dinitrate 10 to 20mg (twice or 3 times daily) in the initial 3 months and with once-daily isosorbide mononitrate EL 50mg for the subsequent 3 months

in a nonblind trial.[18] A total of 1212 patients were evaluable after 6 months.

- Patients receiving once-daily therapy experienced significantly less anginal pain during the period 8am to 10am (pain scores of 7.3 *vs* 8.3, $p < 0.003$) and significantly fewer patients experienced pain during this 2-hour period (21 *vs* 27%, $p < 0.0007$) than those receiving conventional nitrate formulations. Significantly fewer patients forgot to take their daily medication with the once-daily therapy than with the multiple dose therapy (16 *vs* 21%, $p < 0.0001$).

- In addition, once-daily therapy resulted in significantly greater improvements in the mobility and distress quality-of-life indices than multiple dose therapy: immobility score decreased from 27.5 to 26.0 ($p < 0.007$) and psychological distress score decreased from 18 to 17 ($p < 0.006$). At end-point, 89% of patients preferred the once-daily therapy over the multiple dose therapy.

Comparisons with Calcium Antagonists

- Isosorbide mononitrate EL 50mg once daily or sustained-release nifedipine 20mg twice daily led to the same significant reduction in the extent of ST segment depression (by 22.5% from baseline) after 2 weeks in a randomised, double-blind crossover study in 15 patients with stable angina pectoris.[19] Some patients not responding to either drug alone responded to a combination of the two.

- In a further study, patients with angina pectoris not adequately controlled on β-adrenoceptor blockers were randomised to receive either isosorbide mononitrate EL 50 to 100mg (n = 70) or nifedipine (gastrointestinal therapeutic system; GITS) 30 to 90mg (n = 85) once daily or isosorbide dinitrate 40 to 60mg twice daily (n = 74) as add-on therapy for 6 weeks in a double-blind, parallel-group manner. [9]

- Compared with pretreatment values, the median number of weekly anginal attacks decreased significantly in all 3 groups, but significant reductions in weekly nitroglycerin consumption were observed only in nifedipine-GITS and isosorbide mononitrate EL recipients.[9]

- Significant ($p \leq 0.05$) improvements from baseline values in time to 1mm ST depression, time to angina, exercise duration and time to maximum heart rate were observed 24 hours after the last dose (or 16 hours after the last dose of isosorbide dinitrate) in all treatment groups.[9]

- 15 patients with stable angina pectoris received either isosorbide mononitrate EL 50mg once daily for 1 week or immediate-release isosorbide mononitrate 20mg 3 times daily for 1 week or sustained-release nifedipine 20mg 3 times daily for two 1-week periods in a randomised, double-blind, crossover study. There was no washout period and after each 7-day treatment period patients underwent 24-hour ambulatory electrocardiographic monitoring.[20]

- A significant reduction from baseline values in daily number (2.5 episodes per 24 hours) and duration (58 minutes per 24 hours) of ischaemic episodes was observed in all 3 treatment groups: by 68 and 70.7%, respectively, with isosorbide

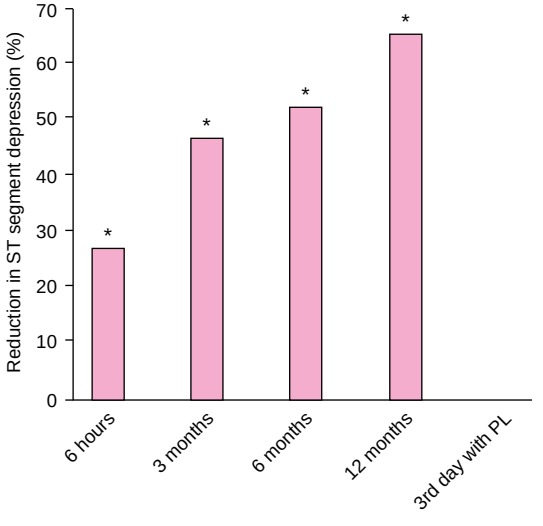


Fig. 2. Long term efficacy of isosorbide mononitrate EL 50mg. Reduction in ST segment depression at a comparable workload of 93W, from a baseline value of -20mV, with oral isosorbide mononitrate EL 50mg administered once daily for 12 months. ST segment depression at comparable workload was also measured 3 days after drug withdrawal.[24] **PL** = placebo; * $p < 0.001$ vs baseline.

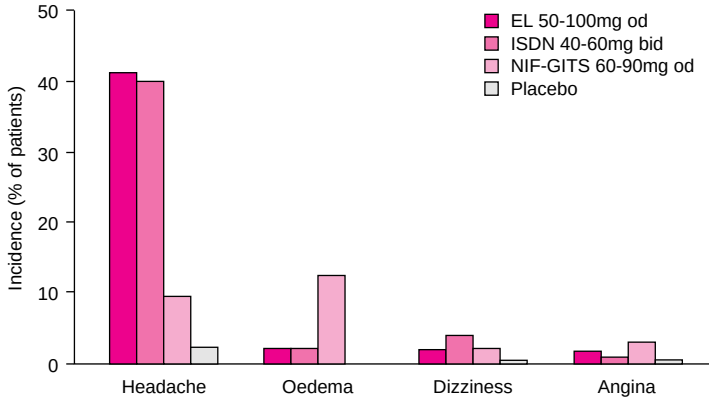


Fig. 3. Adverse events with isosorbide mononitrate (EL) 50 to 100mg, conventional isosorbide dinitrate (ISDN) 80 to 120mg or nifedipine-gastrointestinal therapeutic system (NIF-GITS) 60 to 90mg. Incidence of adverse events in patients with stable angina pectoris not adequately controlled with β-adrenoceptor blockers who received add-on therapy with either EL (n = 70), ISDN (n = 74) or NIF-GITS (n = 85) for a period of 6 weeks in a randomised, double-blind, parallel group trial.[9] A total of 335 patients were included in the 2-week placebo run-in phase prior to the trial. **bid** = twice daily; **od** = once daily.

mononitrate EL 50 mg/day; by 68 and 72.4%, respectively, with immediate-release isosorbide mononitrate 60 mg/day; and by 56 to 60 and 69%, respectively, with sustained-release nifedipine 60 mg/day.[20]

Comparison with Bupranolol

• Two hours after receiving isosorbide mononitrate EL 50mg, but not bupranolol 100mg, 30 patients with stable angina pectoris showed significant reduction in exercise-induced ST segment depression (by 49% from baseline values) in a randomised, double-blind, crossover trial.[21]

• After 12 days' treatment, 30 isosorbide mononitrate EL 50mg recipients showed similar significant reductions from baseline values in ST segment depression at comparable workload (by 47 *vs* 24%), increase in maximal workload (by 36 *vs* 24%) and increase in exercise capacity (by 70 *vs* 51%) to those receiving bupranolol 100mg. However, isosorbide mononitrate recipients showed significantly greater reduction from baseline values in weekly anginal attacks (by 76 *vs* 52%) and nitroglycerin consumption (by 78 *vs* 53%) than bupranolol recipients.[21]

Long Term Efficacy

• Oral administration of isosorbide mononitrate EL 50mg once daily for 12 and 13 months was not associated with the development of tolerance in 3 open-label trials (n = 30 to 45 patients per trial).[22-24] From baseline ST segment depression of 0.20mV, significant reductions with isosorbide mononitrate EL 50mg once daily were evident after 6 hours (26.6%), 3 months (46.7), 6 months (52.5%) and 12 months in one of these studies[24] (fig. 2).

• There was a corresponding significant reduction from pretreatment values in the weekly incidence of anginal episodes (76 to 94.3%) and nitroglycerin consumption (76 to 90%) in all three studies.[22-24]

• ST segment depression, incidence of anginal attacks and nitroglycerin consumption were similar to pretreatment values 3 to 7 days after discontinuation of therapy.[22-24]

4. Tolerability

• Isosorbide mononitrate EL 50mg is well tolerated and no serious adverse events were observed in patients receiving the drug in clinical trials (section 3).

• Headache, a class effect of organic nitrates, was the most common adverse event reported with isosorbide mononitrate EL 50 to 100mg (41[9] to 66.6%[24] of recipients). Headache commonly occurred at initiation of therapy, was of mild to moderate intensity[24] and necessitated drug withdrawal in up to 17% of patients.[9] Other adverse events associated with the use of isosorbide mononitrate EL 50 to 100mg are shown in figure 3.

• Patients receiving isosorbide mononitrate EL 100mg once daily for 3 months reported fewer adverse effects than those receiving once-daily isosorbide mononitrate 50mg or sustained-release isosorbide mononitrate 50 to 60mg for 3 months: side effect index score of 3.55 *vs* 3.45, $p < 0.001$.[17]

5. Long-Acting Isosorbide Mononitrate: Current Status

Isosorbide mononitrate EL is a long-acting organic nitrate with a rapid onset of action. It has shown clinical efficacy in patients with stable angina pectoris and is well tolerated. In addition, nitrate tolerance has not been reported with the continued use of isosorbide mononitrate EL.

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