S-amlodipine – From clinical review

S-amlodipine is the only vaso-active enantiomer of amlodipine. Randomised controlled trials of S-amlodipine in nearly 5000 patients at half the dose of racemate in the treatment of hypertension, have shown it to be as effective as racemic amlodipine. The postmarketing surveillance studies (n = 4089) of S-amlodipine confirmed its antihypertensive efficacy and showed that the incidence of peripheral oedema is negligible with S-amlodipine compared to racemic amlodipine. Further, the patients with peripheral oedema who were switched over from racemic amlodipine to S-amlodipine resolved their oedema associated with the racemate, while sustaining the blood pressure control. Subgroup analyses showed S-amlodipine to be effective and safe in elderly hypertensives and isolated systolic hypertension patients. A clinical study in normotensive angina patients confirmed the anti-anginal efficacy of S-amlodipine at half the dose of racemate. Fixed-dose combinations of S-amlodipine with atenolol and S-amlodipine with hydrochlorothiazide have been shown to be effective and well tolerated in clinical practice. In the light of its efficacy and favourable tolerability profile, S-amlodipine used alone or in combination with other antihypertensive or anti-anginal drugs, is a valuable treatment option in the management of hypertension and angina. (Thacker HP. 2007)

S-Amlodipine – Efficacy and Safety from Clinical Evidence

Study Detail - Multicentric, clinical trial of S-Amlodipine 2.5 mg versus Amlodipine 5 mg in the treatment of mild to moderate hypertension--a randomized, double-blind clinical trial. (Pathak L, et al. 2004)

The efficacy and tolerability of 2.5 mg of S-Amlodipine with 5 mg of Amlodipine in the treatment of mild to moderate hypertension in a double blind, double dummy, randomized, comparative clinical trial was compared. Two hundred OPD patients (97 women and 103 men) with mean age 53.4 +/- 5.58 years, with stage I and stage 2 hypertension were enrolled for the study after obtaining informed written consent. Twelve patients were dropped out as lost to follow up. Ninety seven patients in the S-Amlodipine 2.5 mg treatment group and ninety one
patients in the Amlodipine 5 mg treatment group completed the study. Those with a history of angina pectoris, myocardial infarction or recent cerebrovascular accident in the past six months and those with stage 3 and stage 4 hypertension were excluded from the study. Those showing a history of secondary hypertension were also excluded from the study. For the first two weeks all patients received dummy tablets of both S-Amlodipine and Amlodipine, as a wash out therapy and to get the actual blood pressure reading. After two weeks, enrolled patients received a preparation containing either S-Amlodipine (containing 2.5 mg of S-Amlodipine) and dummy tablets of Amlodipine or Amlodipine besylate (containing 5 mg of racemic Amlodipine) and dummy tablets of S-Amlodipine once daily for a period of six weeks. The results were analyzed by Student's 't' test The reduction in the average systolic and diastolic blood pressure, in the standing, supine and sitting postures in the S-Amlodipine group as well as in the Amlodipine group after six weeks of treatment was highly significant (P < or = 0.0001). The baseline values for average systolic blood pressure in standing, supine and sitting positions in the S-Amlodipine 2.5 mg treatment group were found to be 164.12 +/- 10.28, 165.72 +/- 10.88 and 165.24 +/- 10.66 mm of Hg respectively, which after treatment of six weeks changed to 144.9 +/- 7.4, 146.04 +/- 8.56 and 145.36 +/- 8.32 mm of Hg. The baseline values for average systolic blood pressure in standing, supine and sitting positions in the Amlodipine 5 mg treatment group were found to be 164.57 +/- 10.36, 166.47 +/- 10.58 and 165.81 +/- 10.54 mm of Hg respectively, which after treatment of six weeks changed to 154.42 +/- 6.33, 147.23 +/- 7.11 and 146.57 +/- 7.54 mm of Hg. The baseline values for average diastolic blood pressure in standing, supine and sitting positions in the S-Amlodipine 2.5 mg treatment group were found to be 99.63 +/- 6.22, 101.13 +/- 7.18 and 100.59 +/- 6.6 mm of Hg respectively, which after treatment of six weeks changed to 86.0 +/- 4.70, 87.18 +/- 5.20 and 86.27 +/- 5.68 mm of Hg. While the baseline values for average diastolic blood pressure in standing, supine and sitting positions in the Amlodipine 5 mg treatment group were found to be 98.95 +/- 5.54, 100.86 +/- 6.71 and 100.38 +/- 6.38 mm of Hg respectively, which after treatment of six weeks changed to 86.19 +/- 4.77, 87.52 +/- 5.44 and 87.33 +/- 5.98 mm of Hg. However the difference in the average reduction in systolic and diastolic blood pressures, in the two treatment groups, in the sitting, supine and the standing positions was not found to be statistically significant (p > 0.1) (CI = 0.95). There was no statistically significant change in the levels of serum creatinine, SGOT, SGPT, HDL, LDL, triglyceride and total cholesterol in patients receiving Amlodipine 5 mg. The reduction in total
cholesterol as well as triglyceride level in the S-Amlodipine 2.5 mg treatment group was found to be greater but it failed to show any statistically significant difference.

S-Amlodipine 2.5 mg is found to be equivalent in its efficacy and tolerability when compared to Amlodipine 5 mg in the treatment of mild to moderate hypertension.

**Study Detail - Efficacy and safety profiles of a new S(-)-amlodipine nicotinate formulation versus racemic amlodipine besylate in adult Korean patients with mild to moderate hypertension: an 8-week, multicenter, randomized, double-blind, double-dummy, parallel-group, phase III, noninferiority clinical trial.**

"Chiral switching" from an existing racemate to a pure enantiomeric compound is a popular theme in drug development, especially when the enantiomer is found to have better efficacy and safety profiles. Amlodipine is a racemic mixture, composed of the S(-)-enantiomer, which is the pharmacologically active isomer, and the R(+)-enantiomer, which is 1000-fold less active. S(-)-amlodipine nicotinate, a chirally switched form of amlodipine nicotinate, has been developed and found to be bioequivalent to amlodipine besylate in Phase I clinical trials in Korea. The aim of this study was to compare the efficacy and safety profiles of S(-)-amlodipine nicotinate with those of amlodipine besylate in adult Korean patients with mild to moderate hypertension (diastolic blood pressure [DBP] $\geq$ 90 mm Hg and $\leq$ 109 mm Hg). This was an 8-week, multicenter, randomized, double-blind, double-dummy, parallel-group, Phase III, noninferiority clinical trial. After an initial 2-week placebo run-in period, patients aged 18 to 75 years with sitting DBP (SiDBP) $\geq$ 90 and $\leq$ 109 mm Hg at day 0 (baseline) were randomly allocated to receive S(-)-amlodipine nicotinate 2.5 mg QD or amlodipine besylate 5 mg QD for 8 weeks. The dose of study medication was doubled after 4 weeks in patients who had not responded to treatment (SiDBP $\geq$ 90 mm Hg). The primary end point was noninferiority of the difference in mean SiDBP from baseline to week 8 for S(-)-amlodipine nicotinate compared with amlodipine besylate. Secondary end points were as follows: (1) noninferiority of the difference in mean sitting systolic blood pressure (SiSBP) from baseline to week 8 between the study groups; and (2) SiDBP response rate (defined as the proportion of patients whose SiDBP was $< 90$ mm Hg or whose SiDBP reduction was $> 10$ mm Hg from baseline) after the 8-week treatment. Also, the incidence and severity of adverse events (AEs) and adverse drug reactions (ADRs) were
reported. Severe AEs/ADRs were defined as those associated with any of the following: death; an event associated with a high risk of mortality; an event requiring hospitalization; or development of a permanent disability or congenital malformation.

One hundred fifty-seven patients were assessed for inclusion in the study. Of these, 124 patients were randomly allocated to receive S(-)-amlodipine nicotinate (42 men, 21 women; mean [SD] age, 52.4 [10.3] years [range, 23-70 years]; weight, 67.7 [10.8] kg [range, 44-92 kg]) or amlodipine besylate (45 men, 16 women; mean [SD] age, 54.5 [10.0] years [range, 30-73]; weight, 68.9 [9.8] kg [range, 49-95 kg]). One hundred sixteen patients completed the study, but 11 patients (8.9%) were dropped from the per-protocol analysis due to violations; therefore, 105 patients were included in the modified intent-to-treat population analysis (S[-]-amlodipine nicotinate, 55 patients; amlodipine besylate, 50 patients). There were no significant between-group differences in the baseline characteristics. Baseline mean (SD) SiSBP and SiDBP were 142.6 (11.3) and 94.9 (4.8) mm Hg in the S(-)-amlodipine nicotinate group, and 141.8 (8.3) and 96.1 (4.9) mm Hg in the amlodipine besylate group. Mean (SD) changes in SiSBP were 17.6 (11.2) mm Hg in the S(-)-amlodipine nicotinate group and 18.6 (12.3) mm Hg in the amlodipine besylate group. The SiDBP response rates were 92.7% in the S(-)-amlodipine nicotinate group and 88.0% in the amlodipine besylate group. There were no significant between-group differences in the prevalence of AEs and ADRs. In the S(-)-amlodipine nicotinate group, 15 patients (23.8%) reported a total of 28 AEs, and 19 patients (31.1%) reported a total of 27 AEs in the amlodipine besylate group. Six patients (9.5%) in the S(-)-amlodipine nicotinate group and 7 patients (11.4%) in the amlodipine besylate group experienced a total of 19 ADRs (11 and 8, respectively). The most common ADRs were liver enzyme elevation (3/63 [4.8%]) in the S(-)-amlodipine nicotinate group and facial flushing (3/61 [4.9%]) in the amlodipine besylate group. No cases of severe AEs or ADRs were reported in either group. The reduction of SiDBP after 8 weeks of treatment with S(-)-amlodipine nicotinate was noninferior compared with that of racemic amlodipine besylate in these adult Korean patients with mild to moderate hypertension. The SiDBP response rate and the reduction of SiSBP after 8 weeks of treatment with S(-)-amlodipine nicotinate were not significantly different from those with racemic amlodipine besylate. Both treatments were generally well tolerated.
Study Detail - Comparative estimation of efficiency and safety of racemic amlodipine and its S-enantiomer in hypertensive patients. (Sierkova VK, et al., 2009)

The authors conducted comparative estimation of efficiency and safety of racemic (R+S-) amlodipine and sinistrorotatory isomer--S(-)amlodipine besylate in 63 hypertensive patients from which 32 patients were administered (R+S-) amlodipine and 31-S(-)amlodipine besylate. It was established identity of antihypertensive effect according daily monitoring of blood pressure and monitoring of blood pressure in the office. However, daily dose of S(-) enantiomer was two times less than the dose of (R+S-) amlodipine. Adverse effects (headache, excessive heartbeat, peripheral edema) were less in patients who have received S(-) amlodipine besylate that contributed to more expressed positive clinical dynamic of the state of patients of this group.

Cross BW, et al., (1993) performed an open, non-comparative study of 10 weeks' duration in general practice to assess the safety of amlodipine in patients with mild to moderate hypertension. Of the 5352 patients entering the study, 5135 received amlodipine; 4621 patients (90%) with a mean age of 58.2 years completed the study. Normalisation of blood pressure was achieved in over 80% of patients with a mean reduction of 21/15 mmHg. The mean final dose of amlodipine was 6.8 mg/day. Adverse experiences possibly related to amlodipine were reported by 19.3% of patients, and overall adverse events led to withdrawal in 6.7% of patients. The most common reported side-effect was oedema. The frequency of headache was almost identical in older and younger patients and oedema, flushing and dizziness were seen only slightly more often in elderly patients.

Osterloh I., (1989) assessed safety profile of amlodipine from the pooled data base of clinical research studies. This data base included 4227 subjects, 2495 of whom received amlodipine (including 2189 who received multiple-dose amlodipine); the remainder received comparative agents (placebo 1213; active comparatives 519). Amlodipine treatment was associated with a slightly higher incidence of side effects compared with placebo, but most of this difference was the result of edema, which was usually well tolerated. The data base comparing different calcium antagonists was small; in a study versus verapamil, edema was more common in patients receiving amlodipine, but constipation was more common in patients receiving verapamil.
Messerli FH., (2002) studied that vasodilatory edema, a common adverse effect of antihypertensive therapy with vasodilators, is related to several mechanisms, including arteriolar dilatation (causing an increase in intracapillary pressure), stimulation of the renin-angiotensin-aldosterone system, and fluid volume retention. Vasodilatory edema is dose dependent and most common with direct arteriolar dilators such as minoxidil or hydralazine, and in decreasing order of frequency with the dihydropyridine calcium antagonists, α-blockers, antiadrenergic drugs, and nondihydropyridine calcium antagonists. Not all dihydropyridine calcium antagonists are created equal with regard to vasodilatory edema. At an equal antihypertensive efficacy, lercanidipine and lacidipine are associated with less vasodilatory edema than amlodipine and nifedipine. The addition of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) to a dihydropyridine calcium antagonist significantly reduces vasodilatory edema.

Pedrinelli R, et al., (2000) evaluated occurrence of leg edema with calcium channel blockers (CCBs) that blunt postural skin vasoconstriction, an autoregulatory mechanism that minimizes gravitational increases in capillary pressure and avoids fluid extravasation when standing. To evaluate the dose-response relation between this pharmacological interference and dependent edema, a frequent side effect of CCBs during antihypertensive treatment, skin blood flow (laser Doppler flowmetry) at the dorsum of the foot, both supine and with the limb passively placed 50 cm below the heart level, and leg weight (Archimedes principle) were measured at baseline, during increasing doses of the dihydropyridine amlodipine (5 and 10 mg UID each for 2 weeks), and after drug withdrawal in 10 hypertensive men. Amlodipine (5 mg UID) increased leg weight without modifying postural vasoconstriction (the percent skin blood flow decrease from horizontal to dependent position), which indicates that extravascular fluid shift was independent of postural skin vasoconstriction. At 10 mg UID, however, amlodipine blunted postural vasoconstriction and increased leg weight further, which suggests that skin blood flow autoregulation limited additional fluid transfer.

Malacco E, et al., (2003) evaluated that some antihypertensive therapies are limited by dose-dependent adverse effects (AEs). Amlodipine besylate is a potent dihydropyridine calcium
channel blocker also with dose-related antihypertensive efficacy, but with possible dose-limiting AEs, particularly peripheral edema. This study compared the risk/benefit profiles of valsartan and amlodipine in elderly patients who have isolated systolic hypertension (ISH). The frequency of AEs doubled with amlodipine 10 mg but was not clinically relevant with valsartan 160 mg. Overall, AEs were observed in 31.9% of those receiving amlodipine versus 20.2% of the patients receiving valsartan (P < 0.003), with peripheral edema rates of 26.8% and 4.8%, respectively (P < 0.001). In this study population of elderly patients with ISH, valsartan-given alone or in combination with HCTZ 12.5 mg-showed similar efficacy but better tolerability than amlodipine-based treatment.

Andrésdóttir MB, et al., (2000) compared edema formation on two dihydropyridine calcium channel blockers, using an accurate method for quantitative assessment of foot volume. In a randomized study, we treated 62 patients with essential hypertension for 12 weeks starting with either lacidipine 4 mg o.d. (n = 30) or amlodipine 5 mg o.d. (n = 32). At 6 weeks, the doses were increased to that maximally allowed (lacidipine 6 mg, n = 18; amlodipine 10 mg, n = 12) if trough diastolic blood pressure response was insufficient (>90 mmHg and decrease <10 mmHg). Edema, scored visually, occurred more frequently (p = 0.02) on amlodipine (15/32) than on lacidipine (6/30); this was confirmed by an increase of foot volume above the 95% upper limit of normal variation in 15 patients on amlodipine and in only five patients on lacidipine (p = 0.01). In the whole group of patients, both the increases of foot volume and the decreases of blood pressure just failed to be significantly different between amlodipine and lacidipine (foot volume, +3.3 ± 1.0% on amlodipine and +1.2 ± 0.5% on lacidipine, p = 0.08; mean arterial pressure, -11 ± 1% on amlodipine and -8 ± 1% on lacidipine, p = 0.052). In patients requiring dose increase, the increase of foot volume on amlodipine was more pronounced (p < 0.05), and the antihypertensive effect was larger (p < 0.05) than on lacidipine. In conclusion, our data show a higher incidence of edema on amlodipine than on lacidipine, which has to be explained at least partly by a comparably higher dose c.q. a larger antihypertensive effect of amlodipine. Other mechanisms might have contributed to these differences and need to be explored.
**Stanek EJ, et al., (1997)** studied a case to report a nonfatal intentional overdose of amlodipine. A 42-year-old woman with a history of hypertension reported ingesting 50-100 mg amlodipine besylate and at least 40 ounces of beer in a suicide attempt. The patient's symptoms were mild; BP ranged from 79/50 to 113/76 mm Hg and HR from 92 to 129 beats/min (sinus tachycardia). In this case, an amlodipine overdose was associated with sustained hypotension and sinus tachycardia, as well as transient pulmonary edema following relatively low-volume fluid replacement. A previously published report described an amlodipine overdose that was fatal due to refractory hypotension and was complicated by concomitant oxazepam overdose. Amlodipine overdose produces prolonged hemodynamic effects and may lead to pulmonary edema. Due to a long elimination half-life and delayed onset of effects, patients with amlodipine overdose should receive aggressive decontamination therapy and may require extended clinical monitoring and supportive care if they are hemodynamically unstable.

**Clavijo GA, et al., (1994)** reviewed the chemistry, pharmacology, pharmacokinetics, efficacy, and adverse effects of amlodipine. Amlodipine is a potent peripheral and coronary vasodilator with high selectivity for vascular smooth muscle and minimal effect on myocardial contractility or cardiac conduction. Absorption after oral administration is slow, and the duration of action is long, with a half-life of 36-45 hours. Amlodipine has FDA-approved labeling for use in the treatment of hypertension, chronic stable angina, and vasospastic angina. The agent is also indicated for use in hypertensive or anginal patients who also have congestive heart failure due to systolic dysfunction (New York Heart Association classes II and III). Clinical trials suggest that effective 24-hour control of hypertension and angina is provided by once-daily administration of amlodipine 5-10 mg alone or in combination with other drugs. No clinically important drug interactions have been observed to date. Amlodipine has not shown any unfavorable effects on serum glucose or lipid levels. The most common adverse effect is peripheral edema. Amlodipine is effective and well tolerated when given alone or in combination with other drugs for the treatment of hypertension and angina.

**Oh GC, et al., (2012)** compared the amount of pedal edema experienced by female Korean patients with mild to moderate hypertension when receiving S(-)-amlodipine nicotinate
compared with amlodipine besylate. This study was a 12-week, multicenter, randomized, double-blind, active-controlled, Phase IV clinical trial. Female patients with mild to moderate hypertension were randomly assigned to receive either S(-)-amlodipine nicotinate 2.5 to 5 mg once daily or amlodipine besylate 5 to 10 mg once daily for 12 weeks. The primary objective was to compare the change in ankle-foot volume quantified by using a water displacement method after 12 weeks of therapy. The secondary objectives were to compare the changes in mean sitting systolic and diastolic blood pressures. These female Korean patients with hypertension taking S(-)-amlodipine nicotinate had less ankle edema, with no significant difference in BP-lowering efficacy, compared with those taking amlodipine besylate. S(-)-amlodipine nicotinate may be a suitable alternative for patients intolerant to amlodipine besylate.

Schoeller DA, et al., (2012) performed a study to identify a robust and practical method for measuring drug-induced pedal edema for use in the clinical development of antihypertensives. The efficacy of segmental bioimpedance in the detection of increased pedal edema was compared with that of clinical pitting assessment, ankle circumference, and water displacement volumetry. In this population of healthy subjects and patients with hypertension, segmental bioimpedance was comparable to water displacement and ankle circumference and outperformed clinical assessment of pitting for the detection of ankle edema, supporting the use of segmental bioimpedance as a drug-development tool to objectively quantify amlodipine-induced pedal edema.

A study by Kloner RA, et al., (2001) illustrates the difficulty of accurately reporting edema frequency and severity: "The degree of peripheral edema was assessed at each visit by applying gentle pressure to elicit 'pitting' and was ranked as mild, moderate, or severe according to the following criteria. Mild: edema was present on examination, but the patient was not aware of it (asymptomatic); the edema did not interfere with daily living, and the patient was willing to continue study medication. Moderate: edema was present on examination, and the patient was aware of it (symptomatic); the edema did or did not interfere with daily living, and the patient was willing to continue study medication. Severe: edema was present on examination, and the patient was aware of it (symptomatic); the edema interfered with daily living, and the patient was
unwilling to continue study medication." Although objective criteria were used for determining the presence of edema in that study, the category assignment was extremely subjective.

**Cho S, et al., (2002)** reveals that each of these modes of frequency ascertainment also falls short in that the background frequency of peripheral edema before the start of CCB therapy is rarely identified. Transient peripheral edema is quite common in the general population relating to posture, climactic conditions, and age.

**Gustafsson D, et al., (1989)** evaluated that CCB-related edema can occur with pre-existing volume expanded forms of edema, in which case the edema can be severe. CCB-related edema is caused by preferential arteriolar or precapillary dilation without commensurate dilation in the venous or postcapillary circulation.

**Damasceno A, et al., (1999) and Tsutamoto T, et al., (2003)** evaluated this discrepancy in resistance values increases pre-capillary pressures to a degree that plasma is literally forced from the intravascular compartment into the interstitium -- the origin of peripheral edema with CCB therapy. Under these circumstances the continuous nature of transcapillary fluid movement must exceed the capacity of the lymphatic system for edema to be clinically evident. The issue of CCBs specifically modifying capillary permeability as an additional cause of edema has been debated with no definitive conclusions. In addition, if specific CCBs increase angiotensin-II concentrations it can be expected that venoconstriction might occur with the potential for worsening of the peripheral edema.

**Fogari R, et al., (2000)** evaluated a common pattern with CCB-related peripheral edema is that edema is worse at the end of the day and improves and/or disappears after a patient has remained recumbent throughout the overnight hours. Warm conditions -- be they seasonal or work-related -- can independently vasodilate the arteriolar circulation and worsen edema. Age is an additional determinant of edema in that interstitial tissue typically serves a barrier role to hydrostatically
driven edema formation and the counterbalancing nature (to prevent edema) of such tissue diminishes with age.

**Messereli FH, et al., (2002)** evaluated that Pedal edema is one of the most common adverse effects of calcium antagonists. It has been observed with all available dihydropyridine agents, but it also seems to occur to a lesser extent with verapamil and diltiazem. The incidence of pedal edema is clearly dose dependent and may exceed 80% with very high doses of dihydropyridine calcium antagonists. With starting doses of amlodipine or felodipine, only about 5% of patients will complain of swelling of the feet or ankles. Of clinical interest is the observation in the COHORT study that the incidence of edema gradually increased throughout the study (despite the fact that the calcium antagonist dose was kept constant after 8 weeks) to reach the highest levels at the end of the study in all three calcium antagonist arms. This clearly indicates that pedal edema is not transient (i.e., will not go away with time) but, if anything, becomes more severe with continued calcium antagonist therapy.

**Paudel R, et al., (2007)** studied that S-amlodipine is a stereoisomer of Amlodipine, a dihydropyridine Calcium Channel Blocker (CCB) used in angina and hypertension. This drug is expected to produce a lesser incidence of pedal oedema, as compared to Amlodipine, based on the limited data available from clinical trials. However, conflicting results have been noted with this drug, in relationship to the occurrence of pedal oedema. We report three cases, where the patients either did not recover from pedal oedema, or had a worsening of pedal oedema after substituting S-amlodipine in place of other CCBs that caused pedal oedema.

**S-Amlodipine – Future**

A post marketing surveillance study to evaluate efficacy and tolerability of S-Amlodipine in treatment of mild to moderate hypertension is designed. The objective of this study is to evaluate the efficacy and tolerability of S-Amlodipine 2.5mg in the patients who have been treated with Amlodipine 5mg in daily practice for the management of Hypertension. The intervention will consist of Drug- S-Amlodipine 2.5 mg once daily alone or in combination with concurrent therapy, switching from Amlodipine to S-Amlodipine.
The proposed study will highlight and emphasize the role of S-Amlodipine in the management of Hypertension as compared to Amlodipine.