S-Amlodipine

IN HYPERTENSION

Dr P Bhandari, MD
Director – Medical
Emcure Pharmaceuticals Ltd.

“The five main classes of blood pressure lowering drugs (thiazides, β blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers) were similarly effective (within a few percentage points) in preventing CHD events and strokes, with the exception that calcium channel blockers had a greater preventive effect on stroke (relative risk 0.92, 95% confidence interval 0.85 to 0.98).”

“The effect of blood pressure lowering drugs in reducing the risk of disease is entirely or largely due to blood pressure reduction”
Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis

Compared with other drugs, interindividual variation in SBP was

- reduced by calcium-channel blockers (VR 0.81, 95% CI 0.76–0.86, p<0.0001) and non-loop diuretic drugs (0.87, 0.79–0.96, p=0.007), and

- increased by angiotensin-converting enzyme (ACE) inhibitors (1.08, 1.02–1.15, p=0.008), angiotensin-receptor blockers (1.16, 1.07–1.25, p=0.0002), and β blockers (1.17, 1.07–1.28, p=0.0007).

Compared with placebo only, interindividual variation in SBP was reduced the most by calcium-channel blockers (0.76, 0.67–0.85, p<0.0001).

www.thelancet.com Vol 375 March 13, 2010
Efficacy in African Patients

Heart 2005;91;1105-1109

Emcure
Introduction to Chirality

Mirror

Mirror

Hand and Foot

Molecular Structures

Emcure
Enantiomers differ in action

- Beneficial effects reside in one enantiomer, the other enantiomer having completely separate beneficial activity:
  - Dextropropoxyphene (analgesic); levopropoxyphene (anti-tussive)

- Beneficial effects reside in one enantiomer, the other enantiomer having adverse activity:
  - Esketamine (no hallucination/agitation),
  - Levobupivacaine (no cardiotoxicity)
  - S-metoprolol (beta-1 blocker); R-metoprolol (beta-2 blocker)

- Only one isomer is active, the other is “inactive”:
  - Levocetirizine (active),
  - Levofloxacin (active)
  - S-amlodipine (active)

- One isomer is active, the other is more potent
  - Esomeprazole (more potent)
  - S-pantoprazole (more potent)
  - Dexrabeprazole (more potent)

- Beneficial effects reside in one enantiomer, the other enantiomer having antagonistic activity:
  - Levo-salbutamol (bronchodilator without pro-inflammatory properties)
Advertisement for S-Amlodipine in Korea

Upgrade!

S-암로디핀 레보텐션!
Amlodipine = R + S
Changes of action potential and L-type calcium channel current of Sprague–Dawley rat ventricular myocytes by different amlodipine isomers

Ru-xing Wang and Wen-ping Jiang

Abstract: To investigate the effects of S- and R-amlodipine (Aml) on action potential (AP) and L-type calcium channel current (I_{Ca-L}) in rat ventricular myocytes, the whole-cell patch-clamp technique was used to record AP, I_{Ca-L}, peak currents, steady-state activation currents, steady-state inactivation currents, and recovery currents from inactivation with S-Aml and R-Aml at various concentrations. Increasing concentrations of S-Aml gradually shortened AP durations (APDs). At 0.1, 0.5, 1, 5, and 10 μmol/L, S-Aml blocked 1.5% ± 0.2%, 25.4% ± 5.3%, 65.2% ± 7.3%, 78.4% ± 8.1%, and 94.2% ± 5.0% of I_{Ca-L}, respectively (p < 0.05), and the half-inhibited concentration was 0.62 ± 0.12 μmol/L. Current–voltage curves were shifted upward; steady-state activation and inactivation curves were shifted to the left. At these concentrations of S-Aml, the half-activation voltages were −16.01 ± 1.65, −17.61 ± 1.60, −20.17 ± 1.46, −21.87 ± 1.69, and −24.09 ± 1.87 mV, respectively, and the slope factors were increased (p < 0.05). The half-inactivation voltages were −27.16 ± 4.48, −28.69 ± 4.52, −31.19 ± 4.17, −32.63 ± 4.34, and −35.16 ± 4.46 mV, respectively, and the slope factors were increased (p < 0.05). The recovery times from inactivation of S-Aml were prolonged (p < 0.05). In contrast, R-Aml had no effect on AP and I_{Ca-L} (p > 0.05) at the concentrations tested. Thus, only S-Aml has calcium channel blockade activity, whereas R-Aml has none of the pharmacologic actions associated with calcium channel blockers.

Canadian J Physiol Pharmacol, 2008
R-amlodipine does not decrease BP

Amlodipine Enantiomers on Systolic BP in Spontaneously Hypertensive Rats

Weeks

SBP (mmHg)

control  S-AM 5  S-AM 10  R-AM 5  RAC 10

CARDIOLOGY TODAY
Vol. 11 No. 5  September-October 2007
S-amlodipine controls BP 24 hrs

Effects of S-Amlodipine and Amlodipine treatment on (mean) mean arterial pressure (mmHg)

After Therapy (mean)
MAP in both the groups

(mean) Mean Arterial Pressure (MAP) mmHg

110
100
90
80

Hours of Ambulatory Blood Pressure Monitoring

Indian Medical Gazette — DECEMBER 2007
BP response 2.5 S = 5.0 mg Racemate


Ref: JAPI 2004;52:197-20;
# Negligible edema with S-Amlodipine

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>EDEMA</th>
<th>% EDEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SESA</td>
<td>1859</td>
<td>14</td>
<td>0.75</td>
</tr>
<tr>
<td>SESA-II</td>
<td>2230</td>
<td>43</td>
<td>1.93</td>
</tr>
<tr>
<td>SESA-IV</td>
<td>1051</td>
<td>13</td>
<td>1.24</td>
</tr>
<tr>
<td>TOTAL</td>
<td>5140</td>
<td>70</td>
<td>1.36</td>
</tr>
</tbody>
</table>

- **Amlodipine**: 16%
- **S-Amlodipine**: 1.36%
Russian data

Азомекс 1,6%
рацемический амлодипин 7,8%
Resolution after switching to S-amlo
S-Amlodipine: safe/effective in elderly


- This may be responsible for higher incidence of ADR in elderly.
S-Amlodipine: effective in angina

Reduction in angina episodes after treatment with S-Amlodipine

No. of Angina Attacks in Last 2 Weeks

Baseline 2 Weeks 4 Weeks 6 Weeks 8 Weeks

Time

IMG SEP 2005
S-Amlodipine: effective in ISH

ISH (All) : Reduction in SBP with S(-)Amlodipine

SBP (mmHg) mean +/- SD

180
170
160
150
140
130
120
110

day 0  day 7  day 14  day 21  day 28

IMG JUN 2005
“Monotherapy with S-amlodipine in a dose range of 2.5-5mg once daily achieved normalization of blood pressure in 85% hypertension patients after kidney transplantation.”

Shanghai Institute of Hypertension, Rui jin Hospital, Shanghai, P.R., China
American Journal Hypertension –May 2003–VOL. 16, NO. 5, PART 2
“Conclusions: S-amlodipine not only effectively decreases the hypertension but also remolds the hypertrophied ventricle and reduces intima-media thickness of carotid artery.”*

“All the cardio-protective and vasculo-protective effects of Amlodipine are the class effects attributable principally to the basic calcium channel blocking effect of Amlodipine”

“Antioxidant activity of amlodipine is atributed to both its high lipophilicity and the DHP ring”

* Chinese Factories and Mines Medicine, 20 vol 3, 2007
S-Amlodipine: lesser variability

- Clearance of S-Amlodipine form is subjected to much less inter-subject variation (COV = 25%) than that of R-amlodipine (COV = 52%)

- Removing the variable inactive component further improves homogeneity in BP control by further reducing variations in plasma concentrations

Chirality. 1994;6(7):531-6
S-Amlodipine: longer half-life

- S-Amlodipine has longer half-life (49.6h) than R-Amlodipine (34.9 h) and racemic Amlodipine (44.2 h)

- Half-life of Amlodipine is strongly correlated with and highly predictive for half-life of the (S)-enantiomer.

- A longer half-life of S-Amlodipine ensures BP control during trough hours of dosing.

Chirality, 994;6(7):531-6
S-Amlodipine in African Patients

CLINICAL STUDIES
Protocol No: FHL/MM/ASOMEX/01

A comparative cross-over trial of S-Amlodipine besylate (Asomex) and Amlodipine besylate (Norvasc) in the treatment of mild to moderate hypertension

Key Investigators:
Oke DA¹, Oladapo A (Mrs)², Danbauchi S.S³, Onwubere BJC⁴ and Olayemi S⁵

Co-investigators:
Consultant Cardiologists: Ekpegbeh C.O¹, Dr Emmanuel Ejim⁴, Dr Sam Ike⁴, Dr Mohammed S Isa³;
Senior Registrar, Cardiology: Dr Nelson Oguanobi⁴, Dr Pascal C Azuh³, Dr. E. Nwafor², Dr. M.O. Oyebowale²

Correspondences:
Department of Medicine, College of Medicine University of Lagos¹, Department of Medicine, UCH Ibadan², Department of Medicine, Ahmadu Bello Teaching Hospital Zaria³, Department of Medicine, University of Nigeria Teaching Hospital Enugu⁴, Department of Pharmacology College of Medicine, University of Lagos⁵

Design: open, cross-over, multicentric, comparative

N= 162
Figure 3: Comparative weekly blood pressure changes
S-Amlodipine R&D @ Emcure*

* Including Emcure’s partners
A Novel Method for Resolution of Amlodipine

Dinkar M. Gotrane, Rajendra D. Deshmukh, Prasad V. Ranade, Swapnil P. Sonawane,* Baburao M. Bhawal, Milind M. Gharpure, and Mukund K. Gurjar

API R&D Centre, Emcure Pharmaceuticals Ltd., ITBT Park, Phase-II, MIDC, Hinjewadi, Pune-411057, India

Abstract:

The present invention relates to an industrially feasible and cost-efficient process for the preparation of isomerically pure S-amlodipine besylate hemipentahydrate (1), a useful calcium antagonist inhibitor. Previous workers reported that R-amlodipinetartrate was crystallized out preferentially from the reaction mixture when naturally occurring L-tartaric acid and racemic amlodipine base in DMSO are mixed. In order to crystallize S-amlodipinetartrate, the use of unnatural D-tartaric acid as a resolving agent in DMSO was required. However, the cost of D-tartaric acid was not conducive to overall cost efficiency in the resolution protocol. Subsequent to the above observations, we have developed a novel resolving system in which amlodipine base with natural L-tartaric acid in DMF as a solvent gave preferentially the S-form of amlodipine tartrate directly from the reaction. The optimization of this approach by adjusting the water percentage in DMF ensured consistent purity of S-amlodipine (+99%) and satisfactory resolution efficiency.

that the S-isomer (1) of amlodipine besylate had a better therapeutic profile than the corresponding R-isomer. It has been demonstrated that only the S-(-)-isomer of amlodipine was having the calcium channel blocker activity while the corresponding R-(+)-isomer had little or no calcium channel blocking activity. In fact our company has introduced S-amlodipine besylate for the first time in India under the brand name of Asomex and today chiral S-amlodipine is being marketed by us in more than 30 countries all over the world. The post-marketing surveillance study by Emcure has proven beyond doubt that S-amlodipine besylate is a well-accepted drug for hypertension. Prior art for the preparation of R- and S-enantiomers of amlodipine are (a) resolution of amlodipine azide ester with optically active 2-methoxy-2-phenylethanol, or (b) resolution of racemic amlodipine base with optically active camphanic acid, or (c) resolution of racemic amlodipine base to R-(+)- and S-(-)-isomers with L- or D-tartaric acid, respectively, in the organic solvent, DMSO. The separation of R- and S-amlodipine isomers was also achieved by the resolution.
# S-Amlodipine Pre-Clinical Studies

<table>
<thead>
<tr>
<th>No.</th>
<th>STUDY</th>
<th>SPECIES</th>
<th>PLACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acute IV toxicity</td>
<td>SD Rat</td>
<td>India</td>
</tr>
<tr>
<td>2</td>
<td>Acute IV toxicity</td>
<td>SA Mice</td>
<td>India</td>
</tr>
<tr>
<td>3</td>
<td>Subacute 28 days oral toxicity</td>
<td>SD Rat</td>
<td>India</td>
</tr>
<tr>
<td>4</td>
<td>Subacute 28 days oral toxicity</td>
<td>SA Mice</td>
<td>India</td>
</tr>
<tr>
<td>5</td>
<td>Subchronic 90 days oral toxicity</td>
<td>SD Rat</td>
<td>India</td>
</tr>
<tr>
<td>6</td>
<td>Single dose oral comparative toxicity</td>
<td>SD Rat</td>
<td>Korea</td>
</tr>
<tr>
<td>7</td>
<td>Repeated escalating oral 28 days</td>
<td>Beagle Dog</td>
<td>Korea</td>
</tr>
<tr>
<td>8</td>
<td>Comparative anti-hypertensive PD</td>
<td>SHR (Rat)</td>
<td>Korea</td>
</tr>
<tr>
<td>9</td>
<td>Single oral Pharmacokinetic study</td>
<td>Beagle Dog</td>
<td>Korea</td>
</tr>
</tbody>
</table>

SD = Sprague Dawley  
SA = Swiss Albino  
SHR = Spontaneous Hypertensive Rat
# S-Amlodipine Pharmacokinetic Studies

<table>
<thead>
<tr>
<th>No.</th>
<th>STUDY</th>
<th>Subjects*</th>
<th>PLACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bioequivalence versus Norvasc (1)</td>
<td>24</td>
<td>India</td>
</tr>
<tr>
<td>2</td>
<td>Bioequivalence versus Norvasc (2)</td>
<td>24</td>
<td>India</td>
</tr>
<tr>
<td>3</td>
<td>Bioequivalence of S-amlo/S-metoprolol</td>
<td>24</td>
<td>India</td>
</tr>
<tr>
<td>4</td>
<td>Bioequivalence of S-amlo/HCTZ</td>
<td>24</td>
<td>India</td>
</tr>
<tr>
<td>5</td>
<td>Bioequivalence of S-amlo/Ramipril</td>
<td>24</td>
<td>India</td>
</tr>
<tr>
<td>6</td>
<td>Bioequivalence of S-amlo/Losartan</td>
<td>24</td>
<td>India</td>
</tr>
<tr>
<td>7</td>
<td>Bioequivalence of S-amlo/Atorvastatin</td>
<td>28</td>
<td>India</td>
</tr>
<tr>
<td>8</td>
<td>Bioequivalence of S-amlo/S-atenolol</td>
<td>24</td>
<td>India</td>
</tr>
</tbody>
</table>

* Healthy human volunteers
## S-Amlodipine Clinical Trials

<table>
<thead>
<tr>
<th>No</th>
<th>DESIGN</th>
<th>PHASE</th>
<th>COUNTRY</th>
<th>COMPARATOR</th>
<th>INDICATION</th>
<th>SAMPLE SIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RCT</td>
<td>III</td>
<td>INDIA</td>
<td>NORVASC</td>
<td>Hypertension</td>
<td>188</td>
</tr>
<tr>
<td>2</td>
<td>RCT</td>
<td>III</td>
<td>INDIA</td>
<td>NORVASC</td>
<td>Hypertension</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>RCT</td>
<td>III</td>
<td>INDIA</td>
<td>NORVASC</td>
<td>Hypertension</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>RCT</td>
<td>III</td>
<td>RUSSIA</td>
<td>NORVASC</td>
<td>Hypertension</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>RCT</td>
<td>III</td>
<td>UKRAINE</td>
<td>NORVASC</td>
<td>Hypertension</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>RCT</td>
<td>III</td>
<td>KOREA</td>
<td>NORVASC</td>
<td>Hypertension</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>RCT</td>
<td>III</td>
<td>UKRAINE</td>
<td>NORVASC</td>
<td>Hypertension</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>RCT</td>
<td>III</td>
<td>NIGERIA</td>
<td>NORVASC</td>
<td>Hypertension</td>
<td>162</td>
</tr>
</tbody>
</table>

**RCT** = RANDOMIZED CONTROLLED TRIAL

| TOTAL | 792 |
# S-Amlodipine Clinical Trials

<table>
<thead>
<tr>
<th>No</th>
<th>DESIGN</th>
<th>PHASE</th>
<th>COUNTRY</th>
<th>COMPARATOR</th>
<th>INDICATION</th>
<th>SAMPLE SIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OL</td>
<td>IV</td>
<td>INDIA</td>
<td>NIL</td>
<td>ANGINA</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>OL</td>
<td>IV</td>
<td>INDIA</td>
<td>NIL</td>
<td>ABPM [HTN]</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>OL PMS</td>
<td>IV</td>
<td>INDIA</td>
<td>NIL</td>
<td>HTN</td>
<td>1859</td>
</tr>
<tr>
<td>4</td>
<td>OL PMS</td>
<td>IV</td>
<td>INDIA</td>
<td>NIL</td>
<td>HTN</td>
<td>2230</td>
</tr>
<tr>
<td>5</td>
<td>OL PMS</td>
<td>IV</td>
<td>INDIA</td>
<td>NIL</td>
<td>HTN</td>
<td>1076</td>
</tr>
<tr>
<td>6</td>
<td>OL</td>
<td>IV</td>
<td>INDIA</td>
<td>NIL</td>
<td>HTN</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>RCT</td>
<td>III</td>
<td>SRI LANKA</td>
<td>NORVASC</td>
<td>HTN</td>
<td>(200)</td>
</tr>
</tbody>
</table>

TOTAL 5240*

* Excluding Sri Lanka study  
OL = Open label ; PMS = post-marketing surveillance
### S-Amlodipine FDC Clinical Trials

<table>
<thead>
<tr>
<th>No</th>
<th>DESIGN</th>
<th>PLACE</th>
<th>COMP.</th>
<th>FDC WITH</th>
<th>INDICATION</th>
<th>SAMPLE SIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OL/IV</td>
<td>INDIA</td>
<td>NIL</td>
<td>ATENOLOL</td>
<td>HTN</td>
<td>228</td>
</tr>
<tr>
<td>2</td>
<td>OL/IV</td>
<td>INDIA</td>
<td>NIL</td>
<td>LOSARTAN</td>
<td>HTN</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>OL/IV</td>
<td>INDIA</td>
<td>NIL</td>
<td>ATORVASTATIN</td>
<td>HTN/LIPID</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>OL/IV</td>
<td>INDIA</td>
<td>NIL</td>
<td>ATORVASTATIN</td>
<td>HTN/LIPID</td>
<td>154</td>
</tr>
<tr>
<td>5</td>
<td>OL/IV</td>
<td>INDIA</td>
<td>AM/AT</td>
<td>S-METOPROLOL</td>
<td>HTN/ANGIN</td>
<td>107</td>
</tr>
</tbody>
</table>

**TOTAL** 671
S-Amlodipine R&D Summary

9
PRE-CLINICAL STUDIES

8
PHARMACOKINETIC STUDIES

27
PUBLICATIONS

19
CLINICAL TRIALS

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>8</td>
<td>792</td>
</tr>
<tr>
<td>PHASE IV</td>
<td>6</td>
<td>5240</td>
</tr>
<tr>
<td>FDC</td>
<td>5</td>
<td>671</td>
</tr>
<tr>
<td>TOTAL</td>
<td>19</td>
<td>6703</td>
</tr>
</tbody>
</table>
**S-Amlodipine in Books/Journals***

- American Journal Therapeutics, 2003, 10, 29-31
- Journal of Chromatography, 1994, 655, 225-233
- Clinical Therapeutics, 2006, 28, 11, 1837-1847
- Journal Medicinal Chemistry, 1992, 35, 3341 – 3344
- Chirality, 1994, 6, 531-535
- Lik Sprava, 2009, 3-4, 39-44
- British Medical Journal (South-Asia edition)
- Current Opinion Nephrology & Hypertension

* Other than already mentioned before (click on logo in edit mode to access full-text
<table>
<thead>
<tr>
<th>Central America</th>
<th>Africa</th>
<th>Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominican Republic</td>
<td>Senegal</td>
<td>India**</td>
</tr>
<tr>
<td>Caribbean Islands (JAMAICA)</td>
<td>Burkina Faso</td>
<td>Nepal</td>
</tr>
<tr>
<td>Latin America</td>
<td>Ivory Coast</td>
<td>Myanmar</td>
</tr>
<tr>
<td>Trinidad &amp; Tobago</td>
<td>Ghana</td>
<td>Cambodia</td>
</tr>
<tr>
<td>Columbia</td>
<td>Benin</td>
<td>Vietnam</td>
</tr>
<tr>
<td>Peru</td>
<td>Gabon</td>
<td>Philippines</td>
</tr>
</tbody>
</table>

Russia & CIS Region

<table>
<thead>
<tr>
<th>Russia &amp; CIS Region</th>
<th>Africa</th>
<th>Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belarus</td>
<td>Zambia</td>
<td>India**</td>
</tr>
<tr>
<td>Ukraine**</td>
<td>Malawi</td>
<td>Nepal</td>
</tr>
<tr>
<td>Georgia</td>
<td>Tanzania</td>
<td>Myanmar</td>
</tr>
<tr>
<td>Russia*</td>
<td>Kenya</td>
<td>Cambodia</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>Nigeria*</td>
<td>Vietnam</td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>Uganda</td>
<td>Philippines</td>
</tr>
<tr>
<td></td>
<td>Rwanda</td>
<td>S. Korea</td>
</tr>
</tbody>
</table>

*[TO BE UPDATED]*
Emcure S-Amlodipine Patents

• PATENTS GRANTED:
  – INDIA: IN 222978
  – EUROPE: EP1802576
  – RUSSIA: 2006138705

• Patents filed in:
  – Brazil: BR PI 0511095-5
  – South Korea: KR2006-7024198
  – Columbia: CO 7050204
  – USA: US2008262239
Thank You

Millions across the world say “Thanks” to S-Amlodipine
Role of R-Amlodipine

- R+ → stimulation of local kaliikrein*
- increase in local bradykinin concentration**
- Kinins → local edema
- Kinins → NO → inhibition of sympathetic tone to pre-capillary sphincters

“Bradykinin B2 receptor antagonist HOE 140, attenuated the reduction in perfusion pressure and abolished the rise in venous NOx concentration.”

“The (R)- enantiomer is thought to be associated with NO-mediated vasodilation, which is associated with adverse events (AEs) including peripheral edema and facial flushing.” - Clinical Therapeutics/Volume 32, Number 1, 2010

** British Journal of Pharmacology vol 136 (3)
Reason for negligible edema

Better fit at the DHP receptor and long receptor half-life causing balanced arterial and venular dilatation → negligible edema

- NO Inhibits sympathetic tone of the precapillary sphincters
- ↓ Precapillary vasoconstrictor reflex
- Stimulates local kallikrein

EDEMA