PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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Product: Levoamlodipine Maleate
Indication: Hypertension disorder, systemic arterial
Applicant: CSPC Ouyi Pharmaceutical Co., LTD
Review Division: Cardiovascular and Renal Products
Reviewer: Philip Gatti, Ph.D.
Supervisor/Team Leader: Xuan Chi, M.D., Ph.D.
Division Director: Norman Stockbridge, M.D., Ph.D.
Project Manager: Sabry Soukehal

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1. Executive Summary

1.1 Introduction

This 505b(2) NDA application is to support the approval of levoamlodipine maleate the active enantiomer of amlodipine, the approved 1,4-dihydropyridine L-type calcium channel blocker (NORVASC).

1.2 Brief Discussion of Nonclinical Findings

The nonclinical studies to support this NDA were performed mostly for the approval of the racemate (genetic toxicology, reproductive toxicology and carcinogenicity studies). The basic assumption is that since the approved racemate contains 50% of each enantiomer (R and S), and that only one enantiomer confers activity (the S or levo form), then halving the dose of the racemate would be sufficient to estimate the clinical dose of levoamlodipine.

Therefore, nonclinical studies submitted and accepted by the division as adequate for approval include 1) efficacy or pharmacodynamic studies in normotensive as well as hypertensive animal models; 2) published data that proves that the R or dextroamlodipine has no significant calcium channel blocking activity and thus antihypertensive effect; and 3) a 6-week repeat-dose general toxicology study in beagle dogs with a 28-day recovery period.

1.3 Recommendations

1.3.1 Approvability

This application is approvable from a nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

TBD

2 Drug Information

2.1 Drug

CAS Registry Number: 135969-53-8

Generic Name: levoamlodipine maleate

Code Name: NA

Chemical Name: 4S-(−)-2-(2-azyloxethyl)-4-(2-chlorphenyl)-6-methyl-1, 4 dihydro-3, 5-dicnicotinic acid-3-ethoxycarbonly-5methoxycarbonly-maleate
Molecular Formula/Molecular Weight: $C_{20}H_{23}ClN_2O_5.C_4H_4O_4 \cdot 524.95$

Structure or Biochemical Description:

Pharmacologic Class: L-type calcium channel blocker

2.2 Relevant INDs, NDAs, BLAs and DMFs

Approved as NORVASC (racemate) in NDA 019787; IND 124947 (this product)

2.3 Drug Formulation

<table>
<thead>
<tr>
<th>Component/Grade</th>
<th>Function</th>
<th>mg/Tablet</th>
<th>% (w/w)</th>
<th>IIG Levels**</th>
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<tbody>
<tr>
<td>Levamlodipine maleate *, CP</td>
<td>API</td>
<td>3.209*</td>
<td></td>
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<tr>
<td>β-Cyclodextrin, CP</td>
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<tr>
<td>Pre-gelatinized starch, CP</td>
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<td>Microcrystalline cellulose, CP</td>
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<tr>
<td>Magnesium stearate, CP</td>
<td></td>
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<tr>
<td>Silicon Dioxide, CP</td>
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</tbody>
</table>

* Equivalent to 2.5 mg of levamlodipine free base
** Amount in mg in oral tablets as per IIG database

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Hypertensive patients will receive either levamlodipine (2.5 mg/day for up to 24 months) or amlodipine (5 mg/day for up to 24 months).

2.7 Regulatory Background

A pre-NDA meeting was held on October 11, 2018 (with briefing document submitted under IND 124947) to gain the Agency's concurrence on the content and format of the NDA submission. With regard to the nonclinical section of the NDA submission, it was agreed that it should include a). the study report of the repeat-dose toxicology study of levamlodipine in dogs to support the safety evaluation and b). any results from published literature or original bench research indicating that the L-type
calcium channel blocking activity or antihypertensive activity resides only in the S-enantiomer.

3 Studies Submitted

3.1 Studies Reviewed
   A. Pharmacodynamic studies
   B. Assessment of specificity of R vs. S enantiomer
   C. Six-week repeat-dose toxicology study in beagle dogs

3.2 Studies Not Reviewed
   Single-dose toxicity study in mice

3.3 Previous Reviews Referenced
   IND (124947) safety review of levoamlodipine in DARRTS

4 Pharmacology

4.1 Primary Pharmacology (from the sponsor)

1) Comparison of Antihypertensive Effect of Single Administration of Levoamlodipine Maleate and Amlodipine Besylate in Spontaneously Hypertensive Rat (SHR)

In a single dose study, levoamlodipine maleate was given intragastrically to spontaneously hypertensive rats (SHR) at 0.45, 0.9, or 1.8 mg/kg. Compared to vehicle control SHR or pre-dosing measurements, the systolic blood pressure (SBP) in levoamlodipine treated SHR was significantly (P < 0.05) reduced at 2 hours post dosing in a dose dependent manner. By 5 to 8 hours, the SBP was alleviated, and by 12 hours, the SBP was not different than that in the control group. In the same study, amlodipine besylate was given intragastrically to SHR rats at 0.9, 1.8, or 3.6 mg/kg. Compared to vehicle control SHR or pre-dosing measurements, the SBP in amlodipine besylate treated rats was significantly (p < 0.05) reduced at 2 hours post dosing in a dose dependent manner. By 8 hours the SBP was alleviated, and by 12 hours, the SBP was not different from that in the control group. The calculated ED20 (the effective dose to produce 20% efficacy) for the reduction of SBP were 1.74 mg/kg and 3.97mg/kg for levoamlodipine maleate and amlodipine besylate, respectively. While both compounds had similar efficacy in reducing blood pressure in the SHR after a single dose, levoamlodipine (single enantiomer) was more potent than amlodipine (racemic mixture) by approximately 2.3-fold.

2) Comparison of Antihypertensive Effect of Multiple Administrations of Levoamlodipine Maleate and Amlodipine Besylate in Spontaneously Hypertensive Rat (SHR)

To compare the effects of levoamlodipine and amlodipine over time, SHR rats were dosed intragastrically once a day for 2 weeks. Levoamlodipine was given at doses of 0.45, 0.9 and 1.8 mg/kg and amlodipine was given at doses of 0.9, 1.8, or 3.6 mg/kg.
Systolic blood pressure (SBP) was measured 2 hours before dosing and 2 hours after dosing on Days 1, 4, 7, 10 and 13. Both compounds significantly (p<0.05) reduced blood pressure 2 hours after dosing and the SBP returned to the level of the vehicle control group at the 2 hours pre-dosing measurements. The antihypertensive ED20 values calculated from the SBP data on day 7 were 1.68 mg/kg and 2.74 mg/kg for levoamlodipine maleate and amlodipine besylate, respectively; the ED20 values calculated from the SBP data on day 13 were 1.53 mg/kg and 2.09 mg/kg for levoamlodipine maleate and amlodipine besylate, respectively. While both compounds were effective at reducing blood pressure in SHR over the 2-week study, levoamlodipine was more potent than amlodipine, by approximately 1.6-fold on day 7 and 1.4-fold on day 13.

3) Antihypertensive Effect of Levoamlodipine Maleate After a Single Administration in SHR

Spontaneously hypertensive rats (SHR) were used to compare levoamlodipine maleate to amlodipine besylate for effects on blood pressure and heart rate following a single dose. Groups of conscious SHR rats were dosed intragastrically with levoamlodipine at 0.5, 1.0, and 1.5 mg/kg or amlodipine at 1.5 mg/kg. Systolic blood pressure (SBP) and heart rate were measured before dosing and at 1, 2, 3, 4, 6, 8, 12 and 24 hours after dosing. Compared to the pre-dosing measurements, significant (p < 0.01) reduction in SBP occurred for both levoamlodipine and amlodipine at all measurement points between 1 and 12 hours and peaked at 3 hours. By 24 hours, the SBP returned to the pre-dosing levels with no evidence of a rebound effect. The calculated ED-30 mmHg (the effective dose to reduce blood pressure by 30mmHg) of levoamlodipine maleate was 0.60 mg/kg. Comparing levoamlodipine with amlodipine at the same dose level (1.5 mg/kg), there was a significantly (p <0.001) greater reduction in blood pressure by levoamlodipine than that by amlodipine at 2, 3, 4, and 6 hour time points. There was no significant change in the SHR heart rate related to the test compounds was observed during the study.

4) Antihypertensive Effect of Levoamlodipine Maleate After Multiple Administration in SHR

Spontaneously hypertensive rats (SHR) were intragastrically dosed once a day for 10 days with levoamlodipine maleate at 0.5, 1.0, or 1.5 mg/kg or amlodipine at 1.5 mg/kg. SBP and heart rate were measured every other day at 3 hours prior to and 3 hours after the dose. There was little variation in the SBP and heart rate observed in the vehicle control group. Comparing to the measurements before the first dosing, the SBP of the SHR in the 0.5 mg/kg levoamlodipine group declined significantly (p <0.001) 3 hours after dosing with an average reduction of 24 mmHg over the 10-day administration period while the 3 hours pre-dose measurements remained unchanged. The blood pressure in the SHR dosed with 1.0 and 1.5 mg/kg declined significantly (p <0.001) after dosing with the average decreases of 46 and 67 mmHg, respectively over the 10-day administration period. For these two groups, the pre-dose SBP measurements trended down with average declines of 8 and 13 mmHg for 1.0 mg/kg and 1.5 mg/kg levoamlodipine, respectively. The blood pressure in the SHR dosed with 1.5 mg/kg amlodipine declined significantly (p<0.001) after dosing with an average decrease of 34 mmHg while the pre-dose SBP measurements declined by an average of 11 mmHg over the 10-day administration period. The heart rate in the SHR groups did not
alter significantly with the blood pressure decrease by test compounds during the study.

5) **Antihypertensive Effect of Levoamlodipine Maleate After Singly Oral Administration in RHD**

Renal hypertensive dogs (RHD) were dosed with a single oral capsule of levoamlodipine at 0.1, 0.3, or 1 mg/kg and compared with amlodipine at 0.3 mg/kg. The systolic and diastolic blood pressure (SBP and DBP) were reduced in a dose related manner by levoamlodipine with the onset at 1 hour and peak effect at 3 to 4 hours. The duration of the blood pressure reduction was dose related with 4, 8, and 24 hours for levoamlodipine at 0.1, 0.3 and 1.0 mg/kg respectively. The calculated ED-30 mmHg of levoamlodipine was 0.37 mg/kg. The heart rate of the RHD dogs was not significantly affected by levoamlodipine at 0.1 or 0.3 mg/kg. The heart rate was significantly (p <0.05) increased by levoamlodipine at 1 mg/kg; the heart rate increase started at 1 hour and peaked at 6 hours (with a 52% maximum increase as compared to the predose measurements). The results indicated the increased heart rate accompanied the decrease in blood pressure as part of the antihypertensive process of high dose levoamlodipine. Amlodipine at 0.3 mg/kg significantly (p <0.01) reduced the blood pressure of the RHD dogs starting at 1 hour post dosing and peaked at 3 hours with the maximal reduction of 19 mmHg. There was no significant change in heart rate. At the same dose level of 0.3 mg/kg, the antihypertensive effect of levoamlodipine and amlodipine was similar in RHD.

6) **Antihypertensive Effect of Levoamlodipine Maleate After 14-day Continuous Administration in RHD**

Renal hypertensive dogs (RHD) were dosed with oral capsules of levoamlodipine at 0.1 or 0.3 mg/kg once a day for 14 days. The blood pressure (both SBP and DBP) and heart rate were measured every other day at 3 hours prior to and 3 hours after the dose. Compared to the 5-day control period before the first dose, levoamlodipine significantly (p <0.01) reduced the SBP/DBP in a dose related manner with the average reductions of 14/13 mmHg and 38/38 mmHg for 0.1 and 0.3 mg/kg, respectively. The blood pressure returned to the control period level 3 to 4 days after dosing stopped without any evidence of a rebound effect. There was no significant effect on the heart rate with repeat dose of levoamlodipine at 0.1 and 0.3 mg/kg during the study. No test compounds related abnormal activities, body weight changes, and food consumption were observed during the study.

7) **Impact of Hemodynamics of Levoamlodipine in Anaesthetized Open-Chest Dogs**

Within 15 minutes after intravenous injection of levoamlodipine at 0.1, 0.2, or 0.4 mg/kg into the anesthetized open-chest dogs, the blood pressure declined in a dose-dependent manner, the heart rate, the left ventricular pressure, the +/-LVdp/dtmax, and the left ventricular performance decreased. Meanwhile, the cardiac output obviously increased, the total peripheral resistance notably dropped while the left ventricular end-diastolic pressure was not significantly altered. Intravenous injection of levoamlodipine also markedly increased coronary flow and reduced coronary resistance. As compared to the pre-dosing measurements, the high dose of levoamlodipine (0.4 mg/kg) decreased SBP/DBP by 19%/46%, increased cardiac output by 41%, and decreased total peripheral resistance by 50% increased.
coronary flow by 175%, and decreased coronary resistance by 73.1%. The above results indicated that the antihypertensive effect of levoamlodipien in dogs could be through dilating the peripheral vessels, increasing coronary flow, and reducing coronary resistance. The lack of inhibitory effect on the left ventricular function while reducing the blood pressure suggesting that levoamlodipine maleate could have some protective effect on the heart.

8) Literature review that supports the assertion that the R enantiomer of amlodipine does not block the L-type calcium channel indirectly proving that the antihypertensive effect of racemic amlodipine resides in S-amlodipine (levoamlodipine)

1) *In vitro* studies have demonstrated that the S-enantiomer blocks the calcium channel, while R-enantiomer does not show any pharmacological activity at the calcium channel.

2) *In vivo* non-clinical studies have demonstrated that the S-enantiomer at half dose produces similar reductions on blood pressure as does racemic amlodipine at full dose, while the R-enantiomer showed no antihypertensive efficacy.

3) Multiple randomized, double-blind, active-control clinical trials have demonstrated that the S-enantiomer (levoamlodipine) at half dose generates comparable antihypertensive efficacy as racemic amlodipine at full doses.

Reviewer’s comments: The PD data comparing levoamlodipine to racemic amlodipine (Norvasc) summarized above does not consistently support the assumption that a dose of levoamlodipine is twice as potent as the same dose of amlodipine. Specifically, in a single-dose study comparing the 2 agents in spontaneously hypertensive rats (SHR’s), the antihypertensive ED20 was 1.74 mg/kg for levoamlodipine and 3.97 mg/kg for amlodipine. However, in a repeat-dose study in SHR’s the ED20 for levoamlodipine was 1.53 mg/kg while for amlodipine it was 2.09 mg/kg at day 13. In the renal hypertensive dog, a dose of 0.3 mg/kg of levoamlodipine was equipotent as the same dose of amlodipine.

However, despite these nonclinical observations, there does not appear to be any associated safety issues. The nonclinical findings discussed above was communicated to the medical reviewers at the pre-midcycle team meeting. It was agreed that the nonclinical findings do not impact approvability of the study drug since clinical doses used could be titrated up to achieve the desired antihypertensive effect.

4.2 Secondary Pharmacology

None

4.3 Safety Pharmacology (from the sponsor)

Single intragastric administration of levoamlodipine maleate at 0.5 and 1.5 mg/kg had no significant effect on the spontaneous activities in mice. As compared with the measurements in the vehicle control group, levoamlodipine maleate at 5 mg/kg significantly (p <0.05) decreased the spontaneous activity by 27%.

None of the 3 doses synergized with the sub-threshold dose of sodium pentobarbital in inducing sleep in mice. Together, these data indicated that high dose of levoamlodipine maleate could have an inhibitory effect on the central nervous system in mice.
Single oral dose of levoamlodipine maleate at 0.1 mg/kg had no obvious effect on the blood pressure, heart rate and electrocardiogram parameters in healthy dogs. As compared with the measurements in dogs received empty capsules, levoamlodipine at 0.3 mg/kg resulted a trend of blood pressure reduction and at 1 mg/kg produced a significant (p < 0.01) reduction in blood pressure while had no significant effect on heart rate and electrocardiogram parameters. The results indicated single dose of levoamlodipine maleate at 0.3 and 1.0 mg/kg could decrease the blood pressure in healthy dogs while had no obvious effect on other indicators of cardiovascular system. Single oral dose of levoamlodipine maleate up to 1.0 mg/kg had no significant effect on the respiratory rate of healthy dogs indicating this product had no obvious effect on respiratory system.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: 6-week daily intragastric administration with 4-week recovery toxicity and toxicokinetic study of Levoamlodipine and atorvastatin in Beagle dogs

Study no.: A200940-T012
Study report location: EDR
Conducting laboratory and location: [Blank]
Date of study initiation: Not provided
GLP compliance: Unknown
QA statement: Unknown
Drug, lot #, and % purity: Not provided

Key Study Findings

Every dose group exhibited gastrointestinal reactions such as soft stools, loose stools, decrease in appetite and emesis. Those groups in which atorvastatin was administered exhibited elevated plasma ALT levels, transaminase levels and gallbladder edema and hemorrhage. Overall, toxicity recovered after drug withdrawal.

Methods

Beagle dogs were orally administered the following: 1) solvent control; 2) amlodipine besylate 1.5 mg/kg; 3) amlodipine besylate 3 mg/kg; 4) levoamlodipine maleate 0.75 mg/kg; 5) levoamlodipine maleate 1.5 mg/kg; 6) atorvastatin calcium 24 mg/kg; 7) levoamlodipine maleate 0.5 mg/kg with atorvastatin calcium 8 mg/kg; 8) levoamlodipine maleate 1.0 mg/kg with atorvastatin calcium 16 mg/kg; and 9) levoamlodipine maleate 1.5 mg/kg with atorvastatin calcium 24 mg/kg. The volume administered was 10 mL/kg and there was a 28-day recovery period.
Animal appearance, behavior, glandular secretion, respiratory rate, stool character, genitals, death and other conditions as well as other physiological indicators were recorded after administration. Animal blood pressure was measured every two weeks during the administration and recovery periods. Animal weight and body temperature was measured once every week during administration period and recovery period. Hematological and blood biochemical examinations were made on the fifth and twenty-second day of the experiment and at the end of administration and recovery. Electrocardiogram, urine, stool, fundus and bone marrow examinations were made at the end of administration and recovery period. Toxicokinetic studies were carried out on the first and last day of dosing and after completion of administration and recovery periods. Four dogs taken from each group (half male and half female) and the remaining animals were euthanized for the purpose of gross anatomical and histopathology analysis.

**Observations and Results**

Summary of the 6-week repeat-dose toxicity test in dogs:

Every dose of amlodipine besylate, levoamlodipine maleate, atorvastatin calcium and levoamlodipine maleate-atorvastatin calcium caused soft stools, loose stools, appetite decreased, emesis and other gastrointestinal reactions. The weight, temperature, blood pressure, hematology, stool and urine, bone marrow, electrocardiogram of dogs in any of the groups showed no toxic reactions related to the experimental products. Atorvastatin calcium and levoamlodipine maleate atorvastatin calcium low, medium and high dose slightly increased the dogs' ALT activity, showing that may cause mild damage of liver of dogs, and slightly increased the transaminase activity. In addition, atorvastatin calcium and levoamlodipine maleate-atorvastatin calcium can cause gallbladder damage, mainly indicated by gallbladder mucosa layer edema and hemorrhage.

Overall toxic damage was slight and recovered after drug withdrawal. Atorvastatin calcium and levoamlodipine maleate-atorvastatin calcium low, medium and high dose group reduced the CHOL, TG, LDL, HDL and other blood lipid parameters, which was related with the atorvastatin calcium AT lipid-lowering pharmacological effect. In addition, the amlodipine besylate high dose led to an increase of the organ coefficient of the dogs hearts. Levoamlodipine maleate high dose and atorvastatin calcium caused
a reduction of the dogs’ spleen absolute weight compared to the solvent control group. Toxicokinetic experiments showed that continuous administration of amlodipine besylate, levoamlodipine maleate and atorvastatin calcium had no obvious accumulation in Beagle dogs.

7 Genetic Toxicology

The Ames test was performed up to 10 mg/plate of racemic amlodipine without metabolic activation. Half of this 10 mg would be 5000 μg which is the maximum amount recommended in Ames assays. Results were negative. Chromosomal aberration test: Racemic amlodipine was negative in this assay up to 10 μg/ml. Higher concentrations were cytotoxic. The mouse micronucleus test was negative when racemic amlodipine was administered once at 20 mg/kg and 10 mg/kg for 5 days. In IND levoamlodipine was tested in all 3 genotoxicity assays and found to be negative. (IND review: G. Jagadeesh 2002).

8 Carcinogenicity

Two two-year rodent studies were performed with the racemate. Doses in both studies were: 0.5, 1.25 and 2.5 mg/kg/day. The dose in the mouse approximated the MRHD, but the rat dose was below the MRHD. No evidence of carcinogenic effect was noted. Based on these data, the doses of levoamlodipine were half as much the MRHD as the racemic amlodipine.

9 Reproductive and Developmental Toxicology

Using the racemate, a fertility study was performed in rats (10 mg/kg) a dose 8X the maximum recommended human dose (MRHD of 10 mg on a mg/m2 basis). No adverse effects on fertility were observed. Teratogenicity studies were performed in rat (same dose as above) and rabbit (10 mg/kg). In the rabbit, this dose was 23X the MRHD. No teratogenic effects were noted, but in the rat study litter size was smaller and there was an increase in gestation period duration. If the dose of the racemic amlodipine was 8X the MRHD in rats, then for levoamlodipine it was 4X. For the rabbit, the dose of levoamlodipine can be estimated at 11-12X the MRHD.

10 Special Toxicology Studies

None
11 Integrated Summary and Safety Evaluation

There do not appear to be any additional toxicities with levoamlodipine that were not observed with the racemate amlodipine. These findings plus the data generated in 2001 using levoamlodipine in repeat-dose and genetox studies (IND 10164) lead one to conclude that the doses proposed in the clinical study are safe and that any toxicity (e.g., hypotension) can be monitored.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP J GATTI
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XUAN CHI
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