CENTER FOR DRUG EVALUATION AND RESEARCH

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Clinical Pharmacology/Biopharmaceutics Review

NDA: 19-787
Serial #: SNC to B004
Compound #: Norvasc (amlodipine besylate) tablets
Pfizer Pharmaceuticals
Submission Date: May 27, 1999

Reviewer: Thomas A. Parmelee, Pharm.D.

Type of Submission: Formulation consultation regarding amlodipine suspension for planned pediatric population pharmacokinetic study.

BACKGROUND

Pfizer is currently planning to study amlodipine in the pediatric population in order to gain marketing exclusivity. The sponsor met with the agency in May 1999 to discuss their plans for two studies to be conducted in the pediatric population. These studies included a dose-ranging efficacy study and a population pharmacokinetic study.

The Division made suggestions to the sponsor regarding drug administration techniques for younger patients. Crushing tablets and adding to applesauce (or other suitable vehicle) was discussed. In this submission, the sponsor has included a recently published article describing the stability of two prepared amlodipine suspensions. The sponsor is requesting to use a suspension of amlodipine for dosing in children less than 6 years of age. The sponsor believes that the use of a referenced amlodipine suspension would provide a simpler dosing regimen for drug administration in children. A copy of the published article is included in this review.

RECOMMENDATIONS

The use of amlodipine suspension for drug administration to children in the population pharmacokinetic study is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. Since the sponsor is not planning to market the amlodipine suspension, no bioequivalence study is required at the present time. No further action is warranted at this time.

/S/

Thomas A. Parmelee, Pharm.D. 6/23/99

RD/FT by Patrick Marroum, Ph.D. 6/24/1999

CC: NDA 19-787, HFD-110, HFD-860 (Mehta, Parmelee), CDER document room: Attn. BIOPHARM- CDR

RESEARCH

Stability of Amlodipine Besylate in Two Liquid Dosage Forms

Milap C. Nahata, Richard S. Morosco, and Thomas F. Hipple

Objective: To determine the stability of amlodipine besylate in two liquid dosage forms under refrigeration and at room temperature. **Design:** Commercially available amlodipine tablets (Norvasc—Pfizer) were used to prepare two suspensions: one in extemporaneously prepared 1% methylcellulose in syrup (1:1), and another in equal volumes of commercially available OraPlus/OraSweet. Each suspension containing amlodipine 1 mg/mL was stored in 10 plastic prescription bottles; 5 were stored at 4°C and 5 at 25°C. Samples were collected immediately after preparation (day 0) and on days 7, 14, 28, 42, 56, 70, and 91. Amlodipine concentration was measured by stability-indicating HPLC method (n = 15). **Setting:** Research laboratory at Children's Hospital. **Main Outcome Measures:** Physical and chemical stability (≥ 90% of the initial concentration) of amlodipine in the two extemporaneously prepared suspensions during storage in plastic prescription bottles at 4°C and 25°C. **Results:** Observed mean concentrations exceeded 90% of the initial concentrations in both suspensions for 91 days at 4°C and 56 days at 25°C. No noticeable change in physical appearance or odor was observed; pH changed slightly in the methylcellulose-containing formulation stored at 25°C. **Conclusion:** Amlodipine was stable in two suspensions when stored in plastic prescription bottles for 91 days at 4°C or 56 days at 25°C. These formulations may be considered for pediatric or elderly patients who are unable to swallow tablets. The liquid dosage form would also permit accurate administration of amlodipine doses to infants and young children based on their body weight.

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Calcium antagonists are used in pediatric patients with hypertension. Nifedipine is the most commonly used drug; however, it has a short duration of action and there is no liquid dosage form for children. Amlodipine besylate, another dihydropyridine calcium antagonist, has a longer elimination half-life, allowing once-daily dosing.[1–4] Because oral amlodipine is available only in tablet form, we designed a study to determine its stability in two extemporaneously prepared suspensions stored under refrigeration and at room temperature.

Calcium antagonists are among the majority of the drugs approved only for adults, and yet are routinely used in infants and children. These drugs include albuterol, captopril, digoxin, morphine, and ranitidine. A drug not labeled for pediatric use is often commercially unavailable in a suitable oral liquid dosage form.

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Milap C. Nahata, PharmD, is Charles H. Kimberly professor of pharmacy and pediatrics, The Ohio State University (OSU), and director, Pediatric Pharmacology Research Laboratory, Wexner Institute for Pediatric Research, Children's Hospital. Richard S. Morosco is research associate, OSU and Children's Hospital. Thomas F. Hipple, BS, is former director of pharmacy, Children's Hospital, Columbus, Ohio.

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Correspondence: Milap C. Nahata, PharmD, College of Pharmacy, Ohio State University, 500 West 12th Ave., Columbus, OH 43210. Fax: (614) 292-2688. E-mail: nahata.1@osu.edu.

Methods

Amlodipine besylate (Norvasc—Pfizer; 50 tablets, 5 mg each)[a] tablets were ground to powder using a mortar and pestle, then two 250 mL suspensions were prepared: the first in 1:1 simple syrup NF[b] with 1% methylcellulose[3,c] (see Appendix), while mixing; the second in 1:1 OraSweet[d]: OraPlus,[e] while mixing. Concentration of amlodipine in each suspension was 1 mg/mL.

Both suspensions were stored in 10 amber plastic[f] prescription bottles (2 oz. each). Five bottles of each suspension were stored at 4°C in a refrigerator,[g] and another set of five bottles were stored at 25°C in a temperature-controlled water bath.[h] Each bottle was removed from its 5-minute medium agitation setting (6 on a scale of 1 to 10 at a 30° angle) on the wrist action shaker, and gently inverted three times by hand to avoid trapping unwanted air bubbles. The inversion procedure was repeated between each of the aliquots. Immediately after shaking, three 500 µL samples were drawn from the approximate center of the

Table 1. Stability of Amlodipine in Two Suspensions at 4°C and 25°C

	% Mean (± SD) Initial Concentration Remaining (n = 16)			
	25°C		4°C	
Day	1% MC/Syrup[a]	OS/OP[b]	1% MC/Syrup[a]	OS/OP[b]
0	100% ± 1.28[c] (pH 6.88 ± 0.005)	100% ± 2.14[c] (pH 4.58 ± 0.008)	100% ± 0.87[d] (pH 6.86 ± 0.006)	100% ± 1.88[d] (pH 4.58 ± 0.008)
7	99.21 ± 1.33	100.27 ± 2.15	100.21 ± 1.13	99.99 ± 2.04
14	99.72 ± 1.67	99.05 ± 1.88	99.63 ± 1.01	99.63 ± 1.71
28	97.27 ± 1.62	98.13 ± 2.87	99.17 ± 1.11	99.19 ± 2.18
42	94.76 ± 1.28	96.62 ± 2.84	98.47 ± 1.25	98.64 ± 2.36
56	93.38 ± 2.01	93.47 ± 3.09	97.21 ± 1.44	97.86 ± 2.73
70	88.67 ± 1.69	93.11 ± 3.25	96.92 ± 1.88	97.03 ± 3.04
91	87.63 ± 2.76 (pH 6.60 ± 0.015)	90.72 ± 3.83 (pH 4.61 ± 0.007)	94.27 ± 2.49 (pH 6.68 ± 0.007)	95.87 ± 3.42 (pH 4.59 ± 0.008)

MC = methylcellulose; OP = OraPlus; OS = OraSweet.
[a] 1% methylcellulose in syrup.
[b] 1:1 mixture of OraPlus and OraSweet.
Actual initial concentrations (mean ± SD) were
[c] 1.06 ± 0.01 mg/mL
[d] 0.99 ± 0.02 mg/mL
[e] 1.02 ± 0.04 mg/mL
[f] 1.03 ± 0.06 mg/mL

liquid volume in each bottle on days 0, 7, 14, 28, 42, 56, 70, and 91. A high-performance liquid chromatography (HPLC) method[6] was modified to measure amlodipine concentration in each sample in duplicate. The pH was also measured in each sample using a digital pH meter.

The HPLC instrumentation included Hewlett-Packard (HP) 1050 pump,[g] HP 1050 autosampler,[g] HP 1050 variable wavelength detector,[g] and HP 3396A integrator.[g] Other equipment included a Zorbax CN 3.0 × 150 mm,[m] digital pH meter,[n] Burrell Wrist Action Shaker,[o] and Vortex Genie 2.[p]

The chemicals and reagents were American Chemical Society or analytical grade. These included acetonitrile,[q] methanol,[r] buffer solution pH 7.00,[s] buffer solution pH 4.00,[t] and buffer solution pH 10.00.[u] The mobile phase consisted of 35% 40 mM ammonium acetate[v] and 15% methanol and 50% acetonitrile filtered through a 0.45 mμ nylon 66 filter[w] then degassed with helium.

Stock solution of amlodipine[x] was prepared in methanol then diluted to yield concentrations of 1.50, 1.25, 1.00, 0.75, 0.50, 0.25, and 0.10 mg/mL. Of these, 100 μL of each sample was mixed with 5.0 mL of internal standard solution (desipramine HCl[y] 20.0 μg/mL in mobile phase), centrifuged, and the supernatant was analyzed in the same manner as the samples. Flow rate was 0.4 mL/minute, the detector was set at 240 nm, and injection volume was 10 μL. The column was maintained at ambient temperature.

To establish the stability-indicating nature of the method, amlodipine 1.0 mg/mL was subjected to a forced acid (2.0 M HCl),[z] base (2.0 M NaOH),[aa] hydrolysis and oxidation (0.03% H_2O_2)[ab] at 60°C. The sample was analyzed as described earlier every 30 minutes until about one-half of the amlodipine peak disappeared, to show that the quantification of amlodipine was not influenced by degradation products. Each chromatographic run required about 10 minutes. Amlodipine and desipramine eluted at approximately 6.4 and 8.8 minutes, respectively. Linearity was determined by linear regression analysis of amlodipine concentration based on peak area ratios of amlodipine to internal standard. The correlation coefficient was greater than 0.999 with a coefficient of variation less than 1.9% intraday and 2.6% interday.

Results and Discussion

In each extemporaneously prepared suspension, amlodipine besylate was stable for 91 days at 4°C and 56 days at 25°C (Table 1). No noticeable changes in color or odor were observed in any sample during the 91-day study period; the pH changed slightly in 1% methylcellulose/syrup formulation at 25°C. These data should be useful for preparing a liquid dosage form of amlodipine for pediatric patients who are unable to swallow tablets. In addition, it would be possible to accurately measure doses/kilogram of body weight, as is routinely done in pediatric practice.

When a liquid dosage form is not available commercially, tablets may be crushed to prepare powder papers for individual doses. However, this practice is extremely cumbersome and time consuming. In addition, mixing by caregivers in various vehicles may lead to errors in drug administration.

The stability data in two suspensions offer an opportunity to either use commercially available suspending agent and syrup or to prepare the suspending agent extemporaneously. The latter alternative may be less expensive, but many pharmacists

may not have access to methylcellulose or an interest in preparing it. Both suspensions were sweet and acceptable in taste. The formulation in 1% methylcellulose/syrup settled slightly faster than the Ora Plus/Ora Sweet formulation, but both resuspended easily after shaking.

Based on our data, it would be feasible to provide a liquid formulation of amlodipine in plastic prescription bottles to be stored under refrigeration. Although the drug was stable at room temperature for 8 weeks, we cannot rule out the possibility of microbial contamination during extended storage. The auxiliary label should indicate "Shake Well" and "Refrigerate"; the expiration date at 4°C should be less than 3 months. By showing that frequent prescription refills are not required for amlodipine besylate, our data should improve convenience for the patient and/or caregiver.

Conclusion

Amlodipine besylate was stable in two extemporaneously prepared suspensions stored in plastic prescription bottles for 3 months under refrigeration and 8 weeks at room temperature. These formulations may be considered for pediatric or elderly patients who are unable to swallow tablets. The liquid dosage form would also permit accurate administration of amlodipine doses to infants and young children based on their body weight.

Appendix

Preparation of 1% Methylcellulose (1 Liter)[6]

Purified water (200 mL) was heated to boiling. Methylparaben (200 mg) and propylparaben (100 mg) were added and mixed well. Methylcellulose powder (10 g; 4,000 cps) was added, allowed to stand for 15 minutes, then removed from heat. The cold purified water was added to make a total volume of 1 liter, while mixing well with magnetic stirrer. The mixing was continued to make a clear, homogenous preparation.

[a]Lot 8QP114A, Pfizer Inc., Groton, Conn.
[b]Lot 33874, Humco Laboratory, Texarkana, Tex.
[c]Lot OH10560BMG, Children's Hospital, Columbus, Ohio. OraPlus (microcrystalline cellulose, carboxymethylcellulose, xanthan gum, carrageenan, preservative, and other excipients).
[d]Lot BKE784, Paddock Laboratories, Minneapolis, Minn. OraSweet (sucrose, glycerin, sorbitol, preservatives, and other excipients).
[e]Lot 4E6482, Paddock Laboratories, Minneapolis, Minn.
[f]OI Owens-Illinois, Toledo, Ohio
[g]White-Westinghouse, White Consolidated Inc., Columbus, Ohio.
[h]Lauda RM20, Brinkman Instruments, Inc., Westbury, N.Y.
[i]Hewlett-Packard Co., Analytical Products Group, Palo Alto, Calif.
[j]Hewlett-Packard Co., Analytical Products Group, Palo Alto, Calif.
[k]Hewlett-Packard Co., Analytical Products Group, Palo Alto, Calif.
[l]Hewlett-Packard Co., Analytical Products Group, Palo Alto, Calif.
[m]MAC-MOD Analytical, Inc. Chadds Ford, Pa.
[n]Orion, model 701A, Orion Research Inc., Boston, Mass.
[o]Burrell Corp., Pittsburg, Pa.
[p]Fisher Scientific, Pittsburgh, Pa.
[q]Lot BM672, Burdick & Jackson, Div. of Baxter, Muskegon, Mich.
[r]Lot BN761, Burdick & Jackson, Div. of Baxter, Muskegon, Mich.
[s]Fisher lot 81090-34, Fisher Scientific, Pittsburgh, Pa.
[t]Fisher lot 910043-23, Fisher Scientific, Pittsburgh, Pa.
[u]Fisher lot 908834-24, Fisher Scientific, Pittsburgh, Pa.
[v]Lot 08813TX, Aldrich Chemical Co., Milwaukee, Wisc.
[w]Lot 0082208, Gelman Sciences, Ann Arbor, Mich.
[x]Lot 8C077-060CS-10, Pfizer Inc., Groton, Conn.
[y]Lot 84H086, Sigma Chemical Co., St. Louis, Mo.
[z]Hydrochloric acid lot AB12KBSV, Mallinckrodt Specialty Chemical Co., Chesterfield, Mo.
[aa]Sodium hydroxide lot 00110DY, Aldrich Chemical Co., Milwaukee, Wisc.
[bb]Hydrogen peroxide lot 05427TX, Aldrich Chemical Co., Milwaukee, Wisc.

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