July 29, 2024

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061, HFA-305
Rockville, MD 20852

Subject: **ANDA Suitability Petition for Amlodipine and Benazepril hydrochloride Oral Liquid**

Dear Sir or Madam:

The undersigned submits this ANDA Suitability Petition pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and in accordance with 21 CFR § 10.20, §10.30, and §314.93. The Suitability Petition requests the FDA to confirm that Amlodipine and Benazepril hydrochloride Oral Liquid is suitable for submission in an Abbreviated New Drug Application (ANDA).

Please direct any questions regarding this submission to the undersigned below.

Sincerely,

Seth D. DePuy Digitally signed by Seth D. DePuy
Date: 2024.07.29 12:58:37 -04'00

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Drug Name: **Amlodipine and Benazepril hydrochloride Oral Liquid**

Indication: **For the treatment of hypertension in patients not adequately controlled on monotherapy with either agent**

ANDA SUITABILITY PETITION

Document Date: 29 July 2024

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TABLE OF CONTENTS

1 ACTION REQUESTED

The Suitability Petition requests that the FDA determine that the proposed fixed-dose Amlodipine and Benazepril hydrochloride Oral Liquid is suitable for submission as an Abbreviated New Drug Application (ANDA). This Suitability Petition pursuant to Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetics Act and 21 CFR §314.93, is the appropriate mechanism for securing Food and Drug Administration authorization to submit an ANDA for a drug product that differs in dosage form from the Reference Listed Drug (RLD).

The RLD upon which the petition is based is LOTREL® (amlodipine and benazepril hydrochloride).

LOTREL (NDA 020364) is marketed as an oral capsule and approved in the following dosage strengths:

RLD Dosage Strengths	Amlodipine Besylate (base equivalent)	Benazepril Hydrochloride
1	2.5 mg	10 mg
2	5 mg	10 mg
3	5 mg	20 mg
4	10 mg	20 mg
5	10 mg	40 mg
6	5 mg	40 mg

The Petitioner's proposed Amlodipine and Benazepril hydrochloride product will be developed as an Oral Liquid at the following dosage strengths:

Proposed Dosage Strengths	Amlodipine Besylate (base equivalent)	Benazepril Hydrochloride	Proposed Formulation Amlodipine base + Benazepril HCl
1	10 mg / 5 mL	20 mg /5 mL	10 mg & 20 mg per 5 mL
2	10 mg /5 mL	40 mg / 5 mL	10 mg & 40 mg per 5 mL
3	5 mg / 5mL	40 mg / 5 mL	5 mg & 40 mg per 5 mL

A copy of the currently approved LOTREL product labeling is provided in Appendix 1. In addition, a copy of the relevant page from the current Electronic Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) for LOTREL is provided as Appendix 2.

The drug, the route of administration and the recommendations for use are the same as the RLD product. The proposed drug product will differ only in dosage form from the marketed capsule products.

Approval of this Suitability Petition will allow the Petitioner to submit Amlodipine and Benazepril hydrochloride Oral Liquid as an ANDA and permit convenient dosing and administration by healthcare providers to treat patients with hypertension in accordance with the approved indications for LOTREL.

2 STATEMENT OF GROUNDS

The FDC Act permits, at Section 505(j)(2)(A)(iii) and 21 CFR 314.93, the submission of an ANDA for a drug product that differs in dosage form from the RLD after FDA has approved a petition seeking permission to file such an application.

LOTREL (amlodipine and benazepril hydrochloride) was approved on 03 March 1995 under NDA 020364 and is marketed as an oral capsule at 6 dosage strengths for the treatment of hypertension in patients not adequately controlled on monotherapy with either agent (see Appendix 1 for approved product labeling).

The Petitioner proposes Amlodipine and Benazepril hydrochloride Oral Liquid to be approved for the same indication as LOTREL oral capsules. Table 1 below presents the comparison between the approved RLD product and the proposed drug product.

Table 1 Comparison of Approved Drug Product to Proposed Drug Product – Dosage Strengths

	RLD Product: LOTREL (NDA 020364; Novartis)	**Proposed Amlodipine and Benazepril hydrochloride Product**
Dosage Form	Capsule	Liquid
Route of Administration	Oral	Oral
Dosage Strengths (Amlodipine besylate; Benazepril hydrochloride)	• EQ 2.5 mg base; 10 mg • EQ 5 mg base; 10 mg • EQ 5 mg base; 20 mg • EQ 10 mg base; 20 mg • EQ 10 mg base; 40 mg • EQ 5 mg base; 40 mg	• EQ 10 mg base; 20 mg per 5 mL • EQ 10 mg base; 40 mg per 5 mL • EQ 5 mg base; 40 mg per 5 mL

EQ = equivalent; NDA = New Drug Application; RLD = reference listed drug

Approved Indication and Usage:

Amlodipine and Benazepril as a fixed-dose combination oral capsule product is approved for the treatment of hypertension in patients not adequately controlled on monotherapy with either agent (Novartis Pharmaceuticals Corp. (2023); see Appendix 1).

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle

and cardiac muscle. Amlodipine acts as a peripheral arterial vasodilator through direct action on vascular smooth muscle causing a reduction in peripheral vascular resistance and a reduction in blood pressure.

Benazepril is a prodrug that, when hydrolyzed by esterases, converts into its active form called benazeprilat, a potent Angiotensin Converting Enzyme inhibitor. The mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system by preventing the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor.

Approved Dosage and Administration:

LOTREL is available at 6 dosage strengths (see Table 1). The appropriate oral capsule dose is titrated to clinical effect (Novartis Pharmaceuticals Corp. (2023); see Appendix 1.

> *The recommended initial dose is amlodipine 2.5 mg/benazepril 10 mg orally once-daily.*
>
> *The antihypertensive effect of Lotrel is largely attained within 2 weeks. If blood pressure remains uncontrolled, the dose may be titrated up to amlodipine 10 mg/benazepril 40 mg once-daily. The dosing should be individualized and adjusted according to the patient's clinical response.*
>
> *In clinical trials of amlodipine/benazepril combination therapy using amlodipine doses of 2.5 to 10 mg and benazepril doses of 10 to 40 mg, the antihypertensive effects increased with increasing dose of amlodipine in all patient groups, and the effects increased with increasing dose of benazepril in nonblack groups.*

Proposed Indication/Usage, Dosage, and Administration:

The proposed indication for Amlodipine and Benazepril hydrochloride Oral Liquid product will be consistent with the approved, labeled indication of the RLD (LOTREL).

The proposed Amlodipine and Benazepril hydrochloride Liquid product is intended to be dosed by the same route (i.e., oral) as the RLD.

The proposed Amlodipine and Benazepril hydrochloride Oral Liquid product is intended to be available in 3 dosage strengths (see Table 1). The available dosing range compared to the RLD is presented in Table 2. Dosing instructions will remain consistent with the RLD.

Table 2 Comparison of Approved Drug Product to Proposed Drug Product – Dosing Range

Dose (mg) [Amlodipine besylate; Benazepril hydrochloride]	RLD Product: LOTREL (NDA 020364; Novartis)	Proposed Amlodipine and Benazepril Product
2.5; 10	1 capsule (2.5; 10)	1.25 mL (10; 40 /5 mL)
5; 10	1 capsule (5; 10)	2.5 mL (10; 20 /5 mL)

Table 2 Comparison of Approved Drug Product to Proposed Drug Product – Dosing Range

Dose (mg) [Amlodipine besylate; Benazepril hydrochloride]	RLD Product: LOTREL (NDA 020364; Novartis)	Proposed Amlodipine and Benazepril Product
5; 20	1 capsule (5; 20)	2.5 mL (10; 40 /5 mL)
5; 40	1 capsule (5; 40)	5 mL (5; 40 /5 mL)
10; 20	1 capsule (10; 20)	5 mL (10; 20 /5 mL)
10; 40	1 capsule (10; 40)	5 mL (10; 40 /5 mL)

NOTE: Amlodipine dose presented as EQ base, Benazepril as HCl salt.

The proposed Amlodipine and Benazepril hydrochloride Oral Liquid product does not pose any new questions of Safety or Effectiveness since the proposed strengths are the same as that stated in the approved product labeling of the RLD under NDA 020364. The active ingredients, dosage regimen, uses and route of administration of the proposed strengths will be the same as applicable to the RLD. The Petitioner intends to conduct a study to establish bioequivalence to the RLD.

Draft labeling for the proposed Amlodipine and Benazepril hydrochloride Oral Liquid product is provided in Appendix 3.

3 ENVIRONMENTAL IMPACT

The Petitioner claims a categorical exclusion under 21 CFR 25.31.

4 ECONOMIC IMPACT STATEMENT

The Petitioner does not believe that this requirement is applicable at this time, but will agree to submit economic impact information, in accordance with 21 CFR 10.30(b), if requested by the Agency.

5 CERTIFICATION

The Petitioner certifies that to their best knowledge and belief, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

6 PEDIATRIC RESEARCH EQUITY ACT (PREA)

ANDAs submitted under an approved suitability petition for changes in dosage form, route of administration, or new active ingredient in fixed-combination products are subject to the pediatric assessment requirements that PREA imposes (21 USC 355B). As the proposed Amlodipine and Benazepril hydrochloride Oral Liquid product is a change in dosage from the currently approved LOTREL oral capsule, PREA requirements are triggered.

The Petitioner believes that a pediatric assessment is not applicable to the proposed Amlodipine and Benazepril hydrochloride Oral Liquid product because the proposed change only facilitates the availability of the drug product in a liquid dosage form in place of a capsule dosage, while the active ingredients, indication, route of administration and dosing regimen remain identical to that of the RLD, LOTREL, as approved under NDA 020364 (Appendix 1).

Therefore, the Petitioner does not plan to submit any pediatric assessments with its application. A request for waiver of pediatric studies is included with this Petition.

7 REFERENCES

Novartis Pharmaceuticals Corp. (2023). Approved product labeling for LOTREL (amlodipine + benazepril); oral capsule; (NDA 020364). In *https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=94ae6054-b7ae-4212-a567-4f803af8f2c7&type=pdf*.

8 APPENDICES