CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-410

Name: Nifedipine Extended-release Tablets, USP 90 mg

Sponsor: Osmotica Pharmaceutical Corp.

Approval Date: October 3, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-410

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Tentative Approval Letter	X
Labeling	X
Labeling Review(s)	X
Medical Review	
Chemistry Review(s)	X
Bioequivalence Review(s)	X
Statistical Review	
Microbiology Review(s)	
Administrative & Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-410

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-410

Osmotica Pharmaceutical Corp.
Attention: Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and QA
1205 Culbreth Drive, Suite 200
Wilmington, NC 28405

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated November 19, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Nifedipine Extended-release Tablets USP, 90 mg.

Reference is made to the tentative approval letter issued by this office on December 28, 2006, and to your amendments dated November 22, 2005; March 17, August 4, October 20, and November 30, 2006; and September 20, September 25, and September 28, 2007.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Nifedipine Extended-release Tablets USP, 90 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Procardia XL Tablets, 90 mg, of Pfizer Laboratories (Pfizer).

The reference listed drug (RLD) upon which you have based your ANDA, Pfizer's Procardia XL Tablets, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,264,446 (the '446 patent), is scheduled to expire on November 23, 2010.

Your ANDA contains a paragraph IV certification to the '446 patent under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Nifedipine Extended-release Tablets USP, 90 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Osmotica Pharmaceutical Corp. (Osmotica) for infringement of the '466 patent. You have notified the agency that Osmotica complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Osmotica within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

Furthermore, the 180-day generic drug exclusivity issue noted in our tentative approval letter dated December 28, 2006, is no longer a barrier blocking the final approval of your ANDA. Our office has received a letter from Martec Scientific, Inc. (Martec) dated September 20, 2007, in which Martec indicated their desire to relinquish their right to the 180-day exclusivity for this drug product. Therefore, the agency is no longer blocked from approving your ANDA.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

> Dissolution testing should be conducted in 50 mL of water at 37°C using USP Apparatus VII at 30 cycles per minute. The test product should meet the following "interim" specifications:
>
> | Time (hours) | Range |
> |---|---|
> | 4 hr | NMT 14% |
> | 12 hr | 39-75% |
> | 24 hr | NLT 75% |
>
> The "interim" dissolution tests and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement - Changes Being Effected" if there are no revisions to be made to the "interim" specifications, or if the proposed final

specifications are tighter than the "interim" specifications. In all other instances, the data should be submitted in the form of a Prior Approval Supplement.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert L. West
10/3/2007 11:42:38 AM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-410

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-410

Osmotica Pharmaceutical Corp.
Attention: Mark S. Aikman
Vice President, Regulatory Affairs and QA
1205 Culbreth Drive, Suite 200
Wilmington, NC 28405

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated November 19, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Nifedipine Extended-release Tablets USP, 90 mg.

Reference is also made to your amendments dated November 10, 2005; and March 6, and July 14, 2006. We also acknowledge receipt of your correspondence dated February 14, and April 15, 2005, addressing the patent issues associated with this ANDA.

We have completed the review of this ANDA and based upon the information you have presented to date, we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, final approval of your application is blocked at this time because of the 180-day generic drug exclusivity issue explained below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ANDA, Procardia XL Tablets, 90 mg, of Pfizer Laboratories, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,264,446 (the '446 patent) is scheduled to expire on November 23, 2010.

Your application contains a paragraph IV certification to the '446 patent under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Nifedipine Extended-release Tablets USP, 90 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Osmotica Pharmaceutical Corp. (Osmotica) for infringement of the '466 patent. You have notified the agency that Osmotica complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Osmotica within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

However, we are unable at this time to grant final approval to your Nifedipine Extended-release Tablets USP, 90 mg. This is because Martec Scientific, Inc.'s (Martec) ANDA 75-414 providing for Nifedipine Extended-release Tablets USP, 90 mg and containing a paragraph IV certification to the '446 patent was submitted to the agency prior to the submission of your ANDA. Martec's ANDA was approved on March 23, 2004. Upon approval, Martec became eligible for 180-day generic drug exclusivity for the drug product. Thus, your ANDA will be eligible for final approval on the date that is 180 days after the date the agency receives notice, with respect to Martec's ANDA, of the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv) of the Act.[1]

To reactivate your ANDA prior to final approval, please submit a "MINOR-AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. Your amendment must provide a summary of the legal basis upon which you believe the ANDA should be approved, as well as:

1. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this ANDA, or
2. a statement that no such changes have been made to the ANDA since the date of tentative approval.

---

[1] Because the other ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

Any changes in the conditions outlined in this ANDA and the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the ANDA will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt.

In addition to the amendment requested above, the agency may request at any time prior to the final date of approval that you submit an additional amendment containing the requested information. Failure to submit either amendment may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

This product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of a drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the agency issues the final approval letter, this product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book".

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Esther Chuh, Project Manager, at 301-827-5773.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

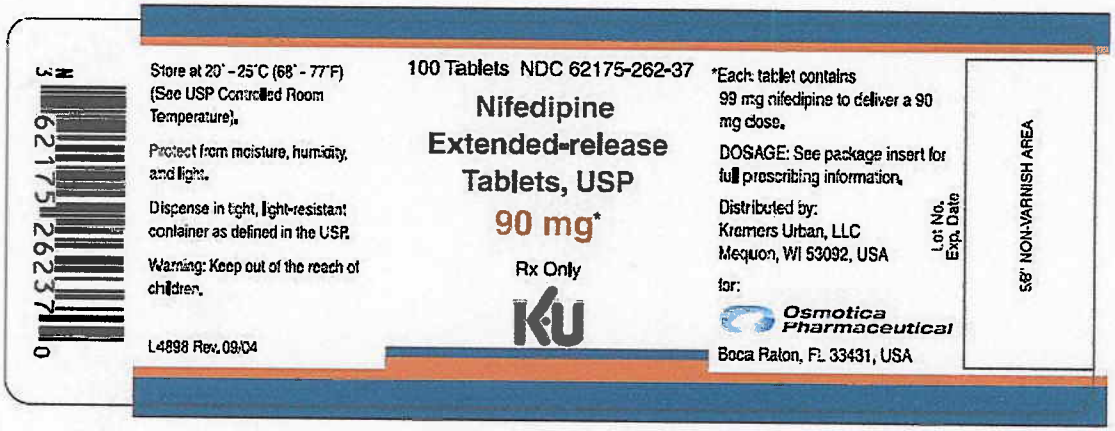
Robert L. West
12/28/2006 10:20:46 AM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-410

LABELING


Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature).
Protect from moisture, humidity, and light.
Dispense in tight, light-resistant container as defined in the USP.
Warning: Keep out of the reach of children.
L4898 Rev. 09/04
100 Tablets NDC 62175-262-37
Nifedipine Extended-release Tablets, USP
90 mg*
Rx Only
*Each tablet contains 99 mg nifedipine to deliver a 90 mg dose.
DOSAGE: See package insert for full prescribing information.
Distributed by:
Kremers Urban, LLC
Mequon, WI 53092, USA
for:
Osmotica Pharmaceutical
Boca Raton, FL 33431, USA
Lot No.
Exp. Date
58" NON-VARNISH AREA

N
3 62175 26255 4

Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature).

Protect from moisture, humidity, and light.

Dispense in tight, light-resistant container as defined in the USP.

Warning: Keep out of the reach of children.

4006368 Rev. 05/06

300 Tablets NDC 62175-262-55

Nifedipine Extended-release Tablets, USP

90 mg*

Rx Only

K·U™

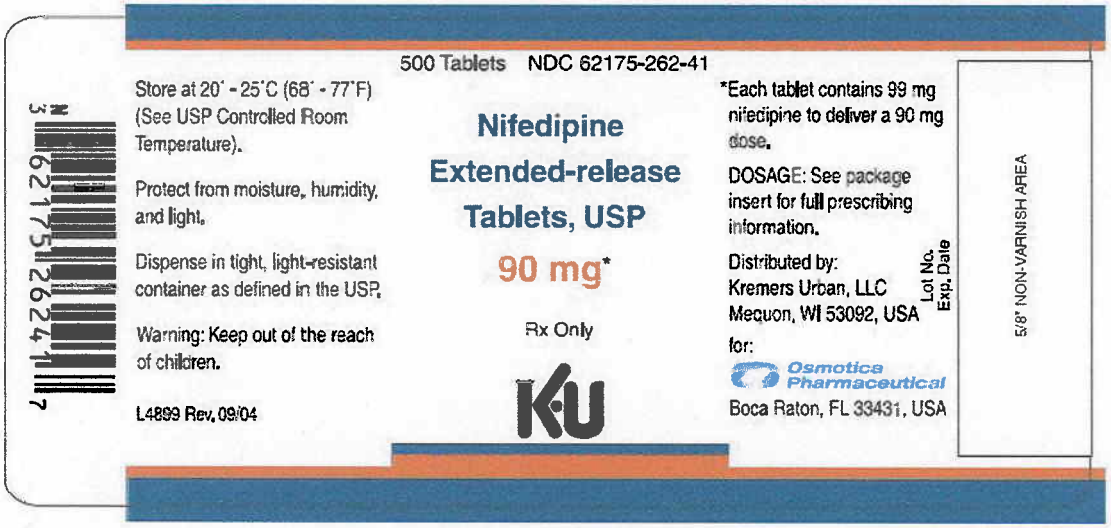
*Each tablet contains 99 mg nifedipine to deliver a 90 mg dose.

DOSAGE: See package insert for full prescribing information.

Distributed by:
Kremers Urban, LLC
Mequon, WI 53092, USA
for:

Osmotica Pharmaceutical
Wilmington, NC 28405, USA

Lot No.
Exp. Date


500 Tablets NDC 62175-262-41
Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature).
Protect from moisture, humidity, and light.
Dispense in tight, light-resistant container as defined in the USP.
Warning: Keep out of the reach of children.
L4899 Rev. 09/04
Nifedipine Extended-release Tablets, USP
90 mg*
Rx Only
K-U
*Each tablet contains 99 mg nifedipine to deliver a 90 mg dose.
DOSAGE: See package insert for full prescribing information.
Distributed by:
Kremers Urban, LLC
Mequon, WI 53092, USA
for:
Osmotica Pharmaceutical
Boca Raton, FL 33431, USA
Lot No.
Exp. Date
5/8" NON-VARNISH AREA
3 N 62175262411 7

Nifedipine

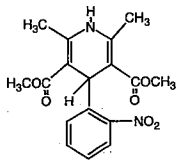
Extended-release Tablets, USP

For Oral Use

PC4759A **Rx Only** 06/06

DESCRIPTION

Nifedipine is a drug belonging to a class of pharmacological agents known as the calcium channel blockers. Nifedipine is 3, 5-pyridinedicarboxylic acid, 1, 4-dihydro-2, 6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, $C_{17}H_{18}N_2O_6$, and has the structural formula:



Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.33. Nifedipine Extended-release Tablet is formulated as a once-a-day extended-release tablet for oral administration designed to deliver 30, 60 or 90 mg of nifedipine.

Inert ingredients in the formulations are: black iron oxide; cellulose acetate; colloidal silicon dioxide; hypromellose; lactose monohydrate; magnesium stearate; microcrystalline cellulose; polyethylene glycol; polyethylene oxide; polysorbate; povidone; propylene glycol; red ferric oxide; sodium chloride; titanium dioxide; triacetin.

System Components and Performance

Nifedipine Extended-release Tablet is similar in appearance to a conventional tablet. It consists, however, of a semipermeable membrane surrounding an osmotically active drug core. As water from the gastrointestinal tract enters the tablet, pressure increases in the core of the tablet, releasing drug through the precision laser-drilled tablet orifice in the one side of the tablet.

Nifedipine Extended-release Tablet is designed to provide nifedipine at an approximately constant rate over 24 hours. This controlled rate of drug delivery into the gastrointestinal lumen is independent of pH or gastrointestinal motility.

Nifedipine Extended-release Tablet depends for its action on the existence of an osmotic gradient between the contents of the tablet core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. Upon swallowing, the biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

USP Drug Release Test (number pending).

CLINICAL PHARMACOLOGY

Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle without altering serum calcium concentrations.

Nifedipine
Extended-release Tablets, USP
For Oral Use
Rx Only
PC4759A 06/06

Mechanism of Action

A) Angina

The precise mechanisms by which inhibition of calcium influx relieves angina has not been fully determined, but includes at least the following two mechanisms:

1) Relaxation and Prevention of Coronary Artery Spasm

Nifedipine dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of nifedipine in vasospastic (Prinzmetal's or variant) angina. Whether this effect plays any role in classical angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

2) Reduction of Oxygen Utilization

Nifedipine regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral vascular resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements, and probably accounts for the effectiveness of nifedipine in chronic stable angina.

B) Hypertension

The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilatation and the resulting reduction in peripheral vascular resistance. The increased peripheral vascular resistance that is an underlying cause of hypertension results from an increase in active tension in the vascular smooth muscle. Studies have demonstrated that the increase in active tension reflects an increase in cytosolic free calcium.

Nifedipine is a peripheral arterial vasodilator which acts directly on vascular smooth muscle. The binding of nifedipine to voltage-dependent and possibly receptor-operated channels in vascular smooth muscle results in an inhibition of calcium influx through these channels. Stores of intracellular calcium in vascular smooth muscle are limited and thus dependent upon the influx of extracellular calcium for contraction to occur. The reduction in calcium influx by nifedipine causes arterial vasodilation and decreased peripheral vascular resistance which results in reduced arterial blood pressure.

Pharmacokinetics and Metabolism

Nifedipine is completely absorbed after oral administration. Plasma drug concentrations rise at a gradual, controlled rate after a Nifedipine Extended-release Tablet dose and reach a plateau at approximately six hours after the first dose. For subsequent doses, relatively constant plasma concentrations at this plateau are maintained with minimal fluctuations over the 24-hour dosing interval. About a fourfold higher fluctuation index (ratio of peak to trough plasma concentration) was observed with the conventional immediate-release nifedipine capsule at t.i.d. dosing than with once daily Nifedipine Extended-release Tablet. At steady-state the bioavailability of the Nifedipine Extended-release Tablet is 86% relative to immediate-release capsules. Administration of the Nifedipine Extended-release Tablet in the presence of food slightly alters the early rate of drug absorption, but does not influence the extent of drug bioavailability. Markedly reduced GI retention time over prolonged periods (i.e., short bowel syndrome), however, may influence the pharmacokinetic profile of the drug which could potentially result in lower plasma concentrations. Pharmacokinetics of Nifedipine Extended-release Tablets are linear over the dose range of 30 to 180 mg in that plasma drug concentrations are proportional to dose administered. There was no evidence of dose dumping either in the presence or absence of food for over 150 subjects in pharmacokinetic studies.

Nifedipine is extensively metabolized to highly water-soluble, inactive metabolites accounting for 60 to 80% of the dose excreted in the urine. The elimination half-life of nifedipine is approximately two hours. Only traces (less than 0.1% of the dose) of unchanged form can be detected in the urine. The remainder is excreted in the feces in metabolized form, most likely as a result of biliary excretion. Thus, the pharmacokinetics of nifedipine are not significantly influenced by the degree of renal impairment. Patients in hemodialysis or chronic ambulatory peritoneal dialysis have not reported significantly altered pharmacokinetics of nifedipine. Since hepatic biotransformation is the predominant route for the disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease. Patients with hepatic impairment (liver cirrhosis) have a longer disposition half-life and higher bioavailability of nifedipine than healthy volunteers. The degree of serum protein binding of nifedipine is high (92-98%). Protein binding may be greatly reduced in patients with renal or hepatic impairment.

Hemodynamics

Like other slow-channel blockers, nifedipine exerts a negative inotropic effect on isolated myocardial tissue. This is rarely, if ever, seen in intact animals or man, probably because of reflex responses to its vasodilating effects. In man, nifedipine decreases peripheral vascular resistance which leads to a fall in systolic and diastolic pressures, usually minimal in normotensive volunteers (less than 5-10 mm Hg systolic), but sometimes larger. With Nifedipine Extended-release Tablets, these decreases in blood pressure are not accompanied by any significant change in heart rate. Hemodynamic studies in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction, left ventricular end diastolic pressure (LVEDP) or volume (LVEDV). In patients with impaired ventricular function, most acute studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure.

Electrophysiologic Effects

Although, like other members of its class, nifedipine causes a slight depression of sinoatrial node function and atrioventricular conduction in isolated myocardial preparations, such effects have not been seen in studies in intact animals or in man. In formal electrophysiologic studies, predominantly in patients with normal conduction systems, nifedipine has had no tendency to prolong atrioventricular conduction or sinus node recovery time, or to slow sinus rate.

INDICATIONS AND USAGE

I. Vasospastic Angina

Nifedipine Extended-release Tablet is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. Nifedipine Extended-release Tablet may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta-blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina)

Nifedipine Extended-release Tablet is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) nifedipine has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients is incomplete.

Controlled studies in small numbers of patients suggest concomitant use of nifedipine and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

III. Hypertension

Nifedipine Extended-release Tablet is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

Known hypersensitivity reaction to nifedipine.

WARNINGS

Excessive Hypotension

Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta-blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta-blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta-Blocker Withdrawal

It is important to taper beta-blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta-blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure

Rarely, patients, usually receiving a beta-blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS

General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Other: As with any other non-deformable material, caution should be used when administering Nifedipine Extended-release Tablet in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of Nifedipine Extended-release Tablet.

Information for Patients: Nifedipine Extended-release Tablets should be swallowed whole. Do not chew, divide or crush tablets. Do not be concerned if you occasionally notice in your stool something that looks like a tablet. In Nifedipine Extended-release Tablet, the medication is contained within a nonabsorbable shell that has been specially designed to slowly release the drug for your body to absorb. When this process is completed, the empty tablet is eliminated from your body.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with Nifedipine Extended-release Tablets. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, Nifedipine Extended-release Tablets did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving Nifedipine Extended-release Tablets in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and an increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect, in certain cases, rare, reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions: Beta-adrenergic blocking agents: (See INDICATIONS AND USAGE and WARNINGS.) Experience in over 1400 patients with nifedipine capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long-acting Nitrates: Nifedipine may be safely coadministered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. There is a literature report of reversible reduction in the ability of human sperm obtained from a limited number of infertile men taking recommended doses of nifedipine to bind to and fertilize an ovum *in vitro*. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C: Nifedipine has been shown to produce teratogenic findings in rats and rabbits, including digital anomalies similar to those reported for phenytoin. Digital anomalies have been reported to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Nifedipine administration was associated with a variety of embryotoxic, placentotoxic, and fetotoxic effects, including stunted fetuses (rats, mice, rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits), and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). On a mg/kg basis, all of the doses associated with the teratogenic embryotoxic or fetotoxic effects in animals were higher (3.5 to 42 times) than the maximum recommended human dose of 120 mg/day. On a mg/m^2 basis, some doses were higher and some were lower than the maximum recommended human dose but all are within an order of magnitude of it. The doses associated with placentotoxic effects in monkeys were equivalent to or lower than the maximum recommended human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. Nifedipine Extended-release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Over 1000 patients from both controlled and open trials with Nifedipine Extended-release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during Nifedipine Extended-release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with Nifedipine Extended-release Tablets was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include:

Adverse Effect	Nifedipine Extended-release Tablets (%) (N=707)	Placebo (%) (N=266)
Headache	15.8	9.8
Fatigue	5.9	4.1
Dizziness	4.1	4.5
Constipation	3.3	2.3
Nausea	3.3	1.9

Of these, only edema and headache were more common in Nifedipine Extended-release Tablet patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone.

Body as a Whole/Systemic: asthenia, flushing, pain
Cardiovascular: palpitations
Central Nervous System: insomnia, nervousness, paresthesia, somnolence
Dermatologic: pruritus, rash
Gastrointestinal: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence
Musculoskeletal: arthralgia, leg cramps
Respiratory: chest pain (nonspecific), dyspnea
Urogenital: impotence, polyuria

Other adverse reactions were reported sporadically with an incidence of 1% or less. These include:

Body as a Whole/Systemic: face edema, fever, hot flashes, malaise, periorbital edema, rigors
Cardiovascular: arrhythmia, hypotension, increased angina, tachycardia, syncope
Central Nervous System: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo
Dermatologic: alopecia, increased sweating, urticaria, purpura
Gastrointestinal: eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase
Musculoskeletal: back pain, gout, myalgias
Respiratory: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis
Special Senses: abnormal lacrimation, abnormal vision, taste perversion, tinnitus
Urogenital/Reproductive: breast pain, dysuria, hematuria, nocturia

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain:
gastrointestinal irritation, gastrointestinal bleeding, gynecomastia.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of nifedipine.

Adverse Effect	NIFEDIPINE CAPSULES (%) (N=226)	Placebo (%) (N=235)
Dizziness, lightheadedness, giddiness	27	15
Flushing, heat sensation	25	8
Headache	23	20
Weakness	12	10
Nausea, heartburn	11	8
Muscle cramps, tremor	8	3
Peripheral edema	7	1
Nervousness, mood changes	7	4
Palpitation	7	5
Dyspnea, cough, wheezing	6	3
Nasal congestion, sore throat	6	8

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with Nifedipine Extended-release Tablets.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving nifedipine with concomitant beta-blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of nifedipine treated patients. (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In postmarketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine. There have been rare reports of exfoliative or bullous skin adverse events (such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) and photosensitivity reactions.

OVERDOSAGE

Experience with nifedipine overdosage is limited. Generally, overdosage with nifedipine leading to pronounced hypotension calls for active cardiovascular support including monitoring of cardiovascular and respiratory function, elevation of extremities, judicious use of calcium infusion, pressor agents and fluids. Clearance of nifedipine would be expected to be prolonged in patients with impaired liver function. Since nifedipine is highly protein-bound, dialysis is not likely to be of any benefit.

There has been one reported case of massive overdosage with Nifedipine Extended-release Tablets. The main effects of ingestion of approximately 4800 mg of Nifedipine Extended-release Tablets in a young man attempting suicide as a result of cocaine-induced depression was initial dizziness, palpitations, flushing, and nervousness. Within several hours of ingestion, nausea, vomiting, and generalized edema developed. No significant hypotension was apparent at presentation, 18 hours post-ingestion. Electrolyte abnormalities consisted of a mild, transient elevation of serum creatinine, and modest elevations of LDH and CPK, but normal SGOT. Vital signs remained stable, no electrocardiographic abnormalities were noted and renal function returned to normal within 24 to 48 hours with routine supportive measures alone. No prolonged sequelae were observed.

The effect of a single 900 mg ingestion of nifedipine capsules in a depressed anginal patient also on tricyclic antidepressants was loss of consciousness within 30 minutes of ingestion, and profound hypotension, which responded to calcium infusion, pressor agents, and fluid replacement. A variety of ECG abnormalities were seen in this patient with a history of bundle branch block, including sinus bradycardia and varying degrees of AV block. These dictated the prophylactic placement of a temporary ventricular pacemaker, but otherwise resolved spontaneously. Significant hyperglycemia was seen initially in this patient, but plasma glucose levels rapidly normalized without further treatment.

A young hypertensive patient with advanced renal failure ingested 280 mg of nifedipine capsules at one time, with resulting marked hypotension responding to calcium infusion and fluids. No AV conduction abnormalities, arrhythmias, or pronounced changes in heart rate were noted, nor was there any further deterioration in renal function.

DOSAGE AND ADMINISTRATION

Dosage must be adjusted according to each patient's needs. Therapy for either hypertension or angina should be initiated with 30 or 60 mg once daily. Nifedipine Extended-release Tablets should be swallowed whole and should not be bitten or divided. In general, titration should proceed over a 7-14 day period so that the physician can fully assess the response to each dose level and monitor blood pressure before proceeding to higher doses. Since steady-state plasma levels are achieved on the second day of dosing, if symptoms so warrant, titration may proceed more rapidly provided the patient is assessed frequently. Titration to doses above 120 mg are not recommended.

Angina patients controlled on nifedipine capsules alone or in combination with other antianginal medications may be safely switched to Nifedipine Extended-release Tablets at the nearest equivalent total daily dose (e.g., 30 mg t.i.d. of nifedipine capsules may be changed to 90 mg once daily of Nifedipine Extended-release Tablets). Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. Experience with doses greater than 90 mg in patients with angina is limited. Therefore, doses greater than 90 mg should be used with caution and only when clinically warranted.

No "rebound effect" has been observed upon discontinuation of Nifedipine Extended-release Tablets. However, if discontinuation of nifedipine is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.

Care should be taken when dispensing Nifedipine Extended-release Tablets to assure that the extended release dosage form has been prescribed.

Coadministration with Other Antianginal Drugs

Sublingual nitroglycerin may be taken as required for the control of acute manifestations of angina, particularly during nifedipine titration. See PRECAUTIONS, Drug Interactions, for information on coadministration of nifedipine with beta-blockers or long-acting nitrates.

HOW SUPPLIED

Nifedipine Extended-release Tablets 30 mg are round, biconvex, pink coated tablets imprinted with "KU 260" in black ink. They are supplied as follows:
Bottles of 100 Tablets NDC 62175-260-37
Bottles of 300 Tablets NDC 62175-260-55

Nifedipine Extended-release Tablets 60 mg are round, biconvex, pink coated tablets imprinted with "KU 261" in black ink. They are supplied as follows:
Bottles of 100 Tablets NDC 62175-261-37
Bottles of 300 Tablets NDC 62175-261-55

Nifedipine Extended-release Tablets 90 mg are round, biconvex, pink coated tablets imprinted with "KU 262" in black ink. They are supplied as follows:
Bottles of 100 Tablets NDC 62175-262-37
Bottles of 300 Tablets NDC 62175-262-55
Bottles of 500 Tablets NDC 62175-262-41

Store at 20°-25°C (68°-77°F) (See USP Controlled Room Temperature).

Protect from moisture, humidity, and light.

Distributed by:
KU™
Kremers Urban, LLC
Mequon, WI 53092, USA
for:
Osmotica Pharmaceutical
Wilmington, NC 28405, USA

PC4759A
Rev. 06/06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-410

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **77-410** Date of Submission: **November 19, 2004**

Applicant's Name: **Osmotica USA Corp**

Established Name: **Nifedipine Extended-release Tablets USP, 90 mg**

Labeling Deficiencies:

1. GENERAL COMMENT

   We note that you have elected to combine the inserts of this ANDA with your ANDA 77-127 for the 30 mg and 60 mg tablets. Please be advised that you will be required to further revise your insert labeling unless these ANDAs are approved at the same time.

2. CONTAINER 100s and 500s

   a. Please ensure that you indicate the distributor name and address where you have indicated that it will appear.

   b. Will there be a company logo on the principal display panel? If so please indicate what it will be and where it will be located.

3. INSERT

   a. GENERAL COMMENTS

      i. See GENERAL COMMENT above.

      ii. "beta-blocker" and "beta-blockers" throughout the insert [add hyphen]

      iii. The established name of a drug is considered a common noun and as such it need not be capitalized unless required by sentence structure.

      iv. See GENERAL COMMENT (1) above.

   b. DESCRIPTION

      Please adjust the location of the subscripts in the structural formula - e.g., "CH_3" rather than "CH3"

   c. CLINICAL PHARMACOLOGY

      Pharmacokinetics and Metabolism, first paragraph, last sentence – "... food for over 150 subjects in pharmacokinetic studies."

d. PRECAUTIONS

Drug Interactions "Cimetidine" - Delete bold print to be the same as the other subsection headings.

e. HOW SUPPLIED

i. Describe the markings on the tablets.

ii. See GENERAL COMMENT above.

iii. We note that you have listed (b) (4) (b) (4) yet you have indicated that . Please comment and/or revise.

Please revise your container labels and insert labeling, as instructed above, and submit each labeling piece in final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels: 100s and 500s
Professional Package Insert Labeling:

	FILE PATH	SUBMIT	ACTION
Label - 100s	\\CDSESUBOGD1\N77410\N_000\2004-11-19\90mg100slabel.pdf	11-19-04	NOT APP
Label - 500s	\\CDSESUBOGD1\N77410\N_000\2004-11-19\90mg500slabel.pdf	11-19-04	NOT APP
Insert	\\CDSESUBOGD1\N77410\N_000\2004-11-19\PC4759Arev10-13-final.pdf	11-19-04	NOT APP

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? NO
What is the RLD on the 356(h) form: Procardia XL
NDA Number: 19-684
NDA Drug Name: Procardia XL (nifedipine extended-release) Tablets
NDA Firm: Pfizer Labs
Date of Approval of NDA Insert and supplement #: 8-12-97 (S-014)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? (b) (4) (b) (4)		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?	X		

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?	X		
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. **Please verify the accuracy of the "System Components and Performance" subsection in the DESCRIPTION section of the insert.**

2. **The firm has failed to describe what markings are on their tablets**

3. **The firm has listed** (b) (4) **yet they have indicated that** (b) (4)

FOR THE RECORD:

1. Review based on the labeling of Procardia XL (NDA 19-684/S-014), revised 1997; approved 8-12-97.

2. Patent/ Exclusivities

Patent Data – 19-684

No	Expiration	Use Code	Use	File	Labeling Impact
5264446	11-23-10			IV	none

Exclusivity Data - 19-684

Code/sup	Expiration	Use Code	Description		Labeling Impact
None			There is no unexpired exclusivity for this product		

3. Storage Conditions:
NDA - Store below 86°F (30°C). Protect from moisture and humidity
ANDA - Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature). Protect from moisture, humidity, and light.
USP - Preserve in tight, light-resistant containers, and store at controlled room temperature.

4. Dispensing Recommendations:
NDA - Dispense in tight containers (USP).
ANDA - Dispense in tight, light-resistant container as defined in the USP.
USP - Preserve in tight, light-resistant containers.

5. Scoring:
NDA - unscored
ANDA - unscored

6. Product Line:
The innovator markets their product in containers of 100s, 300s, 5000s and UD carons of 100s
The applicant proposes to market their product in HDPE containers of 100s, and 500s (both with nonCRC (caps).

7. The firm has not described the markings on the tablet nor its color. I have brought this to the firm's attention in my review.

8. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 4097-4098, 4159, 4264, 4287 - volume B 1.2 - section VII

9. (b) (4) is the manufacturer [p 4336 - section IX - vol B 1.2].

11. IRON CONTENT CALCULATIONS:

MAXIMUM DAILY DOSE 90 mg
RED FERRIC OXIDE PER 90 mg TABLET = (b) (4)
BLACK (b) (4) WHICH CONTRIBUTES "NEGLIGIBLE" WEIGHT TO THE FORMULATION CONTAINS BLACK IRON OXIDE
TOTAL DAILY INGESTION OF RED FERRIC OXIDE = (b) (4)

Date of Review: 5-6-05 Date of Submission: 11-19-04

Primary Reviewer: Adolph Vezza A. Vezza Date: 5/16/05

Team Leader: Captain Lillie Golson L.D. Golson Date: 5/16/05

---

cc: ANDA: 77-410
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
aev/5/6/05|V:\FIRMSNZ\OSMOTICA\LTRS&REV\77410na1.l
Review

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **77-410** Dates of Submission: **March 6 and July 14, 2006**

Applicant's Name: **Osmotica USA Corp**

Established Name: **Nifedipine Extended-release Tablets USP, 90 mg**

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No - PI - ELECTRONIC - LABELS - PRINTERS PROOF
Container Labels: 100s and 500s
Professional Package Insert Labeling:

	FILE PATH - VOLUME NUMBER	SUBMIT	ACTION
Label - 100s	VOLUME A 5.1	3-6-06	APPROVE
Label - 500s	VOLUME A 5.1	3-6-06	APPROVE
Insert	\\Cdsesub1\n77410\N_000\2006-07-14\PC4759A 7-11.pdf	7-14-06	APPROVE

Revisions needed post-approval: NONE

BASIS OF APPROVAL:
Was this approval based upon a petition? NO
What is the RLD on the 356(h) form: Procardia XL
NDA Number: 19-684
NDA Drug Name: Procardia XL (nifedipine extended-release) Tablets
NDA Firm: Pfizer Labs
Date of Approval of NDA Insert and supplement #: 8-12-97 (S-014)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 29	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	

If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? (b) (4) (b) (4)		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?	X		
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Procardia XL (NDA 19-684/S-014), revised 1997; approved 8-12-97.

2. Patent/ Exclusivities

Patent Data – 19-684

No	Expiration	Use Code	Use	File	Labeling Impact
5264446	11-23-10			IV	none

Exclusivity Data - 19-684

Code/sup	Expiration	Use Code	Description		Labeling Impact
None			There is no unexpired exclusivity for this product		

3. Storage Conditions:
NDA - Store below 86°F (30°C). Protect from moisture and humidity
ANDA - Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature). Protect from moisture, humidity, and light.
USP - Preserve in tight, light-resistant containers, and store at controlled room temperature.

4. Dispensing Recommendations:
NDA - Dispense in tight containers (USP).
ANDA - Dispense in tight, light-resistant container as defined in the USP.
USP - Preserve in tight, light-resistant containers.

5. Scoring:
NDA - unscored
ANDA - unscored

6. Product Line:
The innovator markets their product in containers of 100s, 300s, 5000s and UD cartons of 100s
The applicant proposes to market their product in HDPE containers of 100s, and 500s (both with nonCRC (caps).

7. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 4097-4098, 4159, 4264, 4287 - volume B 1.2 - section VII

8. (b) (4) is the manufacturer [p 4336 - section IX - vol B 1.2].

9. IRON CONTENT CALCULATIONS:

MAXIMUM DAILY DOSE 90 mg
RED FERRIC OXIDE PER 90 mg TABLET = (b) (4)
BLACK (b) (4) WHICH CONTRIBUTES "NEGLIGIBLE" WEIGHT TO THE FORMULATION CONTAINS BLACK IRON OXIDE
TOTAL DAILY INGESTION OF RED FERRIC OXIDE = (b) (4)

Date of Review: 7-25-06 Dates of Submission: 3-6-06 and 7-14-06

Primary Reviewer: Adolph Vezza Date: 7/26/06

Team Leader: Captain Lillie Golson Date: 7/27/06

---

cc: ANDA: 77-410
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
aev/7/25/06|V:\FIRMSNZ\OSMOTICA\LTRS&REV\77410.APL.doc
Review

(this supersedes the approval summary done on the 3-6-06 & 7-14-06 submissions)
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **77-410** Date of Submission: **September 28, 2007**

Applicant's Name: **Osmotica USA Corp**

Established Name: **Nifedipine Extended-release Tablets USP, 90 mg**

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes - PI - LABELS - PRINTERS PROOF
Container Labels: 100s, 300s and 500s
Professional Package Insert Labeling:

	FILE PATH - VOLUME NUMBER	SUBMIT	ACTION
Label - 100s	VOLUME A 5.1	3-6-06	APPROVE
Label – 300s	VOLUME T90-591 - A 9.1	9-28-07	APPROVE
Label - 500s	VOLUME A 5.1	3-6-06	APPROVE
Insert	VOLUME T90-591 - A 9.1	9-28-07	APPROVE

Revisions needed post-approval: NONE – Firm to send in electronic PI at a later date.

BASIS OF APPROVAL:
Was this approval based upon a petition? NO
What is the RLD on the 356(h) form: Procardia XL
NDA Number: 19-684
NDA Drug Name: Procardia XL (nifedipine extended-release) Tablets
NDA Firm: Pfizer Labs
Date of Approval of NDA Insert and supplement #: 8-12-97 (S-014)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 30	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	

Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? (b) (4) (b) (4)		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?	X		
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Procardia XL (NDA 19-684/S-014), revised 1997; approved 8-12-97.

2. Patent/ Exclusivities

Patent Data – 19-684

No	Expiration	Use Code	Use	File	Labeling Impact
5264446	11-23-10			IV	none

Exclusivity Data - 19-684

Code/sup	Expiration	Use Code	Description		Labeling Impact
None			There is no unexpired exclusivity for this product		

3. Storage Conditions:
NDA - Store below 86°F (30°C). Protect from moisture and humidity
ANDA - Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature). Protect from moisture, humidity, and light.
USP - Preserve in tight, light-resistant containers, and store at controlled room temperature.

4. Dispensing Recommendations:
NDA - Dispense in tight containers (USP).
ANDA - Dispense in tight, light-resistant container as defined in the USP.
USP - Preserve in tight, light-resistant containers.

5. Scoring:
NDA - unscored
ANDA - unscored

6. Product Line:
The innovator markets their product in containers of 100s, 300s, 5000s and UD cartons of 100s
The applicant proposes to market their product in HDPE containers of 100s, 300s and 500s (all with nonCRC (caps).

7. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

8. (b) (4) is the manufacturer [p 4336 - section IX - vol B 1.2].

9. IRON CONTENT CALCULATIONS:

MAXIMUM DAILY DOSE 90 mg
RED FERRIC OXIDE PER 90 mg TABLET = (b) (4)
BLACK (b) (4) WHICH CONTRIBUTES "NEGLIGIBLE" WEIGHT TO THE FORMULATION CONTAINS BLACK IRON OXIDE
TOTAL DAILY INGESTION OF RED FERRIC OXIDE = (b) (4)

10. The firm added a 300s container size and changed the inactive ingredients with the 9-28-07 submission. 12 FPL hard copies of the insert and the 300s container label were submitted at that time.

Date of Review: 10-1-07 Date of Submission: 9-28-07

Primary Reviewer: Adolph Vezza Date:

Team Leader: Captain Lillie Golson Date:

cc: ANDA: 77-410
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
aev/10/1/07|V:\FIRMSNZ\OSMOTICA\LTRS&REV\77410AP2.LABELING.doc
Review

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Adolph Vezza
10/1/2007 02:17:44 PM
LABELING REVIEWER

Lillie Golson
10/1/2007 02:19:40 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-410

CHEMISTRY REVIEWS

ANDA 77-410

Nifedipine Extended-release Tablets USP, 90 mg

Osmotica USA Corp

Bita Mirzai-Azarm
Division of Chemistry II

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 4

The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 10

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

Chemistry Assessment 11

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....

S DRUG SUBSTANCE [Name, Manufacturer] .....

P DRUG PRODUCT [Name, Dosage form] .....

A APPENDICES .....

R REGIONAL INFORMATION .....

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....

A. Labeling & Package Insert .....

B. Environmental Assessment Or Claim Of Categorical Exclusion .....

III. List Of Deficiencies To Be Communicated .....

This page appears blank in the original review

Chemistry Review Data Sheet

1. ANDA 77-410

2. REVIEW #: 1

3. REVIEW DATE: 24-MAY-2005

4. REVIEWER: Bita Mirzai-Azarm

5. PREVIOUS DOCUMENTS: N/A (Review #1)

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	19-NOV-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Osmotica USA Corp

Address: 7040 Wrightsville Ave.
Suite 103
Wilmington, NC 28403

Representative: Mark S. Aikman

Telephone: 910-509-4235

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Nifedipine Extended-release Tablets,

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Procardia XL®
Innovator Company: Pfizer, Inc.

10. PHARMACOL. CATEGORY:
Vasospastic Angina, Chronic Stable Angina, Hypertension

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 90 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

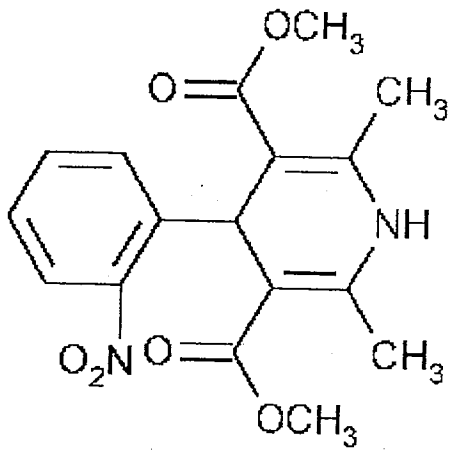
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula: $C_{17}H_{18}N_2O_6$
Molecular Weight: 346.33



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	24-JUL-2002	
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	18-MAR-2005	S. Ferguson
Methods Validation	USP Product		
Labeling	Deficient		A. Vezza
Bioequivalence	Incomplete	04-MAY-2005	Lu
EA	Categorical Exclusions as per 21 CFR part 25.31 (a)		
Radiopharmaceutical			

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-410

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Minor N/A letter recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.33. The DS is manufactured by (b) (4) (DMF (b) (4)). The DMF is satisfactory.

Drug Product:

Nifedipine Controlled-release Tablet is formulated as a once-a-day controlled-release tablet for oral administration designed to deliver 90 mg of Nifedipine. Nifedipine CR Tablets 90 mg are packaged in bottles of 100s and 500s.

The technology used for this product is (b) (4) It is noted that this is true for Nifedipine CR Tablets as it also is for the RLD, Procardia XL®. The 90 mg product contains a 10% overage (total 99 mg) of API which will release in-vivo 90 mg.

Osmotica previously submitted ANDA 77-127 for Nifedipine Extended-Release Tablets, USP 30 mg and 60 mg. All strengths are dose proportional. Formulation design and manufacturing process is identical for all three strengths.

B. Description of How the Drug Product is Intended to be Used

The ANDA storage temperature is 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature). Protect from moisture, humidity, and light. Expiration dating is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

Minor N/A letter recommended.

III. Administrative

A. Reviewer's Signature

B. Endorsements

HFD-647/B.M.Azarm/5/24/05, 6/20/05 (revised) Bita M. Azarm 6/23/05

HFD-647/U.Venkataram/06.06.05 Nahed for (UV) 6/23-05

HFD-617/C.Wiseman/06/21/05

V:\FIRMSNZ\OSMOTICA\LTRS&REV\77410N01.rbm.doc

C. CC: ANDA 77-410
ANDA DUP
DIV FILE
Field Copy

Following this page, 14 pages withheld in full- (b)(4) Chemistry review #1

36. Chemistry Comments to be provided to the ANDA Holder

ANDA: 77-410 Applicant: Osmotica USA Corp.

Drug Product: Nifedipine Extended-release Tablets USP, 90 mg

A. Chemistry Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6.

7.

(b) (4)

8.

9.

10.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please submit available long term stability data.

Sincerely,

Florence F. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-410
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-647/B.M.Azarm/5/24/05, 6/20/05 (revised) Bita M. Azarm 6/23/05

HFD-647/U.Venkataram/ 6.20.05 (for UV) 6-23-05

HFD-617/C. Wiseman/6.22.05 6/23/05

F/T by: CW 6/22/05

V:\FIRMSNZ\OSMOTICA\LTRS&REV\77410N01.RBM.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

Chemistry Review Data Sheet

ANDA 77-410

Nifedipine Extended-release Tablets USP
90 mg

Osmotica Pharmaceutical Corp.

Bita Mirzai-Azarm
Division of Chemistry II

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

III. Administrative ..... **Error! Bookmark not defined.**

A. Reviewer's Signature ..... **Error! Bookmark not defined.**

B. Endorsement Block ..... **Error! Bookmark not defined.**

C. CC Block ..... **Error! Bookmark not defined.**

Chemistry Assessment 9

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....

S DRUG SUBSTANCE [Name, Manufacturer] .....

P DRUG PRODUCT [Name, Dosage form] .....

A APPENDICES .....

R REGIONAL INFORMATION .....

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....

A. Labeling & Package Insert .....

B. Environmental Assessment Or Claim Of Categorical Exclusion .....

III. List Of Deficiencies To Be Communicated .....

Chemistry Review Data Sheet

1. ANDA 77-410

2. REVIEW #: 2

3. REVIEW DATE: 27-APR-2006

4. REVIEWER: Bita Mirzai-Azarm

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	19-NOV-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	10-NOV-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Osmotica Pharmaceutical Corp.

Address: 11205 Culbreth Drive
Suite 200
Wilmington, NC 28405

Representative: Mark S. Aikman

Telephone: 910-509-0114

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Nifedipine Extended-release Tablets, USP

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Procardia XL®
Innovator Company: Pfizer, Inc.

10. PHARMACOL. CATEGORY:
Vasospastic Angina, Chronic Stable Angina, Hypertension

11. DOSAGE FORM: Extended-release Tablet

12. STRENGTH/POTENCY: 90 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

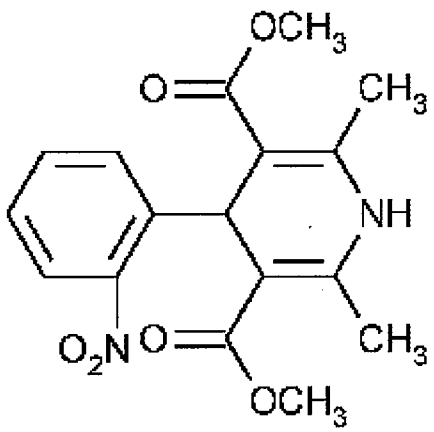
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula: $C_{17}H_{18}N_2O_6$
Molecular Weight: 346.33



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate Info. Request	24-JUL-2002 03-NOV-2005	
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NONE

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	18-MAR-2005	S. Ferguson
Methods Validation	USP Product		
Labeling	Acceptable	27-JUL-2006	A. Vezza
Bioequivalence	Acceptable	01-DEC-2006	S. Lu
EA	Categorical Exclusions as per 21 CFR part 25.31 (a)		
Radiopharmaceutical			

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes _X___ No If no, explain reason(s) below:

Minor Amendment.

The Chemistry Review for ANDA 77-410

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application may be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.33. The DS is manufactured by (b) (4) (DMF (b) (4)). **The DMF is adequate with information request pending.**

Drug Product:

Nifedipine Controlled-release Tablet is formulated as a once-a-day controlled-release tablet for oral administration designed to deliver 90 mg of Nifedipine. Nifedipine CR Tablets 90 mg are packaged in bottles of 100s and 500s.

The technology used for this product is (b) (4) It is noted that this is true for Nifedipine CR Tablets as it also is for the RLD, Procardia XL®. The 90 mg product contains a 10% overage (total 99 mg) of API which will release in-vivo 90 mg.

Osmotica previously submitted ANDA 77-127 for Nifedipine Extended-Release Tablets, USP 30 mg and 60 mg. All strengths are dose proportional. Formulation design and manufacturing process is identical for all three strengths.

B. Description of How the Drug Product is Intended to be Used
The ANDA storage temperature is 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature). Protect from moisture, humidity, and light. Expiration dating is 24 months.

C. Basis for Approvability or Not-Approval Recommendation
This application may be approved.

Following this page, 16 pages withheld in full- (b)(4) Chemistry review #2

months stability data are enclosed. Results are within specifications.

30. MICROBIOLOGY
N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
DS and DP are both compendial.

32. LABELING
Acceptable on 27-JUL-2006 by A. Vezza

Reviewed by Chemist:
Chemical Name: Satisfactory
Molecular Weight: Satisfactory
Molecular Formula: Satisfactory
Inactive Ingredients: Satisfactory
Storage:
ANDA – The ANDA storage temperature is 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature). Protect from moisture, humidity, and light.

33. ESTABLISHMENT INSPECTION
Acceptable on 18-MAR-2005 by S. Ferguson.

34. BIOEQUIVALENCE
Acceptable on 1-DEC-2006 by S. Lu

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

An Environmental impact statement is submitted. The firm is claiming for a Categorical Exclusions as per section 25.31 (b) of the regulations.

cc: ANDA 77-410
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-647/B.M.Azarm/4/27/06

HFD-647/U.Venkataram/

HFD-617/C. Wiseman/

F/T by: E.Chuh

V:\FIRMSNZ\OSMOTICA\LTRS&REV\77410N02RBM

TYPE OF LETTER: APPROVABLE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bita Mirzai-Azarm
12/11/2006 02:36:03 PM
CHEMIST

Richard Adams
12/12/2006 01:08:10 PM
CHEMIST
for Ubrani Venkataram

Esther Chuh
12/20/2006 12:59:30 PM
CSO

#3

CHEMISTRY REVIEW

Chemistry Review Data Sheet

ANDA 77-410

Nifedipine Extended-release Tablets USP, 90 mg

Osmotica USA Corp

Bita Mirzai-Azarm
Division of Chemistry I

Review #3

Table of Contents

Table of Contents .....

Chemistry Review Data Sheet .....

The Executive Summary .....

I. Recommendations .....

A. Recommendation and Conclusion on Approvability .....

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .....

II. Summary of Chemistry Assessments .....

A. Description of the Drug Product(s) and Drug Substance(s) .....

B. Description of How the Drug Product is Intended to be Used .....

C. Basis for Approvability or Not-Approval Recommendation .....

III. Administrative .....

A. Reviewer's Signature .....

B. Endorsement Block .....

C. CC Block .....

Chemistry Assessment .....

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....

S DRUG SUBSTANCE [Name, Manufacturer] .....

P DRUG PRODUCT [Name, Dosage form] .....

A APPENDICES .....

R REGIONAL INFORMATION .....

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....

A. Labeling & Package Insert .....

B. Environmental Assessment Or Claim Of Categorical Exclusion .....

III. List Of Deficiencies To Be Communicated .....

Chemistry Review Data Sheet

1. ANDA 77-410

2. REVIEW #: 3

3. REVIEW DATE: 24-SEP-2007

4. REVIEWER: Bita Mirzai-Azarm

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	19-NOV-2004
Minor Amendment	10-NOV-2005
Tentative Approval	28-DEC-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	20-SEP-2007
Telephone Amendment	25-SEP-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Osmotica Pharmaceutical Corp.

Address: 1205 Culbreth Drive
Suite 200
Wilmington, NC 28405

Representative: Mark S. Aikman

Telephone: 910-509-0114

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Nifedipine Extended-release Tablets, USP

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Procardia XL®
Innovator Company: Pfizer, Inc.

10. PHARMACOL. CATEGORY:
Vasospastic Angina, Chronic Stable Angina, Hypertension

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 90 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

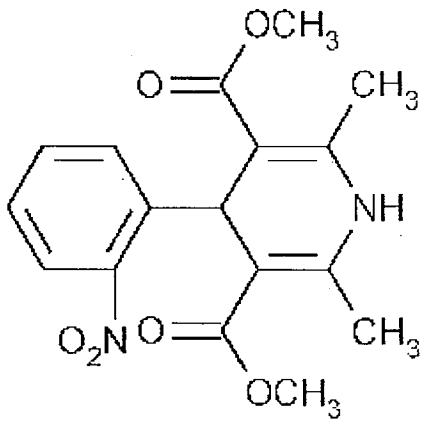
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula: $C_{17}H_{18}N_2O_6$
Molecular Weight: 346.33



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Per Office Policy, the DMFs are not checked for any updates for final approval of the ANDA.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	14-DEC-2006	J.D Ambrogio
Methods Validation	USP Product		
Labeling	Acceptable	01-OCT-2007	A. Vezza
Bioequivalence	Acceptable	01-DEC-2006	S. Lu
EA	Categorical Exclusions as per 21 CFR part 25.31 (a)	CR #1	Bita Mirzai-Azarm
Radiopharmaceutical			

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes _X___ No If no, explain reason(s) below:

Minor Amendment.

The Chemistry Review for ANDA 77-410

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Routine stability commitment.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.33. The DS is manufactured by (b) (4) (DMF (b) (4)).

Drug Product:
Nifedipine Controlled-release Tablet is formulated as a once-a-day controlled-release tablet for oral administration designed to deliver 90 mg of Nifedipine. Nifedipine CR Tablets 90 mg are packaged in bottles of 100s, 300s and 500s.

The technology used for this product is (b) (4) [redacted] It is noted that this is true for Nifedipine CR Tablets as it also is for the RLD, Procardia XL®. The 90 mg product contains a 10% overage (total 99 mg) of API which will release in-vivo 90 mg.

Osmotica previously submitted ANDA 77-127 for Nifedipine Extended-Release Tablets, USP 30 mg and 60 mg. All strengths are dose proportional. Formulation design and manufacturing process is identical for all three strengths.

B. Description of How the Drug Product is Intended to be Used

The ANDA storage temperature is 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature). Protect from moisture, humidity, and light. Expiration dating is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

This application is recommended for approval.

Following this page, 4 pages withheld in full- (b)(4) Chemistry review #3

(b) (4)

[redacted]

30. MICROBIOLOGY
N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
DS and DP are both compendial.

32. LABELING
Acceptable 10/1/07. A. Vezza.

33. ESTABLISHMENT INSPECTION
Acceptable

34. BIOEQUIVALENCE
See CR #2

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
An Environmental impact statement is submitted. The firm is claiming for a Categorical Exclusions as per section 25.31 (b) of the regulations.

cc: ANDA 77-410
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-647/B.M.Azarm/9/26/07

HFD-647/M.Smela/

F/T by:

V:\Chemistry Division I \Team 2\TL Folder\Draft\77410N03RBM.doc

TYPE OF LETTER: APPROVAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bita Mirzai-Azarm
10/2/2007 11:52:57 AM
CHEMIST

Michael Smela
10/2/2007 12:54:32 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-410

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-410
Drug Product Name	Nifedipine Extended-Release Tablets, USP
Strength	90 mg
Applicant Name	Osmotica
Submission Date(s)	November 19, 2004
First Generic	No
Reviewer	Shirley K. Lu
File Location	**V:\firmsnz\osmotica\ltrs&rev\77410D1104.doc**
Clinical Site	PRACS Institute, Ltd. East Grand Forks, MN 56721
Analytical Site	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104
Dissolution Testing Site	**Osmotica-Wilmington, NC, USA**

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

The dissolution testing is incomplete. There are four test methods in USP for this product. The firm conducted dissolution testing on their Nifedipine ER tablets, 90 mg using USP method Test 1 and in several other media. The dissolution data using the USP Test 1 method show that the test product does not meet the USP specifications. Therefore, as per consultation with the DBE dissolution focal point, Dr. Tran (see attachments), the following dissolution method and specifications are recommended for this test product:

Method: 50 mL water using USP apparatus 7 at 15-30 cycles per minute
Specifications:

4 hrs:	(b) (4)
12 hrs	
24 hrs	

The firm should indicate if it accepts the interim dissolution testing method and specifications recommended by the DBE. The labeling of the test product should state: "Dissolution test is pending." After this application is approved, the DBE will communicate this dissolution method and specifications to the USP. The USP will then assign a test number for this product and the product will be relabeled as USP product meeting test number assigned for this product. The test product cannot be labeled as a USP product until the USP assigns a test number for this test product.

The DBE will review the fasted BE study at a later date.

RLD METHOD

Medium	Water
Volume	50 mL
Temperature	37 °C
Apparatus	7
Rotational Speed	15-30 cycles per minute
Specification	4 hours: between 5% and 17% 12 hours: between 43% and 80% 24 hours NLT 80%

Source of Method: USP 28 method test 1 (as of 4/11/05)

Table 1. Summary of In Vitro Dissolution Data

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Units	Collection Times Mean % Dissolved (Range)													Study Report Location
					1 h	2 h	4 h	6 h	8 h	10 h	12 h	14 h	16 h	18 h	20 h	22 h	24 h	
R04-0598	Osmotica /P424401	90 mg ER tab.	**USP Test1:** Medium: **Water** Apparatus 7 (USP) Volume: 50 mL Speed: 30 dpm Temperature: 37°C	12	(b) (4)		8 (4-11)	(b) (4)			48 (42-55)	(b) (4)					78 (72-82)	V 1.1 p. 168
R04-0598	Procardia XL®/37P 065A	90 mg ER tab.		12			9 (4-15)				42 (17-63)						67 (25-103)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Units	Collection Times Mean % Dissolved (Range)													Study Report Location
					1 h	2 h	4 h	6 h	8 h	10 h	12 h	14 h	16 h	18 h	20 h	22 h	24 h	
R04-0598	Osmotica /P424401	90 mg ER tab.	Medium: **0.1 N HCl** + 1% Tween Apparatus 2 (USP) Volume: not given Speed: 100 rpm Temperature: 37°C	12	(b) (4)		7 (5-8)	(b) (4)			49 (44-55)	(b) (4)					87 (83-91)	V 1.1 p. 168
R04-0598	Procardia XL®/37P 065A	90 mg ER tab.		12			15 (11-25)				63 (52-86)						109 (89-112)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Units	Collection Times Mean % Dissolved (Range)												Study Report Location
					1 h	2 h	4 h	6 h	8 h	10 h	12 h	14 h	16 h	18 h	20 h	22 h	24 h	
R04-0598	Osmotica /P424401	90 mg ER tab.	Medium: **pH 4.5 acetate buffer** + 1% Tween Apparatus 2 (USP) Volume: not given Speed: 100 rpm Temperature: 37ºC	12	(b) (4)		6 (2-9)	(b) (4)			49 (37-56)	(b) (4)					90 (85-99)	V 1.1 p. 168
R04-0598	Procardia XL®/37P 065A	90 mg ER tab.		12			15 (10-23)				66 (52-83)						116 (110-118)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Units	Collection Times Mean % Dissolved (Range)												Study Report Location
					1 h	2 h	4 h	6 h	8 h	10 h	12 h	14 h	16 h	18 h	20 h	22 h	24 h	
R04-0598	Osmotica /P424401	90 mg ER tab.	Medium: **pH 6.8 phosphate buffer** + 1% Tween Apparatus 2 (USP) Volume: not given Speed: 100 rpm Temperature: 37ºC	12	(b) (4)		7 (4-9)	(b) (4)			51 (36-56)	(b) (4)					90 (82-95)	V 1.1 p. 168
R04-0598	Procardia XL®/37P 065A	90 mg ER tab.		12			15 (11-20)				64 (57-76)						117 (111-120)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Units	Collection Times Mean % Dissolved (Range)												Study Report Location
					1 h	2 h	4 h	6 h	8 h	10 h	12 h	14 h	16 h	18 h	20 h	22 h	24 h	
R04-0598	Osmotica /P424401	90 mg ER tab.	Medium: **pH 7.5 phosphate buffer** + 1% Tween Apparatus 2 (USP) Volume: not given Speed: 100 rpm Temperature: 37ºC	12	(b) (4)		6 (4-9)	(b) (4)			51 (46-56)	(b) (4)					90 (86-95)	V 1.1 p. 168
R04-0598	Procardia XL®/37P 065A	90 mg ER tab.		12			14 (11-17)				63 (58-70)						115 (110-118)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Units	Collection Times Mean % Dissolved (Range)													Study Report Location
					1 h	2 h	4 h	6 h	8 h	10 h	12 h	14 h	16 h	18 h	20 h	22 h	24 h	
R04-0598	Osmotica /P424401	90 mg ER tab.	Medium: **pH 6.8 phosphate buffer** + 1% Tween Apparatus 2 (USP) Volume: not given Speed: **50 rpm** Temperature: 37ºC	12	(b) (4)		3 (2-5)	(b) (4)			45 (33-53)	(b) (4)					84 (75-87)	V 1.1 p. 168

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Units	Collection Times Mean % Dissolved (Range)													Study Report Location
					1 h	2 h	4 h	6 h	8 h	10 h	12 h	14 h	16 h	18 h	20 h	22 h	24 h	
R04-0598	Osmotica /P424401	90 mg ER tab.	Medium: **pH 6.8 phosphate buffer** + 1% Tween Apparatus 2 (USP) Volume: not given Speed: **75 rpm** Temperature: 37ºC	12	(b) (4)		5 (3-7)	(b) (4)			49 (43-55)	(b) (4)					88 (85-92)	V 1.1 p. 168

Table 2. SAS Transport Files

Are the SAS files located in the EDR ? (Yes/No)	
Fasting BE Study	
Plasma Data	Yes
PK data	Yes
Fed BE Study	
Plasma Data	N/A
PK Data	N/A

COMMENTS

The dissolution testing is incomplete. The firm conducted dissolution testing on their Nifedipine ER tablets, USP, 90 mg using USP method Test 1 and in several other media. The dissolution data using the USP method show that the test product does not meet the USP specifications. Therefore, as per consultation with the DBE dissolution focal point, Dr. Tran (see attachments), the following dissolution method and specifications are recommended for this test product:

Method: 50 mL water using USP apparatus 7 at 15-30 cycles per minute
Specifications:

4 hrs: (b) (4)
12 hrs
24 hrs:

The firm should acknowledge the interim dissolution testing method and specifications proposed by the DBE. The labeling of the test product should state: "Dissolution test is pending." After this application is approved, the DBE will communicate this dissolution method and specifications to the USP. The USP will then assign a test number for this product and the product will be relabeled as USP product meeting test number assigned for this product. The test product cannot be labeled as a USP product until the USP assigns a test number for this test product.

DEFICIENCY COMMENTS

1. The firm should acknowledge the dissolution testing method and specifications proposed by the DBE.

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data summary, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

RECOMMENDATION

The *in vitro* dissolution testing conducted by Osmotica on its test product, Nifedipine ER Tablets, USP, 90 mg comparing it to Pfizer's Procardia XL® tablets, 90 mg is incomplete. The firm should indicate if it accepts the dissolution method and specifications proposed by the DBE.

Shirley K. Lu, Ph.D.
Reviewer, Branch IV
Division of Bioequivalence

5/4/05
Date

Kuldeep R. Dhariwal, Ph.D.
Team Leader, Branch IV
Division of Bioequivalence

5/4/2005
Date

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs

5/4/05
Date

V:\firmsnz\Osmotica\ltrs&rev\77410D1104.doc

ATTACHMENTS

-----Original Message-----
From: Tran, Nhan L
Sent: Monday, April 11, 2005 10:40 AM
To: Lu, Shirley
Subject: RE: Nifedipine

There is no formal rule about setting up the specification at the last time point for ER products. As you point out, normally it is "NLT" but also there are instances where "range" is used, and it is perfectly OK.

-----Original Message-----
From: Lu, Shirley
Sent: Monday, April 11, 2005 9:58 AM
To: Tran, Nhan L
Subject: RE: Nifedipine

Hi Dr. Tran,

Thanks for the guidance on nifedipine. However, after I talked it over with Kuldeep, we were wondering why the 24-hour timepoint that you gave is a range and not "NLT". Isn't the 24-hour limit for an ER product usually "NLT"?

Thanks,
Shirley

-----Original Message-----
From: Tran, Nhan L
Sent: Thursday, April 07, 2005 7:48 AM
To: Lu, Shirley
Subject: RE: Nifedipine

Based on the data submitted by the firm, I think a new spec will be set for the generic firm as follows:

4 hrs: (b) (4)
12 hrs
24 hrs

Their product will not be labeled as a USP product until the application is fully approved and we (DBE) will inform the USP of the new spec. The USP then will give them a Test # (look at Nifedipine ER--3 tests now), and the product will be relabeled to state "meet the USP test #....".
In the meantime, the labeling should state: "Dissolution test is pending".

Hope this will help,

-----Original Message-----
From: Lu, Shirley
Sent: Wednesday, April 06, 2005 5:35 PM
To: Tran, Nhan L
Subject: Nifedipine

Hello Dr. Tran,

I have another question for you. One of the drug products I am reviewing for dissolution is Nifedipine ER tablets, USP. The USP specs are:

4 hours	between %5 and 17%
12 hours	between 43% and 80%
24 hours	NLT 80%

Here are the firm's data:

Time	Mean	Range
4 hours	8	4-11
12 hours	48	42-55
24 hours	78	72-82

Because the 24 hour timepoint doesn't even pass specs at L2, should we come up with a new spec and tell the firm that their product cannot be a USP product? If so, what new spec should I set?

Thanks,
Shirley

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-410 APPLICANT: Osmotica

DRUG PRODUCT: Nifedipine Extended-Release Tablets
90 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence study will be conducted later. The following deficiencies have been identified:

1. The DBE recommends the following dissolution method:

   The dissolution testing should be conducted in 50 mL water, at 37°C using USP Apparatus 7 at 15-30 cycles per minute.

   The DBE requests that the test product should meet the following interim specifications:

   4 hours: (b) (4)
   12 hours:
   24 hours:

   With your response to the above deficiency, please indicate if you accept the above dissolution method and specification.

   Please note that the test product cannot be labeled as a USP product until the USP assigns a test number for your product. In the interim, the labeling should state: "Dissolution test is pending."

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any

other applications pending in the Division and in applications to be submitted in the future.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 77410
Nifedipine ER Tablets

Table 1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	T½ (hr)	K_{el} (hr^{-1})	
Study #	Fasting study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #
Study #	Fed study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean y (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #

Table 2. Statistical Summary of the Comparative Bioavailability Data

Drug Dose (# x mg) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}				
AUC_{∞}				
C_{max}				
Fed Bioequivalence Study				
Parameter	**Test**	**Reference**	**100*Ratio**	**90% C.I.**
AUC_{0-t}				
AUC_{∞}				
C_{max}				

Table 3. Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Provide the name(s) of the analyte(s)
Internal standard (IS)	Identify the internal standard used
Method description	Brief description of extraction method; analytical method
Limit of quantitation	LOQ, units
Average recovery of drug (%)	%
Average recovery of IS (%)	%
Standard curve concentrations (units/mL)	Standard curve range and appropriate concentration units
QC concentrations (units/mL)	List all the concentrations used
QC Intraday precision range (%)	Range or per QC
QC Intraday accuracy range (%)	Range or per QC
QC Interday precision range (%)	Range or per QC
QC Interday accuracy range (%)	Range or per QC
Bench-top stability (hrs)	hours @ room temperature
Stock stability (days)	days @ 4°C
Processed stability (hrs)	hours @ room temperature; hours @ 4°C
Freeze-thaw stability (cycles)	# cycles
Long-term storage stability (days)	17 days @ -20°C (or other)
Dilution integrity	Concentration diluted X-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4. Summary of In Vitro Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	Dissolution: Apparatus Speed of Rotation: rpm Medium: Volume: mL Temperature: °C	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap/Susp.		12					

Table 5. Formulation Data

Ingredient	Amount (mg) / Tablet		Amount (%) Tablet	
	Lower strength	Higher strength	Lower strength	Higher strength
Cores				
Coating				
Total			100.00	100.0

Table 6. Demographic Profile of Subjects Completing the Bioequivalence Study

Study No.		
	Treatment Groups	
	Test Product N =	Reference Product N =
Age (years)		
Mean ± SD	50 ± 15	
Range	20-85	
Groups		
< 18	N(%)	N(%)
18 – 40	N(%)	N(%)
40 – 64	N(%)	N(%)
65 – 75	N(%)	N(%)
> 75	N(%)	N(%)
Sex		
Female	N(%)	N(%)
Male	N(%)	N(%)
Race		
Asian	N(%)	N(%)
Black	N(%)	N(%)
Caucasian	N(%)	N(%)
Hispanic	N(%)	N(%)
Other	N(%)	N(%)
Other Factors		

Table 7. Incidence of Adverse Events in Individual Studies

Body System/Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No.		Fed Bioequivalence Study Study No.		Other Bioequivalence Study Study No.	
	Test	Reference	Test	Reference	Test	Reference
Body as a whole						
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular						
Hypotension						
Etc.						
Gastrointestinal						
Constipation						
Etc.						
Other organ sys.						
Total	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 8. Reanalysis of Study Samples

Study No. Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

CC: ANDA #: 77-410
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ S.K. Lu
HFD/650/ B. Fabian-Fritsch

V:\firmsnz\Osmotica\ltrs&rev\77410D1104.doc
Printed in final on 5/4/05

Endorsements: (Final with Dates)
HFD-650/Lu SKL 5/4/05
HFD-650/Dhariwal 5/4/05
HFD/650/Fabian-Fritsch
HFD-650/Conner 5/4/05

BIOEQUIVALENCE - INCOMPLETE Submission date: 11/19/04

[NOTE: The *in vitro* testing is incomplete. The fasting study is pending review]

1. DISSOLUTION (Dissolution Data) Strength: 90 mg
Outcome: IC

Outcome Decisions: IC –Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-410
Drug Product Name	Nifedipine Extended-Release Tablets, USP
Strength	90 mg
Applicant Name	Osmotica USA Corporation
Address	7040 Wrightsville Avenue, Suite 103 Wilmington, NC 28403
Submission Date(s)	November 19, 2004
Amendment Date(s)	November 22, 2005
Reviewer	Yi Zhang, Ph.D.
First Generic	No
File Location	V:\firmsnz\Osmotica\ltrs&rev\77410N1104.doc

I. Executive Summary

This application references Pfizer's Procardia XL® tablets (nifedipine extended-release (ER) tablets) and the Orange Book lists 90 mg Procardia XL® tablets by Pfizer Inc. as the Referenced Listed Drug (RLD). The firm has submitted one fasting bioequivalence (BE) study on 90 mg nifedipine extended-release tablets, and requested waiver of *in vivo* BE study under fed conditions for the 90 mg nifedipine extended-release tablets based on their previous ANDA 77-127 which contained both a fasting study and a fed study on the 60 mg product..

The fasting study is a single-dose two-way crossover study using 84 normal healthy subjects (Male: 46, Female: 38) given a dose of 90 mg nifedipine extended-release tablets. One subject was removed from statistical analysis because of reported vomiting within nifedipine dosing interval; the DBE concurs with the decision to drop this subject. However, the results from 83 subjects of fasting BE study calculated by the reviewer are: LAUCt of 0.84, **76.68**-92.38%; LAUCi of 0.85, **75.97**-94.75%; and LCmax of 0.93, 86.69-99.84%. The 90% confidence intervals for the ratios of the test/reference LAUCt and LAUCi were outside the acceptable limits of 80-125%. In firm's final statistical report, 8 subjects were excluded due to their failing to finish 80% of the evening meal prior to dosing. The firm's results from 76 subjects (point estimate, 90% CI) of fasting BE study are: LAUCt of 87.12, 82.91-91.54%; LAUCi of 88.07, 83.39-93.02%; and LCmax of 94.45, 89.26-99.94%. Excluding these subjects from final statistical analysis by the firm is not acceptable. The fasting BE study is incomplete. The firm will be asked to identify the samples that were repeated for pharmacokinetic reasons, and to conduct and submit statistical analysis using original assay values as well as repeat values for such repeats.

The dissolution data was reviewed previously by the DBE (77410D1104.doc). There are four test methods in USP for this product. The following dissolution method and specifications were recommended for this test product: 50 mL water using USP apparatus 7 at 15-30 cycles per minute with the specifications of NMT (b) (4) % at 4 hr, (b) (4) % at 12 hr and (b) (4) % at 24 hr. The firm acknowledged the FDA-recommended dissolution

method, specification of NMT (b) (4) % at 4 hour time point, and proposed to change the specification at 12 hour time point from (b) (4) % to (b) (4) % and the specification at 24 hour time point from (b) (4) % to NLT (b) (4) % in an amendment dated 11/22/2005 based on data from stability lots. The DBE will not change the specifications at this time as fresh bio-lot meets the DBE-recommended specifications at L1.

The application is incomplete (see details in Deficiency Comments).

II. Table of Contents

I. Executive Summary 1
II. Table of Contents 3
III. Submission Summary 4
A. Drug Product Information 4
B. PK/PD Information 5
C. Contents of Submission 6
D. Pre-Study Bioanalytical Method Validation 7
E. In Vivo Studies 8
1. Single-dose Fasting Bioequivalence Study 9
2. Single-dose Fed Bioequivalence Study 12
F. Formulation 12
G. In Vitro Dissolution 13
H. Waiver Request(s) 14
I. Deficiency Comments 14
J. Recommendations 15
IV. Appendix 17
A. Individual Study Reviews 17
1. Single-dose Fasting Bioequivalence Study 17
a) Study Design 17
b) Clinical Results 20
c) Bioanalytical Results 23
d) Pharmacokinetic Results 24
B. Formulation Data 29
C. Dissolution Data 30
D. Consult Reviews 32
E. SAS Output 32
F. Additional Attachments 32

III. Submission Summary

A. Drug Product Information

Test Product	Nifedipine ER Tablets, USP, 90 mg
Reference Product	Procardia XL® tablets, 90 mg
RLD Manufacturer	Pfizer Inc.
NDA No.	19-684
RLD Approval Date	September 06, 1989
Indication	It is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents. It is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. It is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm.

B. PK/PD Information

Bioavailability	Nifedipine is completely absorbed after oral administration. At steady-state the bioavailability of the Procardia XL® Extended Release Tablet is 86% relative to Procardia capsules.
Food Effect	Food slightly alters the early rate of drug absorption, but does not influence the extent of drug bioavailability.
Tmax	Plasma drug concentrations rise at a gradual, controlled rate after a single dose of Procardia XL® Extended Release Tablet and reach a plateau at approximately six hours after the first dose.
Metabolism	Nifedipine is extensively metabolized to highly water-soluble, inactive metabolites accounting for 60% to 80% of the dose excreted in the urine.
Excretion	The highly water-soluble, inactive metabolites account for 60 to 80% of the dose excreted in the urine. Only traces (less than 0.1% of the dose) of unchanged form can be detected in the urine. The remainder is excreted in the feces in metabolized form, most likely as a result of biliary excretion.
Half-life	About two hours
Relevant OGD or DBE History	The DBE has reviewed many ANDAs (e.g. ANDA75-108 from Mylan, ANDA75-128 from Watson Laboratories, ANDA75-269, 75-289, (b) (4) (b) (4) 76-070 and (b) (4) from Biovail, ANDA (b) (4), ANDA75-414 and (b) (4) from Martec Scientific, ANDA 75-659 from Elan, ANDA (b) (4) ANDA 77-127 from Osmotica), and control documents (e.g. 02-618 and 04-159 from Osmotica, 04-991 from (b) (4) and 04-940 from Martec Scientific) on nifedipine ER tablets. Fasting and fed studies were conducted on the highest strength and the lower strengths were eligible for waivers. Only the parent compound, nifedipine were measured. There are two RLDs for Nifedipine ER Tablets: Adalat® CC by Bayer and Procardia XL® by Pfizer. For demonstration of bioequivalence of nifedipine ER tablets to the RLD Procardia XL® by Pfizer, the DBE currently recommends the following: 1. A single-dose fasting *in-vivo* bioequivalence study comparing Nifedipine 60 mg ER Tablets to the RLD, Procardia XL® (nifedipine ER) 60 mg Tablets. 2. A single-dose fed *in-vivo* bioequivalence study comparing Nifedipine 60 mg ER Tablets to the RLD, Procardia XL® (nifedipine ER) 60 mg Tablets. 3. Only the parent compound, nifedipine needs to be measured.

	4. Dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA-recommended method: Apparatus: USP 28 apparatus VII (25 cm Plexiglas rod) Speed: 15-30 cycles per minute Medium: Water Volume: 50 mL Sampling times: 1, 2, 4, and every 2 hours thereafter until 24 hrs Specification: 4 hrs: NMT 14% (Q) 12 hrs: 39-75 % (Q) 24 hrs: NLT 75% (Q) Osmotica conducted BE study on the 60 mg nifedipine ER tablets against Procardia XL® 60 mg Tablets, which were submitted under ANDA 77-127. Nifedipine ER tablets 30 mg and 60 mg strengths were approved on November 21, 2005 under ANDA 77-127. The following dissolution method and specifications were recommended to the firm: Dissolution Method: As outlined in above recommendation #4 Specification: 4 hrs: NMT 14% (Q) 12 hrs: 39-75% (Q) 24 hrs: NLT 75% (Q) The DBE informed the firm that only an additional fasting BE study would be requested for addition of the 90 mg strength at a later time.
Agency Guidance	No
Drug Specific Issues (if any)	No

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed		
Steady-state		
In vitro dissolution	Yes	1
Waiver requests		
BCS Waivers		
Vasoconstrictor Studies		
Clinical Endpoints		
Failed Studies		
Amendments	Yes	1

D. Pre-Study Bioanalytical Method Validation

Analyte	Nifedipine
Internal Standard (IS)	(b) (4)
Method Description	Solid phase extraction
Limit of Quantitation (ng/mL)	0.50 ng/mL
Average Recovery of Drug (%)	55.4%
Average Recovery of IS (%)	85.5%
Standard Curve Concentrations (ng/mL)	0.50, 2, 5, 10, 50, 100, 200, 300
QC Concentrations (ng/mL)	1.50, 150, 250
QC Intraday Precision Range (%)	0.78% - 1.72%
QC Intraday Accuracy Range (%)	100.9% - 104.0%
QC Interday Precision Range (%)	3.52% - 8.57%
QC Interday Accuracy Range (%)	103.3% - 105.8%
Bench-top Stability (hrs)	7:49 Hours:minutes @ room temperature
Stock Stability (days)	1 Day @ 4°C
Processed Stability (hrs)	113:10 Hours:minutes @ room temperature
Freeze-Thaw Stability (Cycles)	4 cycles
Long-Term Storage Stability (days)	204 Days @ -20°C
Dilution Integrity	Concentration diluted 4-fold 96.0% - 101.0%
Selectivity	No interfering peaks noted in blank plasma samples

Comments on Pre-Study Assay Validation: The absolute recovery of nifedipine was 33.7% for 0.50 ng/ml, 57.9% for 200.00 ng/ml and 74.6% for 300.00 ng/ml. The absolute recovery among three different concentrations (low, medium and high) is not consistent and has a wide range of variability. The firm should explain this. The pre-study assay validation is incomplete.

E. In Vivo Studies

Summary of Bioavailability Studies

Study Identifier	Study Objective	Study Design	Subjects[1] No. (M/F) Type Age: Mean (range)	Treatments (Dose, Dosage Form, Route) [Product ID]	Arithmetic Mean (± SD) Pharmacokinetic Parameters[2]						Study Report Location
					C_{max} (ng/mL)	AUC_{0-t} (ng-hr/mL)	$AUC_{0-\infty}$ (ng-hr/mL)	T_{max} (hr)	k_e (1/hr)	$t_{1/2}$ (hr)	
R04-0598	A relative bioavailability study of 90 mg nifedipine extended release tablets under fasting conditions	Open, randomized, two-way crossover, single 90 mg dose	84 (46/38) Healthy volunteers 28.60 yr (18 - 58 yr)	Nifedipine 90 mg Controlled-Release Tablets, Oral [Lot No. P424401]	52.05 ± 19.35	1223.11 ± 651.02	1305.67 ± 775.69	13.74	0.1100	9.00	
				Procardia XL® 90 mg Tablets, Oral [Lot No. 37P065A]	57.22 ± 29.38	1405.87 ± 746.29	1459.32 ± 849.46	13.50	0.1081	7.88	

[1]Subjects Completing the Bioequivalence Study
[2]Subjects Used in Final Statistical Report

Reviewer's note: The study report location is in Volume 1.1, Page 162.

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	PRACS R04-0598
Study Design	Single dose, randomized, two-period, two-treatment, two-sequence crossover study
No. of subjects enrolled	86
No. of subjects completing	84
No. of subjects analyzed	84*
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Males: 46 Females: 38
Test product	Nifedipine ER Tablets, USP
Reference product	Procardia XL® tablets
Strength tested	90 mg
Dose	1 x 90 mg**

* In the final statistical report, the firm included only 76 out of total 84 subjects completing the study. Eight subjects (02, 14, 21, 22, 23, 27, 32 and 81) were excluded from the statistical analysis due to consuming less than 80% of the evening meal prior to Period I or Period II. The reviewer did not find such an exclusion criterion in the protocol.

**Each dose was administered with 240 ml of room temperature water after an overnight fasting.

Statistical Summary of the Comparative Bioavailability Data

Nifedipine Dose (1 x 90 mg) Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study R04-0598 N=76[1]				
Parameter	**Test**	**Reference**	**Ratio**	**90% CI**
AUC_{0-t}	1049.56	1204.78	87.12	(82.91, 91.54)
$AUC_{0-\infty}$	1109.03	1259.20	88.07	(83.39, 93.02)
C_{max}	48.00	50.82	94.45	(89.26, 99.94)

[1]Subjects Used in Final Statistical Report

These results are based on statistical analysis using 76 subjects (excluding 8 subjects who did not complete 80% of the evening meal prior to dosing) [see review for details]. Reviewer does not agree with the exclusion of these 8 subjects. Following results are obtained using all subjects but excluding one (#32) who vomited:

Nifedipine Extended-Release Tablets 90 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals N=83 Fasting Bioequivalence Study				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}	1007.42	1197.00	0.84	(**76.68**-92.38)
AUC_{∞}	1064.01	1254.16	0.85	(**75.97**-94.75)
C_{max}	46.66	50.15	0.93	(86.69-99.84)

Reanalysis of Study Samples (Fasting Bioequivalence Study)

Fasting Bioequivalence Study R04-0598				
Reason for Reanalysis	Number of Samples Reanalyzed		Number of Recalculated Values Used After Reanalysis[4]	
	Actual Number (% of Total Samples)		Actual Number (% of Total Samples)	
	Test N=1510[2]	Reference N=1512[2]	Test N=1510[2]	Reference N=1512[2]
	n (%)[3]	n (%)[3]	n (%)[3]	n (%)[3]
Pharmacokinetic[1]	19 (1.26%)	1 (0.07%)	1 (0.07%)	1 (0.07%)
Low IS	18 (1.19%)	12 (0.79%)	-	-
High IS	1 (0.07%)	-	-	-
Processing Error	35 (2.32%)	36 (2.38%)	-	-
Inadvertently Repeated[5]	72 (4.77%)	72 (4.76%)	58 (3.84%)	63 (4.17%)
To Resolve Inconsistent Values	2 (0.13%)	1 (0.07%)	1 (0.07%)	1 (0.07%)
Total[6]	144 (9.54%)	121 (8.00%)	60 (3.97%)	65 (4.30%)

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table
[2] N = Number of samples analyzed for each treatment
[3] n = Number of samples repeated; (%) = percentage of assays repeated (i.e. 100*(n/N)%)
[4] Reported values that are different from the original value
[5] The average value of the original assay and re-assay was reported
[6] Excludes samples that were reanalyzed multiple times to resolve inconsistent values or due to the Inadvertent Repeats

Notes:

1. For Study No. PRACS R04-0598, the reanalyzed sample percentage of total was based on total number of 3022 samples.
2. The study samples, including repeats, were assayed in 37 runs. 12 runs failed due to a couple of reasons, including unacceptable standard curve, QCs failing acceptability criteria, and a processing errors. MD0598R1, MD0598R2 and MD0598R3 were repeated runs.
3. All samples available for subjects 75-78 were reanalyzed although acceptable results had already been obtained for these samples. The firm explained that the inadvertent repeats were not a result of poor organization or dereliction of duty on the part of the project leader, but were simply an oversight. If that is the case, why the averages of original and repeat values are used for these samples?

Comments from Reviewer:

1. The firm performed the statistical analysis on the PK parameters for the subjects completing the study (N=84) using the following model: y=group sequence sequence*group, subj(sequence*group) period(group) treatment group*treatment to detect the presence of a group by treatment interaction. The firm claimed that the group*treatment interaction was not statistically significant for LnAUC0-t, LnAUC∞, and LnCmax based on P>0.1 (The DBE recommends P >0.1 to support lack of statistical significance--See reference 1). The reviewer's analysis (N=83, excluding one subject vomiting) agree with the firm's claim.

2. The results from 84 subjects of fasting BE study (point estimate, 90% CI) calculated by the firm are: LAUCt of 84.12, **76.83**-92.11%; LAUCi of 84.84, **76.76**-93.77%; and LCmax of 92.80, 86.61-99.42%. The 90% confidence intervals for the ratios of the test/reference LAUCt and LAUCi did not meet the acceptable limits 80-125%. Subject 32 reported vomiting at approximately 12 hours after Period II dose administration (reference drug). The 90% confidence intervals for the ratios of the test/reference LAUCt (**76.68**-92.38%) and LAUCi (**75.97**-94.75%) still remains outside the acceptable limits after dropping this subject.

Did use of recalculated Plasma concentration data change study outcome? *

* The firm didn't identify the samples that were repeated for pharmacokinetic reasons. The reviewer wasn't able to conduct statistical analysis using the original values for samples re-assayed for PK reasons.

2. Single-dose Fed Bioequivalence Study

N/A

F. Formulation

Location in appendix	Section I.B, Page 29
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	
If a tablet, is the product scored?	NA
If yes, which strengths are scored?	
Is scoring of RLD the same as test?	
Is the formulation acceptable?	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Testing Site	Osmotica-Wilmington, NC, USA
Source of Method (USP, FDA or Firm)	USP
Medium	a. 0.1N HCl, pH 4.5 Acetate Buffer, pH 6.8 Phosphate Buffer, pH 7.5 Phosphate Buffer; b. Water
Volume (mL)	a. 900 mL for four different media; b. 50 mL for water
USP Apparatus type	a. Apparatus II; b. Apparatus VII
Rotation	a. 50, 75 and 100 rpm b. 30 dpm
Firm's proposed specifications	4 hrs: NMT 14% (Q) 12 hrs: 39 – 75 % (Q) 24 hrs: NLT 75% (Q)
F2 metric calculated?	Yes
If no, reason why F2 not calculated	
Is method acceptable?	No
If not then why?	
Source of Method	USP
Medium	Water
Volume (mL)	50
USP Apparatus type	Apparatus VII
Rotation	15-30 cycles per minute
FDA-recommended specifications	4 hrs: (b) (4) (Q) 12 hrs (Q) 24 hrs (Q)

F2 metric, test compared to reference (90 mg Strength)	
Dissolution Testing Methods	F2 metric
Apparatus 2, 0.1 N HCl + 1% Tween @ 100rpm	40.3
Apparatus 2, pH 4.5 Acetate Buffer + 1% SLS @ 100rpm	37.8
Apparatus 2, pH 6.8 Phosphate Buffer + 1% Tween @ 100rpm	38.8
Apparatus 2, pH 7.5 Phosphate Buffer + 1% Tween @ 100rpm	40.5
Apparatus 7, water USP test 1	58.6

Comments on Dissolution: The DBE previously reviewed the dissolution data of this ANDA (with the FDA-recommended method and specification). The firm conducted dissolution testing on their Nifedipine 90 mg ER tablets using USP method Test 1 and in several other media. The dissolution data using the USP Test 1 method showed that the test product did not meet the USP specifications. Therefore, the following dissolution method and specifications were recommended for this test product:

Dissolution Method: 50 mL water using USP apparatus 7 at 15-30 cycles per minute
Specifications: 4 hrs: (b) (4)

12 hrs (b) (4)
24 hrs:

The firm was asked to indicate if it accepts the interim dissolution testing method and specifications recommended by the DBE. The labeling of the test product should state: "Dissolution test is pending." After this application is approved, the DBE will communicate this dissolution method and specifications to the USP. The USP will then assign a test number for this product and the product will be relabeled as USP product meeting test number assigned for this product. The test product cannot be labeled as a USP product until the USP assigns a test number for this test product. The DBE Review of the dissolution data is archived at V:\firmsnz\Osmotica\ltrs&rev\77410D1104.doc.

The firm acknowledged the FDA-recommended dissolution method, specification of (b) (4) at 4 hour time point, and proposed to change the specification at 12 hour time point from (b) (4) to (b) (4) and the specification at 24 hour time point from (b) (4) to (b) (4) in an amendment dated 11/22/2005 based on data from stability lots. As per consultation with the DBE dissolution focal point, Dr. Tran, the DBE will not change the specifications as fresh bio-lot meets the DBE-recommended specifications at L1. The firm may submit dissolution data on three fresh commercial lots. After reviewing the data, the DBE may revise the specifications, if necessary. The firm should indicate if it accepts the interim dissolution specifications recommended by the DBE. The dissolution testing is incomplete.

H. Waiver Request(s)

Strengths for which waivers are requested	None
Regulation cited	21 CFR 320.22 (d) (2)
Proportional to strength tested in vivo?	
Is dissolution acceptable?	
Waivers granted?	
If not then why?	

I. Deficiency Comments

1. Fasting study (PRACS R04-0598): The 90% confidence intervals for the ratios of the test/reference LAUCt (**76.83**-92.11%) and LAUCi (**76.76**-93.77%) are outside the acceptable limits of 80-125% (N=84). Subject number 32 reported vomiting at approximately 12 hours after Period II dose administration (reference drug). The Division of Bioequivalence (DBE) believes that this subject can be dropped from statistical analysis; however, the 90% confidence intervals for the ratios of the test/reference LAUCt (**76.68**-92.38%) and LAUCi (**75.97**-94.75%) still remain outside the acceptable limits after dropping this subject.

2. The firm excluded 8 subjects in the statistical analysis because they failed to finish 80% of the evening meal prior to dosing. This is not an acceptable reason for excluding these subjects from statistical analysis.

3. The firm should identify the samples that were repeated for pharmacokinetic reasons. The firm should conduct statistical analysis using original assay values as well as repeat values for such repeats.

4. The firm states that all samples for subjects 75-78 were reanalyzed inadvertently and the original values were acceptable. If that was the case, why average of the original and repeat values for these samples were used in statistical analysis. The firm should reanalyze the data using original values.

5. The firm should provide reasons for re-assaying period 1 samples of subject number 21.

6. The firm did not provide the Standard Operating Procedures (SOPs) for bioanalytical methods. The firm should submit all appropriate SOPs including those dealing with analytical method and sample repeats.

7. The absolute recovery at three different concentrations (low, medium and high) is not consistent and has a wide range of variability.

8. The dissolution specifications are set based on the fresh bio-lot and not based on the stability batches. The Division of Bioequivalence (DBE) recommends the following dissolution method: The dissolution testing should be conducted in 50 mL water, at 37°C using USP Apparatus 7 at 15-30 cycles per minute. The DBE recommends that the test product should meet the following interim specifications:

   4 hours: (b) (4)
   12 hours
   24 hours

9. The lot number of the reference product provided on page 162 is 3ZP065A instead of 37P065A as given elsewhere in the submission. Please explain.

J. Recommendations

1. The bioequivalence study conducted under fasting conditions by Osmotica USA Corporation, on its nifedipine extended-release 90 mg tablets, Lot # P424401 comparing it to Procardia XL® 90 mg tablets, Lot # 37P065A manufactured by Pfizer Inc., is incomplete.

2. The *in vitro* dissolution testing conducted by Osmotica on its test product, Nifedipine 90 mg ER Tablets, USP, comparing it to Pfizer's Procardia XL® 90 mg tablets is incomplete.

The firm should be informed of the deficiency comments and recommendations.

01/19/2006

Yi Zhang, Ph.D., Review Branch IV — Date

01/19/2006

Kuldeep R. Dhariwal, Ph.D.
Team Leader, Review Branch IV — Date

1/20/06

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs — Date

V:\firmsnz\Osmotica\ltrs&rev\77410N1104.doc

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	PRACS R04-0598
Study Title	A Relative Bioavailability Study of 90 mg Nifedipine Extended Release Tablets under Fasting Conditions
Clinical Site	PRACS Institute, Ltd. 625 Demers Avenue East Grand Forks, MN 56721
Principal Investigator	James D. Carlson, Pharm. D.
Study/Dosing Dates*	Period 1: July 24 – July 26, 2004 (Subjects 01-56); July 31 – August 02, 2004 (Subjects 57-86) Period 2: August 07 – August 09, 2004 (Subjects 01-86)
Analytical Site	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104
Analytical Director	(b) (6) Ph.D.
Analysis Dates	August 27, 2004 – September 22, 2004
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	60 days (from July 24, 2004 to September 22, 2004)

* As per the protocol, 80 subjects will be enrolled in the fasting BE study. The addition of Group II in period 1 was due to the failure of the clinic to enroll 80 subjects as stated in the protocol. Thirty subjects were enrolled in Group II to complete the enrollment goal and account for any drop-outs secondary to the adverse event profile observed. The protocol amendment #1 of recruiting 30 more subjects was approved on July 29, 2004. Group I of 56 subjects were dosed for period 1 on July 24, 2004. Group II of 30 subjects were dosed for period 1 on July 31, 2004. For period 2, both groups were dosed on August 07, 2004.

Treatment ID	A	B
Test or Reference	Test Product	Reference Product
Product Name	Nifedipine ER Tablets, USP	Procardia XL® tablets
Manufacturer	(b) (4)	Pfizer Inc.
Batch/Lot No.	P424401	37P065A
Manufacture Date	04/27/2004	NA
Expiration Date	NA	01/01/2009
Strength	90 mg	90 mg
Dosage Form	ER Tablets	ER Tablets
Batch Size	(b) (4)	NA
Production Batch Size		NA
Potency	96.9 %	100.7 %
Content Uniformity (mean, %CV)	99.6%, RSD 1.0%	NA
Formulation	See Appendix Section I.B	
Dose Administered	1 x 90 mg	1 x 90 mg
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	14 days washout between Period I and Period II dose administration for subjects 01-56; 7 days washout between Period I and Period II dose administration for subjects 57-86 *The 86 subjects were dosed as two groups: Group I (subjects 01-56) and Group II (subjects 57-86).
Randomization Scheme	AB: Subjects # 01, 02, 04, 05, 07, 09, 10, 12, 15, 17, 19, 20, 21, 23, 25, 26, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 43, 46, 47, 51, 53, 55, 63, 67, 68, 69, 72, 73, 75, 79, 84, 85 and 86 BA: Subjects # 03, 06, 08, 11, 13, 14, 16, 18, 22, 24, 27, 28, 29, 40, 41, 42, 44, 45, 48, 49, 50, 52, 54, 56, 57, 58, 59, 60, 61, 62, 64, 65, 66, 70, 71, 74, 76, 77, 78, 80, 81, 82 and 83
Blood Sampling Times	At pre-dose (within 1 hour prior to dose administration) and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36, 48 and 60 hours post-dose (total 18 samples)
Blood Volume Collected/Sample	1x10 mL
Blood Sample Processing/Storage	Blood samples were collected in EDTA vacutainers by direct venipuncture at sampling time points and centrifuged at 2400 rpm at 4°C for 15 minutes. The plasmas were pipetted into amber polypropylene tubes, frozen and stored at -20°C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	At least 10 hours prior to and for 4 hours post dosing
Length of Confinement	Total 36 hrs with approximately 12 hrs prior to and until at least 24 hours after dosing each period (Subjects were admitted to the clinical research unit the evening prior to dose administration of supper. The intent of the evening supper was to standardize the gastrointestinal tract of the subjects prior to dose administration the next morning.)
Safety Monitoring	Blood pressure and heart rate were measured prior to dosing, at 4, 6, 8, 12 and 24 hours after dose administration, and upon completion of the study.

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 1 Demographic Profile of Subjects Completing the Bioequivalence Study

	Fasting Bioequivalence Study R04-0598 N=84
Age (years)	
Mean ± SD	28.60 ± 11.78
Range	18 - 58
Groups	
<18	-
18-39	68 (80.95%)
40-64	16 (19.05%)
65-75	-
>75	-
Sex	
Female	38 (45.24%)
Male	46 (54.76%)
Race	
Asian	-
Black	1 (1.19%)
Caucasian	80 (95.24%)
Hispanic	2 (2.38%)
Native American	1 (1.19%)
Other	-

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
43	Withdrew prior to Period II dose administration due to personal reasons	II	No
66	Withdrew prior to Period II dose administration due to personal reasons	II	No

Table 3 Incidence of Adverse Events in BE Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study R04-0598	
	Test N=85[2]	Reference N=85[2]
	n (%)[3]	n (%)[3]
Gastrointestinal disorders		
Nausea	3 (3.53%)	4 (4.71%)
Stomach discomfort	1 (1.18%)	-
Vomiting	1 (1.18%)	1 (1.18%)
General disorders and administration site conditions		
Fatigue	1 (1.18%)	-
Hyperhidrosis	-	1 (1.18%)
Injury, poisoning and procedural complications		
Excoriation	1 (1.18%)	-
Musculoskeletal and connective tissue disorders		
Arthralgia	-	1 (1.18%)
Musculoskeletal stiffness	1 (1.18%)	-
Neck pain	-	1 (1.18%)

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study R04-0598	
	Test N=85[2]	Reference N=85[2]
	n (%)[3]	n (%)[3]
Nervous system disorders		
Dizziness	1 (1.18%)	3 (3.53%)
Headache	31 (36.47%)	36 (42.35%)
Syncope	1 (1.18%)	-
Tremor	1 (1.18%)	-
Renal and urinary disorders		
Dysuria	1 (1.18%)	-
Respiratory, thoracic and mediastinal disorders		
Pharyngolaryngeal pain	-	1 (1.18%)
Skin and subcutaneous tissue disorders		
Herpes simplex	1 (1.18%)	-
Total Subjects Reporting at Least One Adverse Event	37 (43.53%)	39 (45.88%)

[1] MedDRA Version 8.0
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event; (%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Note: There were 103 adverse events reported by 50 subjects over the course of the study. Subject 02 reported vomiting on 07/30/04 at 18:30 between study Period I and II. Subject 32 reported vomiting at approximately 12 hours after Period II dose administration (reference drug).

Table 4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Subject took 1.8 mL Xylocaine with 1:100,000 Epinephrine one day before Period I dose administration because of broken crown.	07	07
Subject took Ibuprofen (200 mg) three days before Period I dose administration for headache.	81	81
Subject failed to return for the Period II study at 48 hour time point. No blood sample was collected at 48 hour time point due to the conflict schedule.	14	
No blood sample was collected at 4 hour time point due to the difficulty of collection.	25	
During study Period I, subjects consumed less than 80% of the evening meal prior to dosing.	02, 21, 23, 32	14, 22, 27, 81
During study Period II, subjects consumed less than 80% of the evening meal prior to dosing.	14, 22, 27, 81	02, 21, 23

Note:

1. As per the protocol, subjects should not take any systemic prescription medications within 14 days of Period I dose administration, and any non-prescription medications within 3 days of Period I dose administration.
2. Many subjects took ibuprofen for their headache during the study. The incidence on the test product was comparable to the incidence on the reference product. As stated in PDR, headache is one of the common side effects of nifedipine ER tablets.
3. The reviewer checked the subjects who consumed less than 80% of the evening meal prior dosing period I or period II. There are some discrepancies between the firm's claim and the reviewer's result (see details in the following table).

Subject Number	Period I % Dinner Consumed	Period II % Dinner Consumed
2	90	**40**
14	**75**	85
21	90	**25**
22	80	**75**
23	**75**	90
27	**55**	90
32	**75**	100
81	**60**	80

Comments on Dropouts/Adverse Events/Protocol Deviations: No major adverse events occurred so that the study outcome was altered. There were some sampling time deviations (from 2 min to 215 min). The actual sampling times were adjusted to calculate PK parameters.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Nifedipine							
QC Conc. (ng/mL)	1.50			150.00			250.00	
Inter day Precision (%CV)	6.1			4.2			5.0	
Inter day Accuracy (%)	103.6			101.1			100.3	
Cal. Standards Conc. (ng/mL)	0.50	2.00	5.00	10.00	50.00	100.00	200.00	300.00
Inter day Precision (%CV)	9.00	6.59	5.77	5.53	3.59	4.26	4.81	4.31
Inter day Accuracy (%)	99.2	101.2	103.1	103.1	100.0	98.6	96.6	99.3
Linearity Range (range of R^2 values)	0.9875 – 0.9993							

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially, Subjects # 1-16

Reviewer's Note: The firm submitted the chromatograms from four runs: MD059822 (Subjects 1-4), MD059802 (Subjects 5-8), MD059803 (Subjects 9-12), and MD059804 (Subjects 13-16).

Comments on Chromatograms: Acceptable

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title

*Reviewer's Note: The firm did not submit SOPs in this application.

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	*
Did recalculation of plasma concentrations change the study outcome?	**
Does the reviewer agree with the outcome of the repeat assays?	
If no, reason for disagreement	N/A

*No SOPs were submitted.
** The firm didn't identify the samples that were repeated for pharmacokinetic reasons. The reviewer wasn't able to conduct statistical analysis using the original values for samples re-assayed for PK reasons.

Summary/Conclusions, Study Assays: The study assay is incomplete.

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters (N=83)

Mean Plasma concentrations are presented in

Table 11 and Figure 1

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI	1276.93	59.80	1458.84	57.05	0.88
AUCT	1196.73	53.97	1391.78	52.47	0.86
CMAX	51.25	38.84	56.44	51.24	0.91
KE	0.11	56.55	0.11	41.65	1.00
LAUCI	1072.68	0.06	1259.15	0.04	0.85
LAUCT	1023.16	0.06	1221.11	0.04	0.84
LCMAX	47.20	0.92	51.02	0.86	0.93
THALF	9.22	70.58	7.93	50.33	1.16
TMAX	13.33	51.48	13.56	72.39	0.98

Mean 1 = Test, Mean 2 = Reference
Units: AUCs = ng.hr/mL, Cmax = ng/mL, THALF = hr, Tmax = hr

Table 9 Least Squares Geometric Means and 90% Confidence Intervals (N=83)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1254.39	1433.30	0.88	81.40	93.63
AUCT	1163.35	1352.90	0.86	80.96	91.02
CMAX	50.25	55.16	0.91	83.44	98.77
LAUCI	1064.01	1254.16	0.85	75.97	94.75
LAUCT	1007.42	1197.00	0.84	76.68	92.38
LCMAX	46.66	50.15	0.93	86.69	99.84

Mean 1 = Test, Mean 2 = Reference
Units: AUCs = ng.hr/mL, C_{max} = ng/mL

Table 10 Additional Study Information (N=83)

Root mean square error, AUC_{0-t}	0.355293
Root mean square error, AUC_{∞}	0.388876
Root mean square error, Cmax	0.269554
Ke and AUCi determined for how many subjects?	70 (not for subjects 5, 22, 30, 31, 32, 44, 51, 62, 64, 67, 75, 76, 77 and 81)
Do you agree or disagree with firm's decision?	*
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	No

*The firm did not submit semi-log plots for subjects 02, 14, 21, 22, 23, 27, 32 and 81.

Comments on Pharmacokinetic and Statistical Analysis: The reviewer recalculated the pharmacokinetic parameters and repeated statistical analysis for the firm's datasets including datasets with original values from 76 subjects. The study outcome did not change. However, the firm analyzed only 76 out of total 84 subjects completing the study in the final statistical report. Eight subjects (02, 14, 21, 22, 23, 27, 32 and 81) were excluded from the statistical analysis due to consuming less than 80% of the evening meal prior to Period I or Period II. The reviewer did not find such exclusion criteria stated in the protocol. If the intention was to exclude these subjects, either these subjects should not have been dosed or their samples should not have been analyzed. Excluding these subjects from final statistical analysis by the firm is not acceptable.

The results from 84 subjects of fasting BE study (point estimate, 90% CI) calculated by the firm are: LAUCt of 84.12, **76.83**-92.11%; LAUCi of 84.84, **76.76**-93.77%; and LCmax of 92.80, 86.61-99.42%. The 90% confidence intervals for the ratios of the test/reference LAUCt and LAUCi did not meet the acceptable limits 80-125%. Subject number 32 reported vomiting at approximately 12 hours after Period II dose administration (reference drug). The 90% confidence intervals for the ratios of the test/reference LAUCt (**76.68**-92.38%) and LAUCi (**75.97**-94.75%) still remains outside the acceptable limits after dropping this subject (calculated by the reviewer).

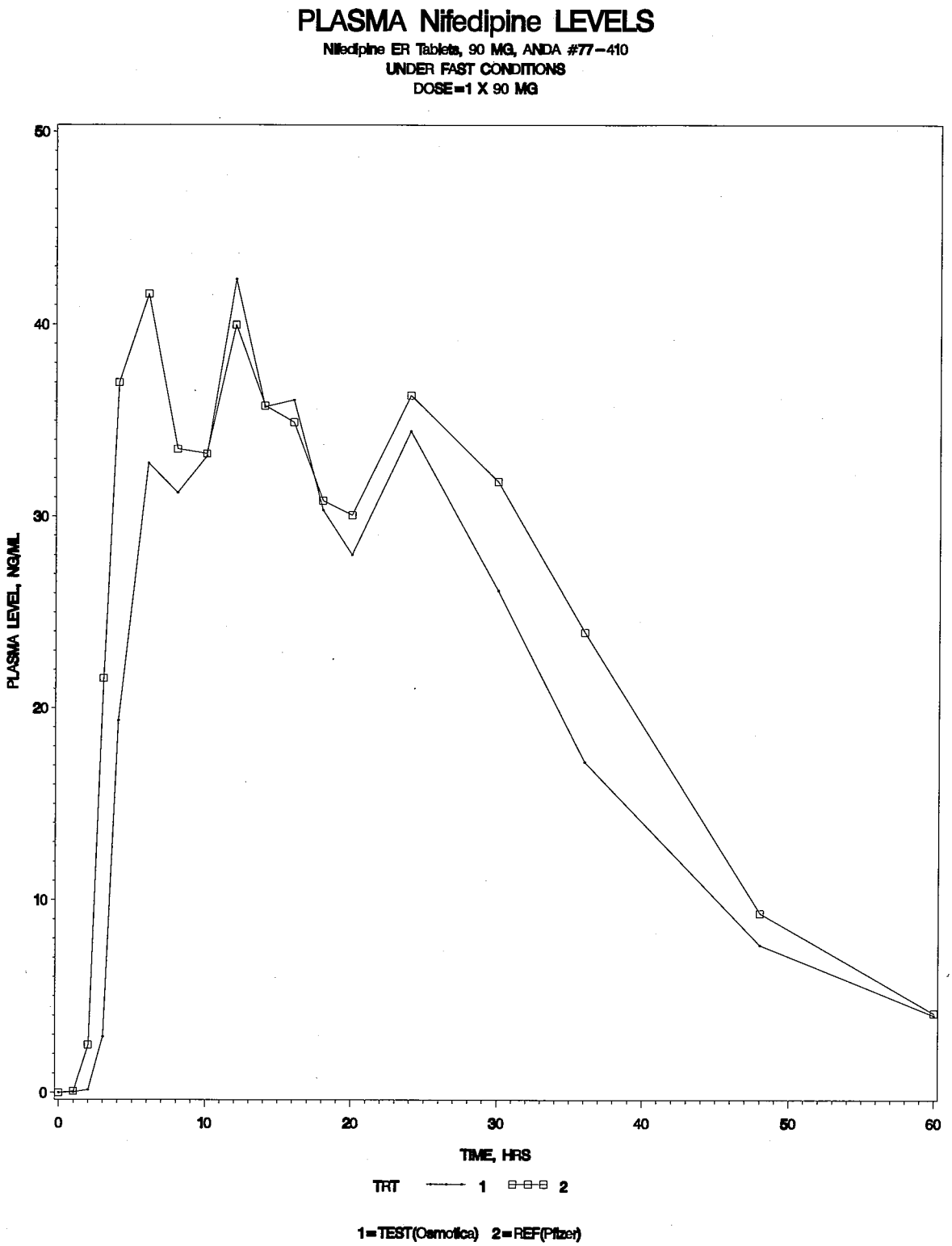
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The single-dose fasting bioequivalence study is incomplete (see Deficiency Comments).

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (unit: ng/ml)

Mean 1 = Test, Mean 2 = Reference, N=83

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
1	0.03	449.76	0.07	608.95	0.40
2	0.15	196.99	2.47	83.97	0.06
3	2.90	91.10	21.55	55.52	0.13
4	19.35	65.34	36.98	49.18	0.52
6	32.78	53.78	41.59	51.53	0.79
8	31.23	52.49	33.51	59.89	0.93
10	33.15	51.18	33.27	72.34	1.00
12	42.35	49.23	39.99	72.49	1.06
14	35.72	44.61	35.78	64.25	1.00
16	36.07	49.23	34.92	61.21	1.03
18	30.33	55.21	30.83	68.17	0.98
20	28.01	56.87	30.07	74.28	0.93
24	34.44	57.78	36.32	57.34	0.95
30	26.14	67.07	31.82	59.92	0.82
36	17.19	85.92	23.96	76.59	0.72
48	7.67	110.13	9.31	115.17	0.82
60	4.02	158.11	4.13	155.12	0.97

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



B. Formulation Data

Ingredient	Amount (mg)/Tablet	Amount (%) Tablet
(b) (4)		

C. Dissolution Data

Summary of In Vitro Dissolution Data

Batch No.	Condition	Collection Times Mean % Dissolved (Range)												
		Time (hours)												
		1	2	4	6	8	10	12	14	16	18	20	22	24
Test	A	(b) (4)		7 (5-8)	(b) (4)			49 (44-55)	(b) (4)					87 (83-91)
Reference	A			15 (11-25)				63 (52-86)						109 (89-113)
Test	B			6 (2-9)				49 (37-56)						90 (85-99)
Reference	B			15 (10-23)				66 (52-83)						116 (110-118)
Test	C			7 (4-9)				51 (36-56)						90 (82-95)
Reference	C			15 (11-20)				64 (57-76)						117 (111-120)

Test = Nifedipine Extended Release Tablets 90 mg, Lot P42440, 12 dosage units
Reference = Procardia XL® 90 mg, Lot 37P065A, 12 dosage units
A = 0.1 N HCl + 1% Tween, Apparatus 2, 100 RPM, 900 mL, 37.5°C
B = pH 4.5 Acetate Buffer + 1% Tween, Apparatus 2, 100 RPM, 900 mL, 37.5°C
C = pH 6.8 Phosphate Buffer + 1% Tween, Apparatus 2, 100 RPM, 900 mL, 37.5°C

Summary of InVitro Dissolution Studies (continued)

Batch No.	Condition	Collection Times Mean % Dissolved (Range)												
		Time (hours)												
		1	2	4	6	8	10	12	14	16	18	20	22	24
Test	D	(b) (4)		6 (4-9)	(b) (4)			51 (46-56)	(b) (4)					90 (86-95)
Reference	D			14 (11-17)				63 (54-70)						115 (110-118)
Test	E			8 (4-11)				48 (42-55)						78 (72-82)
Reference	E			9 (4-15)				42 (17-63)						67 (25-103)

Test = Nifedipine Extended Release Tablets 90 mg, Lot P42440, 12 dosage units
Reference = Procardia XL® 90 mg, Lot 37P065A, 12 dosage units
D = pH 7.5 Phosphate Buffer + 1% Tween, Apparatus 2, 100 RPM, 900 mL, 37.5°C
E = Water, Apparatus 7, 30 DPM, 50 mL, 37.5°C

Summary of InVitro Dissolution Studies (continued)

Batch No.	Condition	Collection Times Mean % Dissolved (Range)												
		Time (hours)												
		1	2	4	6	8	10	12	14	16	18	20	22	24
Test	F	(b) (4)		3 (2-5)	(b) (4)			45 (33-53)	(b) (4)					84 (75-87)
Test	G			5 (3-7)				49 (43-55)						88 (85-92)

Test = Nifedipine Extended Release Tablets 90 mg, Lot P42440, 12 dosage units
F = pH 6.8 Phosphate Buffer + 1% Tween, Apparatus 2, 50 RPM, 900 mL, 37.5°C
G = pH 6.8 Phosphate Buffer + 1% Tween, Apparatus 2, 75 RPM, 900 mL, 37.5°C

D. Consult Reviews

None

E. SAS Output

	Data file	Component			SAS Program	Output file
Single dose fasting study	Fasting2D.xls	**Nifedipine**	**83 subjects**	**With trt*grp**	fast2DG.txt	fast2DGoutput.txt
				Without trt*grp	fast2DGN.txt	fast2DGNoutput.txt
	Fasting1.xls		**76 subjects**	**With trt*grp**	fast1G.txt	fast1Goutput.txt
				Without trt*grp	fast1GN.txt	fast1GNoutput.txt

SAS analysis using the original values of samples reassayed for PK reason

	SAS output	Results in word format
Nifedipine (Fasting study)	N/A	N/A

F. Additional Attachments

Reference 1:

BioControlDocument
98-392.doc

Reference 2:

From: Tran, Nhan L
Sent: Monday, December 05, 2005 2:16 PM
To: Zhang, Yi
Subject: RE: Dissolution specifications of nifedipine ER tablets ANDA 77-410

As you can see from the data of the biolot (freshly made batch), the firm product meets the specifications at L1 level --very important--. This is the batch which has in-vivo biostudy to support its bioequivalence with the RLD.

We do not set dissolution specifications based on stability batches because we do not have in-vivo information to demonstrate bioequivalence to the RLD under storage conditions. So in your situation, if we widen the specification as requested by the firm, we are not sure that those stability batches are equivalent to the RLD. And by widen the specifications, the discrimination of the test will be compromised and we cannot use the test as a reliable quality control tool.
Hence, I suggest that we will not change the specifications because stability batches do meet the specifications at L2 level anyway.

Please discuss with your TL for his recommendation.

-----Original Message-----
From: Zhang, Yi
Sent: Friday, December 02, 2005 2:55 PM
To: Tran, Nhan L
Subject: Dissolution specifications of nifedipine ER tablets ANDA 77-410

Dear Dr. Tran,

I am reviewing the nifedipine ER tablets (ANDA 77-410). The firm just sent in an amendment to request dissolution specification modification on nifedipine ER tablets by using USP test 1 method. Here are the summary of the firm's dissolution data (detailed dissolution profiling data is also included at the end of this email):

Time	Mean	Range
4 hours	8	4-11
12 hours	48	42-55
24 hours	78	72-82

The following is the FDA proposed dissolution specifications as per the previous dissolution review achieved in V:\firmsnz\Osmotica\ltrs&rev\77410D1104.doc:

4 hrs: (b) (4)
12 hrs
24 hrs

The firm agrees for the 4 hour time point specification. However, for the 12 hour time point specification, the firm is concerned that the specification proposed by the FDA may be too narrow to allow for *in vitro* variations seen with this product, including those seen on stability. The firm's recent controlled-room temperature stability data indicates that the ranges of values seen for individual vessel values at this interval on stability through 12 months are:

Bottles of 100 tablets, 40ºC/75%RH: (b) (4)
Bottles of 100 tablets, 25ºC/60%RH:
Bottles of 500 tablets, 40ºC/75%RH:
Bottles of 500 tablets, 25ºC/60%RH:

Based on this data, the firm proposes to change the 12 hour time point specification to (b) (4), which provides a (b) (4) control of the *in vitro* release rate yet allows for reasonable variability which may be seen. For the 24 hour time point specification, the firm is concerned with the use of (b) (4) for the specification. As per the firm's amendment, in fact, several individual vessel values at this interval

on stability were (b) (4). Because the release rate is based on the labeled amount of the drug, it does not seem appropriate that a batch would fail for releasing (b) (4) at the 24 hour time point. Therefore, the firm proposes to modify the FDA recommended for the 24 hour time point specification to (b) (4).

Thanks for your advice on this issue.

Regards
Yi

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-410

APPLICANT: Osmotica USA Corporation

DRUG PRODUCT: Nifedipine Extended-Release Tablets, 90 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) on the cover sheet. The following deficiencies have been identified:

1. Fasting study (PRACS R04-0598): The 90% confidence intervals for the ratios of the test/reference LAUCt (76.83-92.11%) and LAUCi (76.76-93.77%) are outside the acceptable limits of 80-125% (N=84). Subject number 32 reported vomiting at approximately 12 hours after Period II dose administration (reference drug). The DBE believes that this subject can be dropped from statistical analysis; however, the 90% confidence intervals for the ratios of the test/reference LAUCt (76.68-92.38%) and LAUCi (75.97-94.75%) remain outside the acceptable limits after dropping this subject.

2. You excluded 8 subjects in the statistical analysis because they failed to finish 80% of the evening meal prior to dosing. This is not an acceptable reason for excluding these subjects from statistical analysis.

3. Please identify the samples that were repeated for pharmacokinetic reasons. Please conduct and submit statistical analysis using original assay values as well as repeat values for such repeats.

4. You state that all samples for subjects 75-78 were reanalyzed inadvertently and the original values were acceptable. If that was the case, why average of the original and repeat values for these samples were used in statistical analysis. Please reanalyze the data using original values.

5. Please provide reasons for re-assaying period 1 samples of subject number 21.

6. Please provide all Standard Operating Procedures (SOPs) for bioanalytical methods. All appropriate SOPs including those dealing with analytical method and sample repeats should be submitted.

7. Please explain why the absolute recovery at three different concentrations (low, medium and high) is not consistent.

8. The dissolution specifications are set based on the bio-lot and not on the stability batches. Based on the data on fresh bio-lot, the DBE recommends the following dissolution method and interim specifications: The dissolution testing should be conducted in 50 mL water, at 37°C using USP Apparatus 7 at 15-30 cycles per minute.
Specifications:

4 hours: (b) (4)
12 hours:
24 hours:

9. The lot number of the reference product provided on page 162 is 3ZP065A instead of 37P065A as given elsewhere in the submission. Please explain.

Sincerely yours,

for Barbara McSavit

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 77-410

CC: ANDA 77-410
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Zhang

Endorsements: (Draft and Final with Dates)
HFD-650/ Zhang LZ 01/19/2006
HFD-650/ Dhariwal 01/19/06
HFD-650/ Fabian-Fritsch
HFD-650/ D. Conner BMD 1/20/06

V:\firmsnz\Osmotica\ltrs&rev\77410N1104.doc
Printed in final on 01/19/2006

BIOEQUIVALENCE - INCOMPLETE Submission Date: 11/19/2004

✓1. **FASTING STUDY** (STF) Strengths: 90 mg
Clinical: PRACS Institute, Ltd. **Outcome: IC**
625 Demers Avenue
East Grand Forks, MN 56721
Analytical: PRACS Institute, Ltd.
4801 Amber Valley Parkway
Fargo, ND 58104

✓2. **Study Amendment** (STA) Strengths: 90 mg
11/22/2005 **Outcome: IC**

Outcome Decisions:
IC – Incomplete

WinBio Comments: Fasting bioequivalence study is incomplete.

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-410
Drug Product Name	Nifedipine Extended-Release Tablets, USP
Strength	90 mg
Applicant Name	Osmotica USA Corporation
Address	1205 Culbreth Dr, Suite 200 Wilmington, NC 28405
Submission Date(s)	March 17, 2006
Amendment Date(s)	N/A
Reviewer	Yi Zhang, Ph.D.
First Generic	No
File Location	V:\firmsnz\Osmotica\ltrs&rev\77410A0306.doc

Review of an Amendment

I. Executive Summary

The firm has previously submitted one single-dose *in vivo* fasting bioequivalence (BE) study comparing its test product, Nifedipine Extended-Release Tablets USP, 90 mg, to the Reference Listed Drug (RLD) product, Procardia XL® tablets, 90 mg, from Pfizer in the original application, dated on 11/19/04. The BE study was incomplete due to bio-analytical deficiencies and improper statistical analysis (See details in the review of the original application at V:\firmsnz\Osmotica\ltrs&rev\77410N1104.doc). The firm was also advised to acknowledge its acceptance of the current FDA-recommended dissolution method and specifications.

The firm submitted the current amendment in response to the Division of Bioequivalence (DBE) deficiency comments. Except for the firm's responses to deficiencies 2, 5 and 8, all other responses to the deficiency letter are acceptable. The firm claimed that excluding 8 subjects from bioequivalence statistics was based on a valid scientific rationale and complied with the protocol. The firm further reviewed the study data and found that the most significant issue with the study was the statistical outlier subject 21 with an identified clinical reason of erratic meal consumption. The test product is shown to be bioequivalent to the innovator product after dropping this subject. The results from 83 subjects of fasting BE study (point estimate, 90% CI) calculated by the firm are: LAUCt of 87.7, 83.6-92.0%; LAUCi of 89.4, 84.3-94.7%; and LCmax of 95.0, 90.0-100.3%. However, the DBE does not agree with the firm's justification for excluding subject 21 from the statistical analysis. Therefore, the fasting BE study remains incomplete.

The dissolution testing conducted by the firm using the FDA-recommended method was previously reviewed and found acceptable. In this amendment, the firm acknowledged its acceptance of the current FDA-recommended dissolution method (50 mL water using USP apparatus 7 at 15-30 cycles per minute), the specification of (b) (4) % at 4 hr, the

specification of (b) (4) % at 12 hr, and proposed to change the specification at 24 hr from (b) (4) % to (b) (4) %. The DBE will not change the specification at 24 hr as fresh bio-lot meets the DBE-recommended specifications at L1 (See details in attachment).

The application is incomplete (See details in Deficiency Comments).

II. Table of Contents

I. Executive Summary 1
II. Table of Contents 3
III. Submission Summary 3
A. Drug Product Information, PK/PD Information, and Relevant DBE History 3
B. Contents of Submission 3
C. Review of Submission 3
D. Deficiency Comments 8
E. Recommendations 9
F. Attachment 11

III. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DBE History

Please see the review of the original submission (V:\firmsnz\Osmotica\ltrs&rev\77410N1104.doc).

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting		
Single-dose fed		
Steady-state		
In vitro dissolution		
Waiver requests		
BCS Waivers		
Vasoconstrictor Studies		
Clinical Endpoints		
Failed Studies		
Amendments	Yes	1

C. Review of Submission

Deficiency 1:

*Fasting study (PRACS R04-0598): The 90% confidence intervals for the ratios of the test/reference LAUCt (**76.83**-92.11%) and LAUCi (**76.76**-93.77%) are outside the acceptable limits of 80-125% (N=84). Subject number 32 reported vomiting at approximately 12 hours after Period II dose administration (reference drug). The Division of Bioequivalence (DBE) believes that this subject can be dropped from statistical analysis; however, the 90% confidence intervals for the ratios of the test/reference LAUCt (**76.68**-92.38%) and LAUCi (**75.97**-94.75%) still remain outside the acceptable limits after dropping this subject.*

Firm's Response:

The firm took note of the DBE's observation.

Reviewer's Comment:

The firm's response to the deficiency 1 is acceptable.

Deficiency 2:

You excluded 8 subjects in the statistical analysis because they failed to finish 80% of the evening meal prior to dosing. This is not an acceptable reason for excluding these subjects from statistical analysis.

Firm's Response:

The firm claimed that excluding 8 subjects from bioequivalence statistics was based on a valid scientific rationale and complied with the protocol. The protocol included a requirement for patients to enter the clinic early enough the evening prior to dosing so that they can consume an evening meal that was consistent between subjects. The data (As shown in the following table) from the firm's previous study ANDA (b) (4) on the 60 mg product, demonstrated that the prior evening meal was a significant component of reducing the intra-subject variability.

ANOVA Intra-Subject Variability as CV% in ANDA (b) (4)

Study	Fasting Study R03-536	Fed Study RA3-536
Cmax	23.15	**22.26**
AUCt	27.89	**22.05**
AUCi	28.60	**22.09**

Reviewer's Comment:

The firm analyzed only 76 out of total 84 subjects completing the study in the final statistical report. Eight subjects (02, 14, 21, 22, 23, 27, 32 and 81) were excluded from the statistical analysis due to consuming less than 80% of the evening meal prior to study periods. However, the information in the table above does not support the effect of evening meal on the variability of the data in the current fasting study. The firm did not provide enough evidence to justify the effect of the differential amount of the evening meal consumed on the bioequivalence study for drugs to be given next morning after an overnight fast. In addition, the reviewer did not find such exclusion criteria stated in the protocol. If the intention was to exclude these subjects, either these subjects should not have been dosed or their samples should not have been analyzed. Excluding these subjects from final statistical analysis by the firm is not acceptable. The firm's response to the deficiency 2 is not acceptable.

Deficiency 3:

Please identify the samples that were repeated for pharmacokinetic reasons. Please conduct and submit statistical analysis using original assay values as well as repeat values for such repeats.

Firm's Response:

The firm identified the samples that were repeated for pharmacokinetic reasons and provided a table containing the original values, the repeated values and the reported values for these PK repeats (All 18 samples at period 1 for subject 21). The firm conducted statistical analysis using original assay values for such repeats and submitted the results in Appendix A of Attachment I in this amendment (See details in Deficiency 4).

Reviewer's Comment:

The firm's response to the deficiency 3 is acceptable.

Deficiency 4:

You stated that all samples for subjects 75-78 were reanalyzed inadvertently and the original values were acceptable. If that was the case, why average of the original and repeat values for these samples were used in statistical analysis. Please reanalyze the data using original values.

Firm's Response:

The firm clarified that these samples were repeated by mistake. According to its Bioanalytical Laboratory's SOP, the mean of the original and repeat values for these samples were used in statistical analysis. However, as requested by the DBE, the firm reanalyzed the data by using the original assay values of subjects 75-78, and submitted the statistical results in Appendix A of Attachment I in this amendment.

Reviewer's Comment:

The reviewer also reanalyzed the data using original assay values. The study outcome did not change from the firm's results (See details in the following attached files). The firm's response to the deficiency 4 is acceptable.

SAS analysis using the original values of samples repeated inadvertently and repeated for PK reason.

Nifedipine		SAS output	Results in word format
Fasting Study (PRACS R04-0598) N=84	With trt*grp	fastATOGoutput.txt	fastATOGtab.doc
	Without trt*grp	fastATONGoutput.txt	fastATONGtab.doc

Note from Reviewer: Subjects 43 and 66 withdrew prior to Period II dose administration due to personal reasons.

Deficiency 5:

Please provide reasons for re-assaying period 1 samples of subject number 21.

Firm's Response:

Subject 21 is a 23 year-old Caucasian female who received the test product in period 1 and the reference product in period 2. This subject exhibited anomalous absorption of the test product. The firm claimed that the Cmax ratio and results during period 1 for subject 21 was approximately 10 times lower than the period 2 results. In addition, the period 1 results were significantly different from those for other study subjects. It is also noted that subject 21 had the largest differential in the amount of prior evening meal consumption among all of the subjects with consuming 90% in period 1 but only 25% in period 2. The firm asked an outside consultant, (b) (4) to review the data. It is concluded that subject 21 is a statistical outlier with an identified clinical reason of erratic meal consumption and has to be excluded from the BE statistics. The data supporting the firm's conclusion is included in Attachment II of this amendment. The firm conducted statistical analysis on 83 study subjects (Excluding subject 21) and submitted the results in Attachment II of this amendment.

Reviewer's Comment:

The reviewer also reanalyzed the data on all study subjects except subject 21. The study outcome did not change from the firm's results (See details in the following attached files). Exclusion of subject 21 results in the 90% confidence intervals for the ratios of the test/reference LAUCt (80.58-92.81%), LAUCi (81.48-95.86%) and LCmax (87.74-104.39) meeting the acceptable limits of 80% to 125%. The test product is shown to be bioequivalent to the innovator product after dropping subject 21. However, the DBE disagrees with the firm's conclusion of dropping subject 21 from the final statistical analysis. Using the differential amount of the evening meal consumed by subject 21 as a justification for excluding this subject from the statistical analysis is not acceptable. The firm's response to the deficiency 5 is not acceptable.

SAS analysis excluding subject 21.

Nifedipine		SAS output	Results in word format
Fasting Study (PRACS R04-0598) N=83	With trt*grp	fastAOG.txt	fastAOGtab.doc
	Without trt*grp	fastAONG.txt	fastAONGtab.doc

Note from Reviewer: Subjects 43 and 66 withdrew prior to Period II dose administration due to personal reasons.

Deficiency 6:

Please provide all Standard Operating Procedures (SOPs) for bioanalytical methods. All appropriate SOPs including those dealing with analytical method and sample repeats should be submitted.

Firm's Response:

The firm provided all appropriated SOPs: SOP III 3.0 004-14 for Quality Control Samples, SOP III 6.0 007-23 for Study Subject Sample Analysis, SOP III 25.0 068-04 for Calibration/Standard Curves, SOP III 45.0 088-02 for Sample Re-injection, SOP III 46.0 089-02 for Sample Reintegration and Reprocessing, SOP III 47.0 090-02 for Sample Re-analysis, SOP III 48.0 091-03 for Laboratory Investigation, SOP III 51.0 098-02 for Summary of Validation and Study Acceptance Criteria, and SOP 05030-03 for Standard Statistical Procedures.

Reviewer's Comment:

The firm's response to the deficiency 6 is acceptable.

Deficiency 7:

Please explain why the absolute recovery at three different concentrations (low, medium and high) is not consistent.

Firm's Response:

The firm investigated this inconsistency and found that it was due to the recovery test being performed in a manner not consistent with the firm's practice. The firm ran the recovery test again comparing extracted spiked matrix with extracted blank matrix reconstituted in a solution spiked with analyte at the actual sample concentrations. The new data demonstrated a recovery of 57.2% at 1.50 ng/mL, 56.8% at 150 ng/mL and 59.4% at 250 ng/mL with an internal standard recovery of 57.8%. The concentrations of the new recovery test are different from that in the original validation (Low is 1.50 ng/mL vs. 0.50 ng/mL, medium is 150 ng/mL vs. 200 ng/mL, and high is 250 ng/mL vs. 300 ng/mL.) The firm claimed that the new concentrations were more appropriate based on the guidance document (The low concentration is three times the LLOQ, the medium concentration is in the middle of the curve and the high concentration is more than 80% of the high standard concentration).

Reviewer's Comment:

The firm's response to the deficiency 7 is acceptable.

Deficiency 8:

The dissolution specifications are set based on the bio-lot and not on the stability batches. Based on the data on fresh bio-lot, the DBE recommends the following dissolution method and interim specifications: The dissolution testing should be conducted in 50 mL water, at 37°C using USP Apparatus 7 at 15-30 cycles per minute.

Specifications: *4 hours:* (b) (4)
12 hours.
24 hours.

Firm's Response:

The firm acknowledged its acceptance of the FDA-recommended dissolution method, the specification of NMT (b) (4) % at 4 hr, the specification of (b) (4) % at 12 hr, and proposed to change the specification at 24 hr from (b) (4) % to (b) (4) % in this amendment.

Reviewer's Comment:

The DBE will not change the specification at 24 hr as fresh bio-lot meets the DBE-recommended specifications at L1. The firm's response to the deficiency 8 is not acceptable.

Deficiency 9:

The lot number of the reference product provided on page 162 is 3ZP065A instead of 37P065A as given elsewhere in the submission. Please explain.

Firm's Response:

The firm states that the correct lot number is 37P065A. The lot number 3ZP065A of the reference product provided on page 162 was a typographical error.

Reviewer's Comment:

The firm's response to the deficiency 9 is acceptable.

D. Deficiency Comments

1. Eight subjects were excluded from the firm's statistical analysis due to consuming less than 80% of the evening meal prior to study periods. The firm claimed that excluding 8 subjects from bioequivalence statistics was based on a valid scientific rationale and complied with the protocol. However, the firm did not provide enough evidence to justify the effect of the differential amount of the evening meal consumed on the bioequivalence study for drugs to be given next morning after an overnight fast. In addition, the reviewer did not find such exclusion criteria stated in the protocol. If the intention was to exclude these subjects, either

these subjects should not have been dosed or their samples should not have been analyzed. Excluding these subjects from final statistical analysis by the firm is not acceptable.

2. The firm submitted the statistical analysis results to demonstrate the test product bioequivalent to the innovator product after dropping subject 21. However, the DBE disagrees with the firm's conclusion of dropping subject 21 from the final statistical analysis. Using the differential amount of the evening meal consumed by subject 21 as a justification for excluding this subject from the statistical analysis is not acceptable.

3. The firm's dissolution testing in 50 mL water, at 37°C using USP Apparatus 7 at 15-30 cycles per minute is acceptable. However, the firm proposed to change the dissolution specification at 24 hour time point from (b) (4) % to (b) (4) %. The DBE will not change the specification at 24 hr as fresh bio-lot meets the DBE-recommended specifications at L1. The firm should be advised to acknowledge its acceptance of the following FDA-recommended dissolution specifications:

4 hours: (b) (4)
12 hours
24 hours

E. Recommendations

1. The bioequivalence study conducted under fasting conditions by Osmotica USA Corporation, on its nifedipine extended-release 90 mg tablets, Lot # P424401 comparing it to Procardia XL® 90 mg tablets, Lot # 37P065A manufactured by Pfizer Inc., is incomplete.

2. The *in vitro* dissolution testing conducted by Osmotica on its test product, Nifedipine 90 mg ER Tablets, USP, comparing it to Pfizer's Procardia XL® 90 mg tablets is incomplete. The dissolution testing should be conducted in 50 mL water, at 37°C using USP Apparatus 7 at 15-30 cycles per minute. The test product should meet the following FDA-recommended dissolution specifications:

4 hours: (b) (4)
12 hours
24 hours

The firm should be informed of the deficiency comments and recommendations.

06/29/06

Yi Zhang, Ph.D., Review Branch IV — Date

6/29/2006

Yih-Chain Huang, Ph.D.
Team Leader, Review Branch IV — Date

6/30/06

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs — Date

V:\firmsnz\Osmotica\ltrs&rev\77410A0306.doc

F. Attachment

From: Tran, Nhan L
Sent: Friday, June 09, 2006 7:43 AM
To: Zhang, Yi
Subject: RE: Dissolution spec of Nifedipine Extended Release Tablets USP, 90 mg, ANDA 77-410

As we discussed, I do not see a need for changing the spec at 24 hr time point. Unless the firm has a valid reason, I would stick to our recommended spec at 24 hr as before.

Thanks,

From: Zhang, Yi
Sent: Thursday, June 08, 2006 3:45 PM
To: Tran, Nhan L
Subject: Dissolution spec of Nifedipine Extended Release Tablets USP, 90 mg, ANDA 77-410

Dear Dr. Tran,

I am reviewing the amendment of ANDA 77-410 for the nifedipine ER tablets. The following is the FDA proposed dissolution specifications as per the previous dissolution review (V:\firmsnz\Osmotica\ltrs&rev\77410D1104.doc) and the previous ANDA review (V:\firmsnz\Osmotica\ltrs&rev\77410N1104.doc):

4 hrs: (b) (4)
12 hrs
24 hrs

Note: In both reviews, the proposed dissolution specifications were set up after consulting with you.

In this amendment, the firm acknowledged the specification of NMT (b) (4) % at 4 hour time point and the specification of (b) (4) % at 12 hour time point. However, the firm proposed to change the specification at 24 hour time point from (b) (4) % to (b) (4) %.

Based on the firm's dissolution data (also included in this email for your reference), the specification at 24 hour time point is very reasonable to me (which also cover the firm's data very well). I do not see any need to change the specification.

Thanks for your advice on this issue.

Batch No.	Condition	Collection Times Mean % Dissolved (Range)												
		Time (hours)												
		1	2	4	6	8	10	12	14	16	18	20	22	24
Test	D	(b) (4)		6 (4-9)	(b) (4)			51 (46-56)	(b) (4)					90 (86-95)

Reference	D	(b) (4)	14 (11-17)	(b) (4)	63 (54-70)	(b) (4)	115 (110-118)
Test	E		8 (4-11)		48 (42-55)		78 (72-82)
Reference	E		9 (4-15)		42 (17-63)		67 (25-103)

Test = Nifedipine Extended Release Tablets 90 mg, Lot P42440, 12 dosage units
Reference = Procardia XL® 90 mg, Lot 37P065A, 12 dosage units
D = pH 7.5 Phosphate Buffer + 1% Tween, Apparatus 2, 100 RPM, 900 mL, 37.5°C
E = Water, Apparatus 7, 30 DPM, 50 mL, 37.5°C

egards
Yi

CC: ANDA 77-410
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Zhang

Endorsements: (Draft and Final with Dates)
HFD-650/ Zhang 06/29/06
HFD-650/ Dhariwal
HFD-650/ Fabian-Fritsch
HFD-650/ D. Conner 6/30/06

V:\firmsnz\Osmotica\ltrs&rev\77410A0306.doc
Printed in final on 06/29/2006

BIOEQUIVALENCE - INCOMPLETE Submission Date: 03/17/2006

1. **Study Amendment** (STA) Strengths: 90 mg
Outcome: IC

Outcome Decisions:
IC – Incomplete

WinBio Comments: Fasting bioequivalence study is incomplete.

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-410
Drug Product Name	Nifedipine Extended-Release Tablets, USP
Strength	90 mg
Applicant Name	Osmotica USA Corporation
Address	1205 Culbreth Dr, Suite 200 Wilmington, NC 28405
Submission Date(s)	November 19, 2004
Amendment Date(s)	October 20, 2006
Reviewer	Shirley K. Lu, Ph.D.
First Generic	No
Firm's Representative:	Mark S. Aikman
Telephone:	910-509-4235

Review of an Amendment

I. Executive Summary

This amendment was submitted in response to a request from the Division of Bioequivalence (DBE) to provide stability data for the test product and acknowledgement of the USP dissolution specification. The firm accepted the dissolution specification, however the stability data provided does not span the total time between the manufacture date of the test product and the re-dosing date. The application remains incomplete.

II. Table of Contents

I. Executive Summary 1
II. Table of Contents 1
III. Response to Deficiencies 2
IV. Deficiency Comments 2
V. Recommendations 3

III. Response to Deficiencies

Deficiency #1: *The test lot was manufactured on 4/27/2004 while the re-dosing study was conducted between 06/06/2006 and 06/15/2006. Your proposed expiration dating period is 24 months based on 3 months accelerated stability data. Therefore, please provide data to support that the test product is still within the expiration dating period when the re-dosing study was conducted.*

Firm's Response: The firm submitted 24-month stability data to support the condition of the test product at the time of dosing.

Reviewer's Comments: The redosing study was initiated on June 15, 2006. The test lot was manufactured on April 27, 2004. The total time between these two dates is approximately 25.5 months. Since the stability data submitted by the firm spans only 24 months, the stability of the test product that was used for the redosing study cannot be ensured. The firm should submit stability data that encompasses this time period (26 months or longer).

Deficiency #2: *Please acknowledge your acceptance of USP (Test 5) dissolution specifications of NMT 14% in 4 hours, 39-75% in 12 hours, and NLT 75% in 24 hours for your test product. In addition, please verify that the amount dissolved is expressed in terms of the labeled tablet strength rather than in terms of the labeled total contents.*

Firm's Response: The firm accepts the USP test 5 dissolution specifications above. The firm also verified that the amount dissolved is expressed in terms of the labeled tablet strength.

Reviewer's Comments: The firm's response is acceptable.

IV. Deficiency Comments

1. The firm should submit data for its test product that demonstrates stability for 26 months or longer.

V. Recommendations

1. The bioequivalence study conducted under fasting conditions by Osmotica USA Corporation, on its nifedipine extended-release 90 mg tablets, Lot # P424401 comparing it to Procardia XL® 90 mg tablets, Lot # 37P065A manufactured by Pfizer Inc., is incomplete.

2. The *in vitro* dissolution testing conducted by Osmotica on its test product, Nifedipine 90 mg ER Tablets, USP, comparing it to Pfizer's Procardia XL® 90 mg tablets is complete. The dissolution testing method is as follows: 50 mL water, at 37°C using USP Apparatus 7 at 30 cycles per minute. The test products should meet the following USP dissolution specifications (Test 5):

   4 hours: NMT 14%
   12 hours: between 39% and 75%
   24 hours: NLT 75%

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-410 APPLICANT: Osmotica Pharmaceutical

DRUG PRODUCT: Nifedipine Extended-Release Tablets USP, 90 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

1. The data you submitted in this amendment are incomplete. Your test product has a tentative 24-month expiration dating based on 3-month accelerated stability data. Since the amount of time elapsed between the manufacturing date of your test product and the re-dosing date exceeds the 24-month stability testing period, please submit data for your test product that demonstrates stability for 26 months or longer.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-410

BIOEQUIVALENCE - INCOMPLETE

Submission date: 10/20/06

1. **STUDY AMENDMENT** (STA)

Strengths: 90 mg
Outcome: IC

Outcome decision: IC - Incomplete

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shirley Lu
11/27/2006 09:13:32 AM
BIOPHARMACEUTICS

Yih Chain Huang
11/27/2006 09:38:04 AM
BIOPHARMACEUTICS

Barbara Davit
11/27/2006 09:55:09 AM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-410
Drug Product Name	Nifedipine Extended-Release Tablets, USP
Strength	90 mg
Applicant Name	Osmotica USA Corporation
Address	1205 Culbreth Dr, Suite 200 Wilmington, NC 28405
Submission Date(s)	November 19, 2004
Amendment Date(s)	November 30, 2006
Reviewer	Shirley K. Lu, Ph.D.
First Generic	No
Firm's Representative:	Mark S. Aikman
Fax:	910-509-0115

Review of an Amendment

I. Executive Summary

This amendment was submitted in response to a request from the Division of Bioequivalence (DBE) for the firm to provide stability data for the test product for at least the duration of time that had elapsed between the test product manufacture date and the date of the re-dosing study. The stability data provided is acceptable. The application is complete.

II. Table of Contents

I. Executive Summary 1
II. Table of Contents 1
III. Response to Deficiencies 2
IV. Deficiency Comments 2
V. Recommendations 3

III. Response to Deficiencies

Deficiency #1: *The data you submitted in this amendment are incomplete. Your test product has a tentative 24-month expiration dating based on 3-month accelerated stability data. Since the amount of time elapsed between the manufacturing date of your test product and the re-dosing date exceeds the 24-month stability testing period, please submit data for your test product that demonstrates stability for 26 months or longer.*

Firm's Response: To confirm that the test product was still within specifications when the re-dosing study was conducted, the firm removed the controlled-room temperature samples from the chambers and tested them in October 2006. The firm submitted 29-month stability data to support the condition of the test product at the time of dosing.

Reviewer's Comments: The re-dosing study was initiated on June 15, 2006. The test lot was manufactured on April 27, 2004. The total time between these two dates is approximately 25.5 months. The firm's 29-month data is sufficient to demonstrate the stability of their product. The assay of the active ingredient, nifedipine, was 100.9% when fresh (0 months) and 103.6% at 29 months. This is within specification for this test (90-110%). All drug release data are within the dissolution specifications set for this drug product. The data are summarized in the following table.

Drug Release	0 month mean (range)	29 months mean (range)	Specifications	Meet Spec?
4 hours	(b) (4)		NMT 14%	Yes
12 hours			between 39% and 75%	Yes
24 hours			NLT 75%	Yes

Based on the data provided, the condition of the test product at the time of the re-dosing study appears to have similar potency and dissolution characteristics as the test product at the date of manufacture. The firm's response is acceptable.

IV. Deficiency Comments

None

V. Recommendations

1. The bioequivalence study conducted under fasting conditions by Osmotica USA Corporation, on its nifedipine extended-release 90 mg tablets, Lot # P424401 comparing it to Procardia XL® 90 mg tablets, Lot # 37P065A manufactured by Pfizer Inc., is acceptable.

2. The *in vitro* dissolution testing conducted by Osmotica on its test product, Nifedipine 90 mg ER Tablets, USP, comparing it to Pfizer's Procardia XL® 90 mg tablets is complete. The dissolution testing method is as follows: 50 mL water, at 37°C using USP Apparatus 7 at 30 cycles per minute. The test products should meet the following USP dissolution specifications (Test 5):

   4 hours: NMT 14%
   12 hours: between 39% and 75%
   24 hours: NLT 75%

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-410 APPLICANT: Osmotica Pharmaceutical

DRUG PRODUCT: Nifedipine Extended-Release Tablets USP, 90 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the dissolution testing is conducted using the following USP-recommended method (Test 5):

Medium:	Water
Volume:	50 mL
Apparatus:	USP apparatus VII
Speed:	30 cycles per minute
Temperature:	37°C

Your test product should meet the following specifications:

4 hr: NMT 14%
12 hr: 39-75%
24 hr: NLT 75%

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-410

BIOEQUIVALENCE - ACCEPTABLE

Submission date: 11/28/06

1. **STUDY AMENDMENT** (STA)
   (New stability data)

Strengths: 90 mg
Outcome: **AC**

Outcome decision: AC - ACCEPTABLE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shirley Lu
12/1/2006 02:09:42 PM
BIOPHARMACEUTICS

Yih Chain Huang
12/1/2006 03:01:19 PM
BIOPHARMACEUTICS

Barbara Davit
12/1/2006 03:11:42 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-410

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OSMOTICA

November 19, 2004

RECEIVED
DEC 01 2004
OGD / CDER

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

505(b)(2) 77-410

NEW ABBREVIATED NEW DRUG APPLICATION FOR NIFEDIPINE EXTENDED-RELEASE TABLETS, USP, 90 MG

Dear Mr. Buehler,

Please reference a communication from the Division of Bioequivalence (Reference Number OGD #02-618). Reference is also made to previously submitted ANDA 77-127 for Nifedipine Extended-Release Tablets, USP 30 mg and 60 mg. Reference is also made to a telephone conversation with Saundra Middleton, Consumer Safety Officer, on August 30, 2004.

Although it is preferred by the Agency to have additional strengths of previously submitted products submitted as amendments to those applications, complicating issues exist in the present circumstances that require otherwise. ANDA 77-127 was submitted for Nifedipine Extended-Release Tablets, USP 30 mg and 60 mg with a Paragraph IV notification. The required notifications were made to the holder of the application of the RLD and the assignee of the patent for which the Paragraph IV notification was made. No litigation was initiated within the 45 day period and the Agency was notified of such. Another Paragraph IV notification is required for the submission of the 90 mg strength, whether submitting as an amendment to 77-127 or as a separate application. Because the possibility exists that litigation could occur with the 90 mg even though it did not occur with the 30 mg and 60 mg strengths, it preferable to submit the 90 mg as a separate application to prevent any impact on the approval of the 30 mg and 60 mg.

In addition, the 90 mg product currently has Waxman-Hatch exclusivity for a previously approved product which has not been triggered as of the date of this application. Therefore, it is also preferable to submit the 90 mg as a separate application to prevent exclusivity issues with the 90 mg from impacting the approval of the 30 mg and 60 mg. The rationale for submission of the 90 mg strength as a separate application was agreed to by Martin Shimer, Branch Chief, Regulatory Support Branch. This approval was communicated to Osmotica by Saundra Middleton during the previously reference telephone conversation on August 30, 2004.

Osmotica USA Corp is, therefore, submitting an abbreviated new drug application (ANDA) for Nifedipine Extended-Release Tablets, USP 90 mg. The reference listed

7040 Wrightsville Avenue, Suite 103 • Wilmington, NC 28403 USA
Phone: 910 509-4235 • **Facsimile:** 910 509-4236
info@osmoticausa.com

drug (RLD) product for this ANDA is Procardia XL® Tablets (Pfizer) and this application contains a Paragraph IV patent certification. There are no exclusivities listed in Approved Drug Products with Therapeutic Equivalence Evaluations that are applicable.

This submission contains 14 volumes. The data from the bioequivalence study is also being submitted in electronic format in SAS Transport File format and the labeling is being also provided in Microsoft Word format. There is no sterility assurance data contained within this application.

Bioequivalence to the reference listed drug was demonstrated under fasting conditions for the 90 mg strength. The 90 mg product is dose-proportional to the 30 mg and 60 mg strengths submitted in ANDA 77-127 which contained both a fasting and non-fasting bioequivalence study on the 60 mg product. Because the three strengths are dose-proportional and demonstrated in-vitro equivalency, this ANDA contains a request for a waiver of in-vivo bioequivalence being demonstrated under non-fasting conditions. This strategy and approach was previously approved by the Agency recommendations set forth in a communication from the Division of Bioequivalence (Reference Number OGD #02-618). Please note that based on the fact that the 90 mg is being filed as a separate ANDA due to administrative reasons and all three strengths are dose-proportional, Osmotica believes that it is appropriate to cross reference data between applications, both now and for necessary post-approval changes.

The technology used for this product is (b) (4) This is true for Nifedipine Controlled-Release Tablets in this application as it is also true for the reference listed drug, Procardia XL®. The 90 mg product contains a 10% overage (total 99 mg) of active pharmaceutical ingredient which will release in-vivo 90 mg. This is demonstrated by the equivalent extent of absorption, as demonstrated by AUC, when compared to the RLD under fasted and fed conditions, which also contains a 10% overage for these two strengths.

The product is manufactured and tested by a third-party (b) (4) (b) (4) using a formulation and process developed by Osmotica. The product is packaged into bottles at the (b) (4). Because the manufacturing and testing is performed by a third-party contract manufacturer, the Field Copy of the CMC sections of this application are being sent to the (b) (4) District Office which has jurisdiction over that facility. A letter is also being sent to the Atlanta District Office, which has jurisdiction over Wilmington, NC, providing notification that the CMC sections of this application were sent to the (b) (4) District Office.

The size of the exhibit batches and the largest intended commercial batches are based upon the capacity of the manufacturing equipment located in the (b) (4) facility. The (b) (4)

Attachment I and II contain diagrams which highlight the comparability of the exhibit and largest intended commercial batch size. The scale up from the exhibit batches to the largest intended commercial batch is only (b) (4) in the final batch size. However, the (b) (4) coating, and drilling operations used for the exhibit batch are identical in process and scale with those used for the largest intended commercial batches. Therefore, the exhibit batch is very representative of the commercial process.

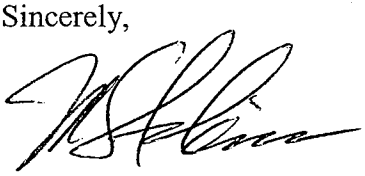
This application contains the data from one exhibit batch. ANDA 77-127 contained three lots of both the 30 mg and 60 mg product which are dose-proportional to the 90 mg product submitted in this application, providing significant supportive information. In that application, three different lots of active pharmaceutical ingredient were used to manufacture three different lots of (b) (4). From each of these

There is a monograph in the current United States Pharmacopeia for Nifedipine Extended-Release Tablets and this product complies with the elements of the monograph other than the drug release acceptance criteria. It is anticipated that once this ANDA has been approved, the USP will be requested to include the drug release criteria for this product. Therefore, this is anticipated to be a USP product. The initial tentative drug release criteria were initially based on the USP methodology found in dissolution Test 1 and was modified for use as the tentative acceptance criteria for stability data.

The drug substance and finished product analytical methods are those found in the current USP and method verification was performed to demonstrate the finished product method's appropriateness for use. Osmotica commits to resolve any issues which are identified in the methods validation process after approval. Because the analytical methods for both the active ingredient and the finished product comply with USP 27 – NF 22, Supplement 2 official August 1, 2004, the additional bound copies of the analytical methods are not provided.

Please feel free to contact the undersigned should any questions arise regarding this application.

Sincerely,



Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

Telecon Record

Date: 1/7/05

ANDA: 77-410

Firm: Osmotica USA Corp

Drug: Nifedipine Extended-release Tablets USP, 90 mg

FDA Participants: Iain Margand

Industry Participants: Mark Aikman

Phone: 910-509-4235

Agenda:

1. Iain requested the following:

   Please provide a Financial Certification form 3454. Statement in application refers to certification, but is not in referenced section.

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-410 **FIRM NAME:** OSMOTICA USA CORP

RELATED APPLICATION(S): SEE 77-127 FOR NIFEDIPINE CONTROLLED - RELEASE TABLETS USP, 60 MG AND 30 MG FROM OSMOTICA USA CORP. (PN 4/19/04)

First Generic Product Received? NO

Bio Assignments:		Micro Review
☒ BPH	☐ BCE	☐
☐ BST	☒ BDI	

DRUG NAME: NIFEDIPINE

DOSAGE FORM: EXTENDED-RELEASE TABLETS USP, 90 MG

Random Queue: 8

Chem Team Leader: Venkataram, Ubrani PM: Stanley Shepperson Labeling Reviewer: Adolph Vezza

Letter Date: NOVEMBER 19, 2004 **Received Date:** DECEMBER 1, 2004

Comments: EC - 1 YES **On Cards:** YES

Therapeutic Code: 1010300 CALCIUM CHANNEL BLOCKERS

Archival Format: PAPER **Sections I** **(356H Sections per EDR Email)**

Review copy: YES E-Media Disposition: YES SENT TO EDR

Not applicable to electronic sections

Field Copy Certification (Original Signature) YES

Methods Validation Package (3 copies PAPER archive) **NO**
(Required for Non-USP drugs)

Cover Letter YES **Table of Contents** YES

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST **Iain Margand**

Date 1/7/05

Recommendation:

☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: **Date:** 18 JAN 2005

ADDITIONAL COMMENTS REGARDING THE ANDA:

See T-con dated 1/7/05

Top 200 Drug Product:

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	**Basis for Submission** **NDA# : 19-684** Ref Listed Drug: PROCARDIA XL Firm: PFIZER, INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: IV patent '446 PII patents '008, '989, '337 2. Expiration of Patent: 11-23-2010 A. Pediatric Exclusivity Submitted? N/A B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** NA	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use OK 2. Active ingredients OK 3. Route of administration OK 4. Dosage Form OK 5. Strength OK	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL Y 2. 1 RLD label and 1 RLD container label Y 3. 1 side by side labeling comparison with all differences annotated and explained Y 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) NA **2. Request for Waiver of In-Vivo Study(ies): YES ON 90 MG, BASE ON RECOMMENDATION FROM BIO REFERENCE NO# 02-618 UNDER 77-127** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) 90mg strength is proportional to 60mg strength (ANDA 77-127) **4. Lot Numbers of Products used in BE Study(ies):** P424401 **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING ONLY FOR 90 MG (FASTING AND FED DONE ON 30 MG AND 60 MG FOR 77-127) AUCt 82.67 – 91.17 a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) AUC∞ 83.97 – 93.13 b. EDR Email: Data Files Submitted: YES SENT TO EDR Cmax 83.76 – 98.76 c. In-Vitro Dissolution: YES Pg. 4079 - 4090	☒

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. Adhesion Study c. Skin Irritation/Sensitization Study	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation Pg. 4097 2. Inactive ingredients as appropriate Excipients are acceptable per IIG and COMIS	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers Y b. Type II DMF authorization letters or synthesis DMF# (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) Y d. Applicant certificate of analysis Y e. Testing specifications and data from drug product manufacturer(s) Y f. Spectra and chromatograms for reference standards and test samples Y g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified Y b. Testing specifications (including identification and characterization) Y c. Suppliers' COA (specifications and test results) Y d. Applicant certificate of analysis Y	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address Y 2. Functions Y 3. CGMP Certification/GLP Y 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) Pg. 4349 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3.If sterile product: Aseptic fill / Terminal sterilization N/A 4.Filter validation (if aseptic fill) N/A 5. Reprocessing Statement pg. 4562	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation (b) (4) 2. In-process Controls - Specifications and data Y Packaged: (b) (4)	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) Pg. 4706 2. Components Specification and Test Data (Type III DMF References) Y 3. Packaging Configuration and Sizes 100 and 500 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data Y 2. Certificate of Analysis for Finished Dosage Form pg. 4789	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted Y 2. Post Approval Commitments pg. 4971 3. Expiration Dating Period 24 months 4. Stability Data Submitted a. 3 month accelerated stability data Y b. Batch numbers on stability records the same as the test batch Lot # 42440	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: Pg. 4994 1. Drug Substance Y 2. Finished Dosage Form Y 3. Same lot numbers Y	☒
Sec. XVII	**Environmental Impact Analysis Statement** Pg. 4995	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) N/A 4. Field Copy Certification (original signature) YES	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 77-410 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

N/A 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. PROCARDIA XL 90mg

N/A 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission. PROCARDIA XL 90 19-684

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ✓ yes ____ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature_____ date_____

ANDA 77-410

Osmotica USA Corp
Attention: Mark Aikman
7040 Wrightsville Avenue
Suite 103
Wilmington, NC 28403

JAN 19 2005

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated January 7, 2005 and your correspondence dated January 7, 2005

NAME OF DRUG: Nifedipine Extended-release Tablets USP, 90 mg.

DATE OF APPLICATION: November 19, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 1, 2004

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken

by each person provided notice.

- You must submit a copy of a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Stanley Shepperson
Project Manager
(301) 827-5849

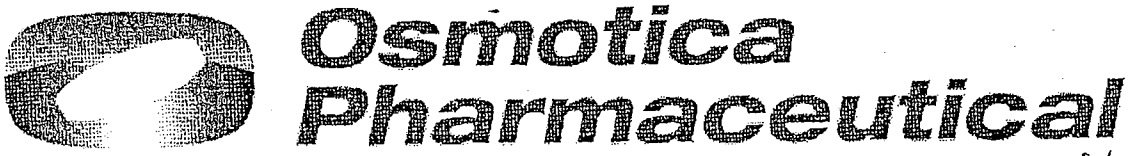
Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-410
DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement: HFD-615/MShimer, Chief, RSB _____ date 18 Jan 05
HFD-615/IMargand, CSO _____ date 1/18/05
Word File V:\Firmsnz\Osmotica\Ltrs&rev\77-410.ack
FT/ 1/7/05
ANDA Acknowledgment Letter!

Osmotica Pharmaceutical



Osmotica Pharmaceutical
7040 Wrightsville Ave., Suite 103
Wilmington, NC 28403
Phone (910) 509-4235

O.K. to use Fed Ex for notice for this ANDA
[illegible]
21 Jan 2005

Fax Memorandum

To: Martin Shimer, Branch Chief, Regulatory Support Branch

Fax Number: (301) 594-1174

Date: January 19, 2005

From: Mark S. Aikman, Pharm.D.,
Vice President, Regulatory Affairs and Quality Assurance

Fax Number: (910) 509-4236

Number of Pages (including cover): One

Subject: Paragraph IV notification letter, ANDA 77-410

☐Urgent ☐For Review ☐ Please Comment X Please Reply

Comments: In accordance with the FDA letter dated January 19, 2005 on file acceptance for ANDA 77-410, notification of the patent holder or sponsor of the RLD application may rely on a form of documentation other than US registered or certified mail with return receipt requested only if FDA has agreed to such documentation in advance.

The assignee of patent 5,264,446 is Bayer AG in Leverkusen, Germany. Because it is uncertain whether US registered or certified mail with return receipt requested is acceptable for notification at a foreign address, Osmotica requests FDA agreement on the use of documentation from Federal Express as documentation of notification.

We appreciate your assistance and a prompt response to our request

This document may contain Confidential and/or Trade Secret information subject to 18 U.S.C. 1905 and to which all claims of privilege and confidentiality are asserted in both statutory and common law.

Osmotica Pharmaceutical

ORIG AMENDMENT
N/MC

January 24, 2005

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

GENERAL CORRESPONDENCE

Dear Mr. Buehler,

Please refer to ANDA 77-127, Nifedipine Extended-Release Tablets 30 mg and 60 mg and ANDA 77-410, Nifedipine Extended-Release Tablets 90 mg. At this time, both of these applications are pending approval by the Agency.

In the above referenced applications, the name of the sponsor was noted as Osmotica USA Corp. Please note that the name of the sponsor of these applications has been changed to Osmotica Pharmaceutical Corp. Please find attached a copy of the official declaration from the Secretary of State for the state of Delaware.

Please feel free to contact the undersigned should you have any questions regarding this name change.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

RECEIVED
JAN 25 2005
OGD / CDER

7040 Wrightsville Avenue, Suite 103 • Wilmington, NC 28403 USA
Phone: 910 509-4235 • **Facsimile:** 910 509-4236
info@osmotica.com

Osmotica Pharmaceutical

February 14, 2005

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

N/GP

PATENT AMENDMENT
ANDA 77-410
NIFEDIPINE EXTENDED-RELEASE TABLETS, USP 90 MG

Please refer to the Agency letter dated January 19, 2005 providing notification of the acceptability for filing of this application.

In accordance with 21 CFR §314.95(b), Osmotica Pharmaceutical Corp certifies that Paragraph IV notifications have been provided to both the sponsor of the application of the reference listed drug, i.e. Procardia XL®, Pfizer, Inc., and the assignee of patent 5,264,446 for which the Paragraph IV certification was made, Bayer AG. The notice met the content requirements under §314.95(c). A copy of the notice, dated January 28, 2005, is attached.

Copies of the documentation of the receipt of the notices are also provided in this amendment. Please note that as a courtesy, a second notification for Bayer AG was also provided. This notification was sent to Bayer Corporation of West Have, CT by certified mail, return receipt requested. However, as of the date of this letter, a return receipt for this notification has not been received. Because this notification was done as a courtesy and the sponsor of the application and assignee of the patent both received notification, Osmotica considers the notification complete.

Please note that the notification provided to Bayer AG in Leverkusen, Germany was sent via Federal Express. Verbal authorization for this method of notification was provided by Martin Shimer, Branch Chief, Regulatory Support Branch, on January 24, 2005. The Bayer AG notification was noted as received on January 31, 2005 and the Pfizer, Inc. notification was noted as received on February 1, 2005.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

RECEIVED
FEB 15 2005
OGD / CDER

7040 Wrightsville Avenue, Suite 103 • Wilmington, NC 28403 USA
Phone: 910 509-4235 • **Facsimile:** 910 509-4236
info@osmotica.com

Osmotica Pharmaceutical

N/MC. Not sued within 45 days / S. Middleton 4/21/05

April 15, 2005

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

GENERAL CORRESPONDENCE

NIFEDIPINE EXTENDED-RELEASE TABLETS, USP 90 MG

ANDA 77-410

Dear Mr. Buehler,

Please refer to an Agency letter to Osmotica dated January 19, 2005 providing notification of acceptance for filing of ANDA 77-410.

In the above referenced letter, it was requested that if Osmotica is not sued within the 45-day period, that we provide a letter stating that no legal action has been taken. Please consider this letter such notification.

In an amendment to this application dated February 14, 2005, Osmotica provided evidence to the Agency that notifications were provided to the sponsor of the reference listed drug product, Pfizer, Inc. and the assignee of the patent 5,264,446 for which the Paragraph IV certification was made, Bayer AG. The Bayer AG notification was noted as received on January 31, 2005 and the Pfizer, Inc. notification was noted as received on February 1, 2005. The 45-day period, therefore, ended on March 18, 2005. As of the date of this letter, Osmotica is not aware of any legal action that has been taken by either party related to our submission of this ANDA.

Please contact me should you have any questions or concerns regarding this information.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

RECEIVED
APR 18 2005
OGD / CDER

7040 Wrightsville Avenue, Suite 103 • Wilmington, NC 28403 USA
Phone: 910 509-4235 • **Facsimile:** 910 509-4236
info@osmotica.com

Osmotica Pharmaceutical

November 10, 2005

ORIG AMENDMENT

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

Abbreviated New Drug Application 77-410
Nifedipine Extended-release Tablets, 90 MG USP

MINOR AMENDMENT

Dear Mr. Buehler,

This minor amendment is in response to the chemistry comments received via facsimile on June 23, 2005. All deficiencies noted in that communication have been addressed. For the ease of review, the chemistry comments are being provided along with the response.

A. Chemistry Deficiencies:

(b) (4)

Following this page, 3 pages withheld in full- (b)(4)

RECEIVED
NOV 14 2005
OGD / CDER

4800 N. Federal Highway, Bldg. B, Suite 200 • Boca Raton, FL 33431 USA
Phone: 561 362 8112 • **Facsimile:** 561 362 8167
info@osmotica.com • www.osmotica.com

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please submit available long term stability data.

An updated stability report is provided in Attachment IV.

Osmotica Pharmaceutical Corp certifies that a field copy of this response to chemistry comments has been sent to the (b) (4) District office of the FDA. The (b) (4) District was chosen as the recipient of the field copy as the district office responsible for the (b) (4) at which the exhibit batches were manufactured and laboratory data generated.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

Osmotica Pharmaceutical

ORIG AMENDMENT

NL/AB

November 22, 2005

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

Abbreviated New Drug Application 77-410
Nifedipine Extended-release Tablets, 90 MG USP

RESPONSE TO BIOEQUIVALENCE DEFICIENCIES

Dear Mr. Buehler,

This amendment is in response to the bioequivalence comments received via facsimile on May 5, 2005. All deficiencies noted in that communication have been addressed. For the ease of review, the comments are being provided along with the response.

1. The DBE recommends the following dissolution method:

The dissolution testing should be conducted in 50 mL water, at 37°C using USP Apparatus 7 at 15-30 cycles per minute.

The DBE requests that the test product should meet the following interim specifications:

4 hours: (b) (4)
12 hours:
24 hours:

With your response to the above deficiency, please indicate if you accept the above dissolution method and specification.

Please note that the test product cannot be labeled as a USP product until the USP assigns a test number for your product. In the interim, the labeling should state: "Dissolution test is pending."

RECEIVED
NOV 23 2005
OGD / CDER

4800 N. Federal Highway, Bldg. B, Suite 200 • Boca Raton, FL 33431 USA
Phone: 561 362 8112 • **Facsimile:** 561 362 8167
info@osmotica.com • www.osmotica.com

The dissolution method proposed by the Agency is the same as that proposed by Osmotica in the original ANDA. Therefore, Osmotica agrees with the dissolution method. However, Osmotica does not agree with the dissolution specifications proposed. The reasons for the disagreement will be outlined and discussed by time point.

For the 4 hour time point specification, Osmotica agrees with the Agency suggestion of (b) (4) %

For the 12 hour time point specification, Osmotica is concerned that the specification proposed by the Agency may be too narrow to allow for in-vitro variations seen with this product, including those seen on stability. Recent controlled-room temperature stability data indicates that the ranges of values seen for individual vessel values at this interval on stability through 12 months are:

Bottles of 100 tablets, 40°C/75%RH: (b) (4)
Bottles of 100 tablets, 25°C/60%RH:
Bottles of 500 tablets, 40°C/75%RH:
Bottles of 500 tablets, 25°C/60%RH:

Please note that the stability data referenced above was provided in the minor chemistry amendment response dated November 10, 2005.

Based on this data, Osmotica proposes to change the 12 hour specification to (b) (4) (b) (4) %. This change (b) (4) the range from (b) (4) percentage points as proposed in the original application to (b) (4) percentage points. The current USP Test 1 specification for the 12 hour time point contains a range of 37 percentage points which is (b) (4) than that proposed by Osmotica in the original application.

This range provides for (b) (4) control of the in-vitro release rate yet allows for reasonable variabilities which may be seen. Although this is a single lot of product, the 30 mg and 60 mg Nifedipine Extended-release Tablet products approved in ANDA 77-127 are dose proportional to the 90 mg product in this application and the knowledge gained from those products also supports the use of the (b) (4) range at the 12 hours time point.

For the 24 hour time point specification, Osmotica is concerned with the use of (b) (4) (b) (4) for the specification. In fact, several individual vessel values at this interval on stability were (b) (4) %. Because the release rate is based on the labeled amount of the drug (90 mg), it does not seem appropriate that a batch would fail for releasing (b) (4) % at the 24 hour time point. Therefore, Osmotica proposes to modify the Agency's suggestion specification to be (b) (4).

In summary, Osmotica does not agree with the suggested in-vitro release specifications but is, instead, proposing the following compromise specifications:

Interval	Original ANDA	Agency Proposal	New Osmotica Specs
4 hours		(b) (4)	
12 hours			
24 hours			

Osmotica is also confused with the Agency statement that the Nifedipine Extended-release Tablet 90mg product cannot be labeled as USP until a number has been assigned. This is in conflict with the guidance previously provided by the Agency in ANDA 77-127, Nifedipine Extended-release Tablet 30 mg and 60 mg.

In the labeling comments for ANDA 77-127 dated July 19, 2004, the Agency stated "You may use the "USP" in association with the established name if you wish." In the package insert for the product, the Agency at that time recommended to include the statement "USP Drug Release Test number pending" in the labeling. This statement is similar to that now suggested by DBE. However, the previous recommendation acknowledges that the criteria of the monograph, other than the in-vitro release rate, have been met.

Osmotica desires to keep the labeling uniform between strengths of the product and requests that labeling for the 90 mg include the use of the USP designation should it be desired.

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

The requested information in the templates suggested is provided both in electronic and hard copy formats in Attachments I and II.

Please contact the undersigned for questions or additional information regarding this amendment or the application.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

Osmotica Pharmaceutical

ORIGINAL

March 6, 2006

labeling review drafted 6/23/06 ORIG AMENDMENT N / AF

Gary J. Buehler, MD
Director, Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

RE: Labeling Amendment to ANDA 77-410, Nifedipine Extended-release Tablets, USP 90 mg

Dear Dr. Buehler,

Please refer to Osmotica's ANDA 77-410 for Nifedipine Extended-release Tablets, USP 90 mg and the Labeling Deficiencies dated May 16, 2005.

Osmotica has revised the labeling in accordance with the comments contained in the above referenced deficiency letter. The comments and Osmotica's responses are provided.

The revised labeling for the bottles (100 and 500 counts) and the package insert are provided. Also, a comparison of the revised labeling (proposed FPL) and the labeling provided in the original ANDA is provided. A comparison of the revised labeling (proposed FPL) and the approved labeling for Osmotica's Nifedipine Extended Release, USP 30 mg and 60 mg product labeling is also provided.

An electronic copy (one CD) of the proposed package insert is provided in Word and pdf formats along with the insert comparison in Word.

Also, Osmotica plans to combine the labeling (package insert) for the 30, 60, and 90 mg in ANDA 77-127 and ANDA 77-410 respectively and keep both applications updated accordingly.

Sincerely,

Mark S. Aikman, Pharm.D.
VP Regulatory Affairs and Quality Assurance

RECEIVED
MAR 0 7 2006
OGD / CDER

4800 N. Federal Highway, Bldg. B, Suite 200 • Boca Raton, FL 33431 USA
Phone: 561 362 8112 • **Facsimile:** 561 362 8167
info@osmotica.com • www.osmotica.com

Osmotica Pharmaceutical

March 17, 2006

ORIGINAL

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
Metro Park North 4 HFD-600
7519 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N / AB

Abbreviated New Drug Application 77-410
Nifedipine Extended-release Tablets, 90 MG USP

RECEIVED
MAR 20 2006
OGD / CDER

RESPONSE TO BIOEQUIVALENCE DEFICIENCIES

Dear Mr. Buehler,

This amendment is in response to the bioequivalence comments received via facsimile on May 5, 2005. All deficiencies noted in that communication have been addressed. For the ease of review, the comments are being provided along with the response.

1. Fasting study (PRACS R04-0598): The 90% confidence intervals for the ratios of the test/reference LAUCt (76.83%-92.11%) and LAUCi (76.76-93.77%) are outside the acceptable limits of 80-125% (N=84). Subject number 32 reported vomiting at approximately 12 hours after Period II dose administration (reference drug). The DBE believes that this subject can be dropped from statistical analysis; however, the 90% confidence intervals for the ratios of the test/reference LAUCt (76.68-92.38%) and LAUCi (75.97-94.75%) remain outside the acceptable limits after dropping this subject.

Osmotica takes note of the Agency's observations.

2. You excluded 8 subjects in the statistical analysis because they failed to finish 80% of the evening meal prior to dosing. This is not an acceptable reason for excluding these subjects from statistical analysis.

Although the exclusion of 8 subjects because they failed to finish at least 80% of the prior evening meal may appear to have been somewhat arbitrary, Osmotica submitted such an analysis based on scientifically valid rationale. The protocol design included a requirement for patients to enter the clinic early enough the evening prior to dosing so that they can consume an evening meal that was consistent between subjects. This requirement was based on public information regarding the impact of food on the absorption of Nifedipine and data from previous studies with the Nifedipine Extended-release Tablet 60 mg product approved in ANDA 77-127.

4800 N. Federal Highway, Bldg. B, Suite 200 • Boca Raton, FL 33431 USA
Phone: 561 362 8112 • **Facsimile:** 561 362 8167
info@osmotica.com • www.osmotica.com

The data from ANDA 77-127 for the Nifedipine Extended-release Tablets 60 mg is relevant in that the 30 mg, 60 mg, and 90 mg products are all dose-proportional. There were two pharmacokinetic studies submitted in ANDA 77-127 on the 60 mg tablet using Procardia XL® 60 mg as the reference product. R03-536 was the fasting study provided in the application and RA3-036 was the fed study provided in the application.

In the earlier fasting study R03-536 conducted on the Nifedipine Extended-release Tablet 60 mg product, subjects were brought into the clinic late in the evening prior to dosing and were given only light snacks before bedtime. In the subsequent fed study RA3-036, the subjects were brought into the clinic early enough the evening prior to dosing so that they can consume an evening meal that was consistent between subjects. Although this is a comparison of a fed and a fasting study, Osmotica believes that the prior evening meal was a significant component of reducing the intrasubject variability. It was for this reason that the protocol element of consistent prior evening meals was included in the fasting 90 mg study.

ANOVA intrasubject variability as CV%

	R03-536	RA3-036
Cmax	23.15	22.26
AUC0-t	27.89	22.05
AUCinf	28.60	22.09

The above table implies that the prior evening meal consumption helped reduce the intrasubject variability of the extent of the absorption of Nifedipine.

This is logical in that the absorption curves of the data from the studies show that the absorption process continues up to 30 - 40 hours more than the average GI transit time of the device. Therefore, it can be assumed that after the drug is released into the GI media, a significant part of the drug is absorbed from the distal GI tract where the absorption rate is slower than release rate. The GI tract acts as a "reservoir" for the Nifedipine released from the drug product. Certainly, once the tablet arrives in the colon, it could be influenced by the previous night's meal.

Osmotica chose to perform the statistical analysis on subjects who demonstrated consistent prior evening meals by removing from analysis those subjects who consumed less than 80% of the provided meal and complied with the protocol. This approach maintained the largest number of subjects in the analysis and Osmotica believes this was a reasonable approach.

3. Please identify the samples that were repeated for pharmacokinetic reasons. Please conduct and submit statistical analysis using original assay values as well as repeat values for such repeats.

The following samples were repeated for pharmacokinetic reasons. Subject 21 was repeated by request from the sponsor. The original values, the repeated values and the reported values are given in a separate table in the bioanalytical report and is also present in the table below.

Reported Values for Subject 21 Period 1

Sample (hour)	MD059828	MD0598R2	Average Value	Reported Value
1			(b) (4)	
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				

The following sample was repeated again to obtain a value to report.

Sample	Original Value	Value 2	Value 3	Reported Value	Mean/Median
			(b) (4)		

4. You state that all samples for subjects 75-78 were reanalyzed inadvertently and the original values were acceptable. If that was the case, why average of the original and repeat values for these samples were used in statistical analysis. Please reanalyze with the data using original values.

These samples were repeated in error. Because both the original and repeat values are acceptable, one cannot determine which is correct. According to our Bioanalytical Laboratory's SOP, the mean of the two acceptable values is reported. As requested, the data was reanalyzed using the original values for Subjects 75, 76, 77, and 78. Please see Appendix A in Attachment I for the results.

5. Please provide reasons for re-assaying period 1 samples of subject number 21.

The reanalysis was done at the request of Osmotica. Appendix B in Attachment I contains an internal memo from PRACS regarding the reanalysis.

Subject number 21 was a 23 y/o caucasian female who exhibited absorption of the test product that was anomalous. Subject 21 received the test product in period 1and received the reference product in period 2. The extent of absorption that was detected for the test product as measured by AUC was less than 2% of that of the reference product.

Although there is intersubject variability in the absorption of Nifedipine, this was an anomaly. It is for this reason that the Period 1 samples for subject 21 were repeated. The repeat analysis confirmed the results of the first analysis.

There are two reasons that such an anomalous result could be obtained. The first would be poor performance of the specific tablet that this patient took. The second would be something that occurred regarding the patient which affected the absorption. Osmotica believes that it is not possible that the product would deliver the Nifedipine into the GI contents in a manner that would have only allowed less than 2% of the drug to be absorbed compared to the innovator. Furthermore, Osmotica believes that there are potential explanations for the anomalous absorption demonstrated by this patient.

The tablet-to-tablet variability in the release of the Nifedipine from the Osmotica tablet is relatively minor. The (b) (4) used to compress the tablet cores is the same as that used for the 30 mg and 60 mg product approved in ANDA 77-127 and is a validated process. The coating process used to apply the semi-permeable membrane is the same as the validated 30 mg and 60 mg product approved in ANDA 77-127 and is a standard coating process using standard coating equipment known to provide very uniform coating to tablets.

Lastly, the laser drilling process is also the same as the validated 30 mg and 60 mg product approved in ANDA 77-127. This process uses a validated visual inspection system to eliminate any undrilled tablets from the process. In the unlikely event that an undrilled tablet would be allowed to be released, it is important to also note that tablets with no hole drilled into the semi-permeable membrane coating still release the Nifedipine from the tablet.

The graph below shows the in-vitro release rate of 60 mg tablets which were not drilled.

(b) (4)

It can be seen from the graph above that the Nifedipine release from tablets without drilled holes and cannot be a reason for such anomalous absorption. Therefore, any difference in absorption could only be explained by differences in absorption of the Nifedipine from the GI contents or physical events which would affect the amount of Nifedipine suspension in the GI tract.

Such physical events could either be an emesis or high GI motility such as diarrhea. As stated previously, the absorption process continues to be carried out up to 30 - 40 hours more than the average GI transit time of the device. Therefore, physical events such as diarrhea or other significant increases in GI motility could reduce the extent of absorption similarly to emesis by removing the Nifedipine from the GI tract before it could be absorbed.

There is no documentation that indicates this subject had emesis. However, there was also no required documentation of frequency and consistency of bowel movements which could have significantly affected the absorption of Nifedine. It is interesting to also note that subject 21 had the largest differential in the amount of prior evening meal consumption among all of the subjects with consuming 90% in one period but only 25% in the other period.

Osmotica asked an outside consultant, (b) (4) to review the data. (b) (4) noted that subject 21 was a definite statistical outlier. The data supporting this finding is provided in Attachment II. In addition, it was noted that because of this finding, supported by our observations noted above, Subject 21 should, in fact, be excluded from the bioequivalence statistics. The extent of the anomaly is too large not to exclude this subject. Statistics including all of the subjects except subject 21 are provided in Attachment II.

Based on the information available, it would appear that something out of the ordinary happened which affected the amount of Nifedipine absorbed in the first period by subject 21 which cannot be attributed to a quality or performance issue with the tablet. This resulted in Subject 21 being a statistical outlier. Exclusion of Subject 21 results in the 90% confidence intervals for the geometric mean test/reference area and Cmax ratios being inside the acceptable limits of 80% to 125%. The test product is shown to be bioequivalent to the innovator product.

6. Please provide all Standard Operating Procedures (SOPs) for bioanalytical methods. All appropriate SOPs including those dealing with analytical method and sample repeats should be submitted.

The requested applicable SOPs that were in effect at the time the study samples were analyzed are provided in Appendix C in Attachment I.

7. Please explain why the absolute recovery at three different concentrations (low, medium, and high) is not consistent.

The inconsistency of the recovery was noted during validation of the analytical method #026.4 (Validation of Nifedipine in human plasma by LC/MS/MS).

At a concentration of 300ng/mL the observed recovery was 74.6%. At a concentration of 200ng/mL the observed recovery was 57.9% and at the low concentration of 0.5ng/mL the recovery was 33.7%.

After investigation, the inconsistency was found to be due to the test being performed in a manner not consistent with our practice. The original recovery compared extracted matrix with drug in solution.

Although the original recovery tests were inconsistent; the method was able to consistently quantitate the drug across all concentrations as demonstrated by the standards and QCs data. In addition, during the review process, it was noted that the Dilution Integrity test resulted in accuracy of a 1:4 (one part sample plus three parts blank plasma) dilution was 101.0% which is exactly the same as the accuracy of the undiluted sample. A plot of the residuals for each standard in the standard curves for linearity, accuracy and precision tests display a random behavior with the exception of having greater variation at the high end of the curve than at the low end. This behavior is the reason for using a $1/x^2$ weighting in the linear regression. Also the LLOQ sample is above 10 times noise level despite the low recovery.

As a final test, we ran the recovery test again comparing extracted spiked matrix with extracted blank matrix reconstituted in a solution spiked with analyte at the actual sample concentrations. The new data indicates a recovery at 1.50 ng/mL of 57.2%, at 150 ng/mL of 56.8% and at 250 ng/mL of 59.4% with an internal standard recovery of 57.8%. Although the concentrations in this new test are different from that in the original validation (low is 1.50 ng/mL vs 0.50 ng/mL, mid is 150 ng/mL vs 200 ng/mL, and high is 250 ng/mL vs300 ng/mL), the new concentrations are more in line with the guidance document in that the

low is three times the LLOQ and the mid is in the middle of the curve and the high is > 80% of the high standard.

8. The dissolution specifications are set based on the bio-lot and not on the stability batches. Based on the data on fresh bio-lot, the DBE recommends the following dissolution method and interim specifications: The dissolution testing should be conducted in 50 mL water, at 37°C using USP Apparatus 7 at 15-30 cycles per minute.
Specifications:

4 hours: (b) (4)
12 hours:
24 hours:

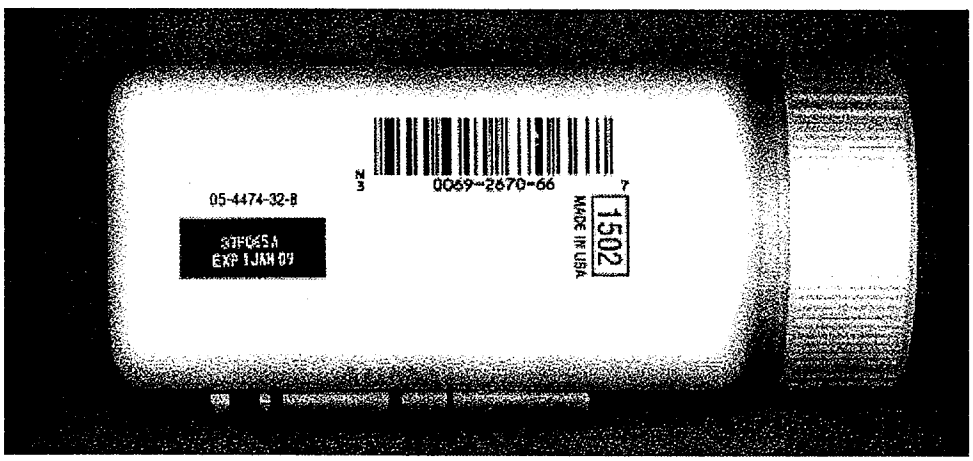
As stated in the previous amendment dated November 22, 2005, Osmotica does not believe that it is appropriate for a 24 hour specification to have (b) (4) for in-vitro dissolution. Please keep in mind that the in-vitro release specifications are based upon the labeled amount (90 mg) and not the amount contained (99 mg). However, Osmotica understands that there may be a concern with the release of more that 100% of the labeled amount of Nifedipine (which would include the 10% overage).

Therefore, Osmotica proposes the following interim specifications using 50 mL water, at 37°C using USP Apparatus 7 at 15-30 cycles per minute:

4 hours: (b) (4)
12 hours:
24 hours:

9. The lot number of the reference product provided on page 162 is 3ZP065A instead of 37P065A as given elsewhere in the submission. Please explain.

This was an error on page 162. The correct lot number is 37P065A. The photo below is of the side of a bottle from this lot.



In summary, Osmotica submitted the bioequivalence statistics with 8 subjects excluded because we believed that the prior meal consumption was an important element of the protocol. In further review of the data with a consultant, it became evident that the most significant issue with the study was the fact that Subject 21 was a statistical outlier, with an identifiable clinical reason (erratic meal consumption), and should be excluded from the study. Utilizing this exclusion, the test product is demonstrated to be bioequivalent to the innovator product.

Please contact the undersigned for questions and additional information. Please note that Osmotica is presently moving its office to Wilmington, NC to the address noted on the FDA 356h. An official notice with the new contact information on letterhead is forthcoming.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

Osmotica Pharmaceutical

8.1

March 29, 2006

Please file in NDA 77-410

Gary J. Buehler, MD
Director, Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

RE: ANDA 77-410, Nifedipine Extended-release Tablets, USP 90 mg - Osmotica Pharmaceutical Corp. – Change of Address

Dear Dr. Buehler,

Osmotica Pharmaceutical Corp. is submitting a formal change of address and contact information. Osmotica recently has moved from Boca Raton, FL to Wilmington, NC. Please use the following information to contact Osmotica in the future.

The new address is:

Osmotica Pharmaceutical Corp.
1205 Culbreth Drive
Suite 200
Wilmington, NC 28405

Our main phone number is 910.509.0114
Mark Aikman, VP of Regulatory Affairs and QA – extension 1006
Tim Davis, Manager of Regulatory Affairs – extension 1013

Our fax number is 910.509.0115

Our email addresses remained the same:
Mark Aikman – aikman@osmotica.com
Tim Davis – davis@osmotica.com

Sincerely,

Timothy W. Davis

Timothy W. Davis
Manager, Regulatory Affairs

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

Osmotica Pharmaceutical

labeling review drafted 7/25/06 AVezza

ORIGINAL

July 14, 2006

ORIG AMENDMENT
N / AF

Gary J. Buehler, MD
Director, Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North IV, HFD-600
7519 Standish Place
Rockville, MD 20855

RE: Labeling Amendment to ANDA 77-410, Nifedipine Extended-release Tablets, USP 90 mg

Dear Dr. Buehler,

Please refer to Osmotica's ANDA 77-410 for Nifedipine Extended-release Tablets, USP 90 mg and the Labeling Deficiencies dated May 16, 2005. Reference is also made to the Amendment dated March 6, 2006.

Dr. Adolph Vezza called Osmotica on June 28, 2006 regarding the March 6, 2006 Amendment. Dr. Vezza advised Osmotica that the inert ingredient section for the packaging insert must include all the relevant components of the inks unless they are proprietary.

Osmotica has revised the packaging insert and is revising our March 6, 2006 Amendment accordingly. The side-by-side comparison of the proposed insert and the insert provided in the original ANDA is provided. Changes are in bold font in the Differences column.

An electronic copy (one CD) of the proposed package insert is provided in Word and pdf formats along with the insert comparison in Word.

Please note that once ANDA 77-410 is approved, Osmotica plans to combine the labeling (package insert) for the 30, 60, and 90 mg in ANDA 77-127 and ANDA 77-410 respectively and keep both applications updated accordingly.

RECEIVED
JUL 17 2006
OGD / CDER

Sincerely,

Mark S. Aikman, Pharm.D.
VP Regulatory Affairs and Quality Assurance

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

Osmotica Pharmaceutical

August 4, 2006

ORIGINAL

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN IV, HFD-600
7519 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/AB

Abbreviated New Drug Application 77-410
Nifedipine Extended-release Tablets, 90 MG USP

BIOEQUIVALENCY AMENDMENT

Dear Mr. Buehler,

Please refer to the Agency fax containing bioequivalency deficiencies dated July 17, 2006. This amendment addresses all of the issues and is a complete response. For the ease of review, the comments are being provided along with the response.

1. Eight subjects were excluded from your statistical analysis due to consuming less than 80% of the evening meal prior to study periods. You claimed that excluding 8 subjects from bioequivalence statistics was based on a valid scientific rationale and complied with the protocol. However, you did not provide enough evidence to justify the effect of the differential amount of the evening meal consumed on the bioequivalence study for drugs to be given next morning after an overnight fast. In addition, the reviewer did not find such exclusion criteria stated in the protocol. If the intention was to exclude these subjects, either these subjects should not have been dosed or their samples should not have been analyzed. Your exclusion of these subjects from final statistical analysis is not acceptable.

Osmotica takes note of the Agency's observation.

2. You submitted the statistical analysis results to demonstrate the test product bioequivalent to the innovator product after dropping subject 21. However, the DBE disagrees with your conclusion of dropping subject 21 from the final statistical analysis. Using the differential amount of the evening meal consumed by subject 21 as a justification for excluding this subject from the statistical analysis is not acceptable.

Osmotica believes that subject 21 should be dropped from the final statistical analysis. However, the rationale for doing so is not based on the amount of evening meal

RECEIVED
AUG 08 2006
OGD / CDER

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

consumed by the subject. Instead, the reason for doing is based on the practice currently accepted by DBE for handling of outlier subjects.

Subsequent to the March 16, 2006 amendment, Osmotica was able to redose this subject and control subjects from the previous study with the same product lots dosed in R04-0598 to confirm that subject #21 was, indeed, an outlier. The following table summarizes the Test/Reference Percent Ratios from study R04-0598 previously submitted in the application and study R-06-0666, the rechallenge study, for the subjects involved. The final report for the rechallenge study is provided as an Attachment.

		R04-0598			R06-0666	
Subject #	AUC 0-t %	AUC inf %	Cmax %	AUC 0-t %	AUC inf %	Cmax %
1	90.94	90.53	95.24	108.77	115.11	82.27
16	104.43	97.37	133.72	92.33	70.63	180.44
21	1.82	1.95	9.80	71.94	71.95	79.15
32	78.43	***	67.70	84.35	113.53	37.54
61	88.18	88.54	85.22	135.59	155.65	129.12
74	93.19	106.00	118.90	108.78	119.22	134.99
Range- all subjects*	47.47-223.22	47.03-280.99	42.64-225.92			

*except subject #21

In the rechallenge study, it is apparent that subject 21 responded within the range of expected values (see above table). Therefore, in accordance with Agency recommendations, subject 21 should be excluded from the bioequivalence calculations of study R04-0598. Exclusion of Subject 21 results in the 90% confidence intervals for the geometric mean test/reference area and Cmax ratios being inside the acceptable limits of 80% to 125%. The test product is, therefore, shown to be bioequivalent to the innovator product. The statistics for study R04-0598 with only subjects 32 and 21 excluded are also included on page 216 of Appendix C of the Attachment. Please note that subject 32 vomited and exclusion of this subject was previously deemed acceptable by the Agency.

3. Your dissolution testing in 50 mL water, at 37° using USP Apparatus 7 at 15-30 cycles per minute is acceptable. However, you proposed to change the dissolution specification at 24 hour time point from (b) (4) %. The DBE will not change the specification at 24 hr as fresh bio-lot meets the DBE-recommended specifications at L1. Please acknowledge your acceptance of the following FDA-recommended dissolution specifications:

4 hours: (b) (4)
12 hours:
24 hours:

Osmotica requests a teleconference with the Agency to discuss the recommended dissolution specifications. If Osmotica is to accept the specifications recommended by

the Agency, further information is needed regarding the scientific rationale behind them. Not only would this information be useful for Osmotica to accept the Agency recommendation, but it would also assist Osmotica is setting appropriate dissolution specifications in future applications.

For example, Osmotica would like to understand how the range is established for the 12 hour test interval, especially when compared to current dissolution specifications for Nifedipine Extended-release products in the USP. The Agency's recommended specification has a significantly (b) (4) range than the current USP specifications. Osmotica would prefer to comply with the specifications established in USP Test 5 for Nifedipine Extended-release Tablets.

All of the dissolution specifications noted in the table below are for the 12 hour test interval of a 24 hour product with testing performed in USP Apparatus 7.

	Specification	Range
USP Test 1	43% to 80%	37%
USP Test 5	39% to 75%	36%
Agency Recommendation	(b) (4)	

Please contact the undersigned to establish a date and time for the requested teleconference and for questions and additional information.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

Osmotica Pharmaceutical

October 20, 2006

ORIG AMENDMENT
N-AB

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

Abbreviated New Drug Application 77-410
Nifedipine Extended-release Tablets, 90 MG USP

RECEIVED
OCT 2 3 2006
OGD / CDER

BIOEQUIVALENCY AND CHEMISTRY AMENDMENT

Dear Mr. Buehler,

Please refer to the Agency fax containing bioequivalency deficiencies received October 19, 2006. This amendment addresses all of the issues and is a complete response. Based upon the recommendation of Beth Fritsch, Project Manager in the DBE, this amendment has been marked as both a bioequivalency amendment and a chemistry amendment based on the inclusion of stability data. For the ease of review, the comments are being provided along with the response.

1. The test lot was manufactured on 4/27/2004 while the re-dosing study was conducted between 06/06/2006 and 06/15/2006. Your proposed expiration dating period is 24 months based on 3 months accelerated stability data. Therefore, please provide data to support that the test product is still within the expiration dating period when the re-dosing study was conducted.

The 24 month controlled room temperature stability for this lot was conducted in May 2006. The re-dosing study was conducted from June 6, 2006 to June 15, 2006 using lot P424401. Therefore, the 24 month stability data should be very representative of the condition of the test product at the time of dosing in the re-dosing study.

The table below lists key parameters between the initial release and 24 month stability point which represent the quality of the product in bottles of 100 (which were provided for dosing of the BE studies) at the time of the initial and re-dosing BE studies. There is nothing to suggest that the product had changed such that the BE data from the re-dosing study would not be acceptable for the purpose of demonstrating that subject 21 was an outlier in the first study, R04-0598. The complete 24 month stability data is presented in Attachment I.

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

	Specification	Initial (May-04)	May-06
Assay	(b) (4)	(b) (4)	
Total Impurities			
Drug Release			
4 hour (range)	NMT 14%		
12 hour (range)	39 - 75%		
24 hour (range)	NLT 75%		

2. Please acknowledge your acceptance of USP (Test 5) dissolution specifications of NMT 14% in 4 hours, 39-75% in 12 hours, and NLT 75% in 24 hours for your test product. In addition, please verify that the amount dissolved is expressed in terms of the labeled tablet strength rather than in terms of the labeled total contents.

Osmotica accepts the USP Test 5 dissolution specifications as noted. It is also verified that the dissolution is expressed in terms of the labeled tablet strength and not the amount of drug contained in the tablet. This is best demonstrated in the calculations in the Analytical Method AP-3260-02 provided in the original submission on page 4769. For ease of review, the pertinent page with the calculations is again provided in Attachment II.

Osmotica also acknowledges the three recommendations made by the DBE for any future application.

If there are any additional questions, please contact me at your convenience.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

Osmotica Pharmaceutical

November 30, 2006

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
AB

ORIGINAL

Abbreviated New Drug Application 77-410
Nifedipine Extended-release Tablets, 90 MG USP

BIOEQUIVALENCY AMENDMENT

Dear Mr. Buehler,

Please refer to the Agency fax containing bioequivalency deficiencies received October 19, 2006 and the response from Osmotica Pharmaceutical Corp dated October 20, 2006. Also, please refer to the Osmotica fax dated November 28, 2006 and the Agency fax dated November 30, 2006.

RECEIVED
DEC 01 2006
OGD/CDER

The information requested in the November 30th Agency fax was provided in the fax from Osmotica two days prior in the fax to the Agency dated November 28th. For ease of review, Osmotica is restating the Agency concern and resubmitting this information.

1. **The data you submitted in this amendment are incomplete. Your test product has a tentative 24-month expiration dating based on 3-month accelerated stability data. Since the amount of time elapsed between the manufacturing date of your test product and the re-dosing date exceeds the 24-month stability testing period, please submit data for your test product that demonstrates stability for 26 months or longer.**

In the Osmotica response dated October 20, 2006, Osmotica presented controlled-room temperature stability data for the 24 month controlled room temperature stability conducted in May 2006 for the test lot in bottles of 100 (which was what was provided to the clinical site).

In the Osmotica fax dated November 28, 2006, stability data was provided for controlled-room temperature samples pulled from the stability chambers and tested at 29 months. The key results are noted in the table below for the initial release, 24 month stability point, and a 29 month stability point, tested in October, 2006.

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

	Specification	May-04 Initial	May-06 24 Month	Oct-06 29 Month
	(b) (4)	(b) (4)		
Assay				
Total Impurities				
Drug Release				
4 hour (range)	NMT 14%			
12 hour (range)	39 - 75%			
24 hour (range)	NLT 75%			

This data confirms that the test product was still within specifications when the re-dosing study was conducted. The complete stability data for this biolot is attached.

This information fully addresses the issue noted and Osmotica believes that all issues with the ANDA 77-410 have been addressed and that a tentative approval may be issued as soon as possible.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

Osmotica Pharmaceutical

September 20, 2007

RECEIVED
SEP 21 2007
OGD

N/MC

Gary J. Buehler, MD
Director, Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

RE: Minor Amendment – Final Approval Requested - ANDA 77-410

Dear Dr. Buehler,

Please refer to ANDA 77-410 for Nifedipine Extended-release Tablets, USP 90 mg, specifically the Tentative Approval Letter dated December 28, 2006.

Osmotica is requesting final approval for ANDA 77-410 based on the following information:

- As stated in the Tentative Approval Letter, Martec Scientific, Inc. was eligible for 180-day exclusivity. This exclusivity was never triggered. However, Martec has recently relinquished their rights to the exclusivity eligibility. Provided in Attachment I is a copy of the letter sent to the Agency from Martec.
- No changes to labeling of the reference listed drug have been made since the date of tentative approval. As a point of reference, the labeling publicly available on the Pfizer website for Procardia XL® has a revision date of August 2003. There have been two minor changes made regarding the chemistry, manufacturing and control information, both of which are of an annual reportable nature, that are reflected in the labeling of the Osmotica product.
    - The ANDA originally contained two packaging configurations, bottles of 100 and 500 tablets. In addition to these packaging sizes, the product is also being marketed in bottles of 300 tablets. This new packaging size is appropriate in that the container closure system for all three sizes is the same and the components are from the same suppliers.

      All of the closures are similar polypropylene caps with a (b) (4) induction seal liners. The containers are all similar white opaque HDPE bottles comprised of (b) (4) resin (150cc bottle for 100 tablets, 500cc bottle for 300 tablets, 750cc bottle for 500 tablets). All three sizes contain identical desiccants. Therefore, the stability of the new package

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

size is bracketed within that which was submitted in the application. The post approval stability program has been revised to consider this new package size as well.

Please also note that the new container closure system for the 300 count bottle of the 90 mg strength is identical to that used for the 1000 count bottle of Nifedipine Extended-release Tablets 30 mg approved in ANDA 77127. This change for the 90 mg strength would be appropriate as an annual reportable change. The specifications for the new container closure system are provided in Attachment II.

- Also, since the time of the tentative approval, (b) (4), the manufacturer of the ink used for imprinting upon the tablets, changed the formulation of the ink. However, this change was only the deletion of an ingredient ((b) (4) and a change from (b) (4) (both of which are (b) (4)). Therefore, the listing of the inactive ingredients in the labeling no longer includes (b) (4) This change would also be appropriate as an annual report.

The new labeling, which incorporates these changes, is provided in Attachment III. The change in the package sizes listed in the How Supplied Section and the listing of the inert ingredients are the only changes to the labeling.

- (b) (4) the drug product manufacturer and testing facility, continues to have an acceptable current Good Manufacturing Practices status. This site was inspected (b) (4) by (b) (4) National Expert Pharmaceutical Inspections and (b) (4) FDA Investigator. No FDA-483 observations were provided following this inspection.

If you have any questions, please feel free to call me at 910.509.0114.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

9.1

Osmotica Pharmaceutical

Labeling review
Initial 10/1/07
A Vezza

N-000-AF

September 28, 2007

Gary J. Buehler, MD
Director, Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

RE: Final Printed Labeling - ANDA 77-410

Dear Dr. Buehler,

Please refer to Osmotica's ANDA 77-410 for Nifedipine Extended-release Tablets, USP 90 mg , specifically the Tentative Approval Letter dated December 28, 2006 and the Minor - Amendment – Final Approval Requested letter dated September 18, 2007. This correspondence is in regards to the phone call between Dr. Adolph Vezza and myself.

During the phone call, the Agency has requested final printed labeling. The final printed labeling is provided.

If you have any questions, please feel free to call me at 910.509.0114.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

RECEIVED

OCT 01 2007

OGD

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

OGD APPROVAL ROUTING SUMMARY

ANDA # 77410 Applicant Osmotica Pharmaceutical Corp.
Drug Nifedipine Extended-release Tablets USP Strength(s) 90 mg

APPROVAL ☐ **TENTATIVE APPROVAL** ☒ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 12/12/2006 Date 12/28/06
Chief, Reg. Support Branch Initials MHS Initials rlw/for

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = _____ NDA# 19-684
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: TA
Comments: PIV to the '446 and not sued within 45 days. Martec with ANDA 75-414 was approved 3/23/2004 and granted 180 day exclusivity. Martec has not triggered their exclusivity and therefore will block Osmotica from receiving a Full Approval.

2. Project Manager, Esther Chuh Team 2 Date 12/11/2006 Date _____
Review Support Branch Initials EC Initials _____

Original Rec'd date 12/1/2004
Date Acceptable for Filing 12/1/2004
Patent Certification (type) IV
Date Patent/Exclus.expires 11/23/2010
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 12/14/2006
Date of Office Bio Review 12/1/2006
Date of Labeling Approv. Sum 12/18/2006
Date of Sterility Assur. App. n/a
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Acceptable Bio reviews tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date 12/18/06 Date 12/18/06
Name/Initials Adolph Vezza/aev Name/Initials chp

Comments:

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 12/18/06
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DTR
Comments: Apparently an "approval" (not a TA) template was use in the preparation of the letter. PM contacted re making necessary changes.

5. Div. Dir./Deputy Dir. Date 12/19/06
Chemistry Div. II Initials RCA

Comments: CMC OK, see attached spreadsheet.

6. Frank Holcombe **First Generics Only** Date 12/28/06
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. Martec's ANDA 75-414 for this drug product was approved on March 23, 2004. Upon approval, Martec was granted 180-day generic drug exclusivity. Martec has not "triggered" this exclusivity.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Procardia XL Extended-release Tablets 90 mg NDA 19-684 (003)
Pfizer Laboratories

8. Peter Rickman Date 12/28/06
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Bioequivalence study (fasting) found acceptable 12/1/06 (DFS). Dissolution testing also found acceptable (Test 5). Waiver for fed study granted based upon acceptable fed and fasting studies under "sister" ANDA 77-127 for the 30 mg and 60 mg strengths. Bio study sites have acceptable DSI inspection histories. Bio endorsed in DFS by B. Davit.

FPL found acceptable for approval 7/27/06 (as endorsed 12/18/06 above).

CMC found acceptable for approval (chemistry review #2) 12/12/06 DFS.

Note: This is the "sister" ANDA to Osmotica's ANDA 77-127 for the 30 mg And 60 mg tablet strengths.

OR

8. Robert L. West Date 12/28/06
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 12/14/06 (Verified 12/28/06). No "OAI" Alerts noted.

Osmotica made a paragraph 4 certification to the '446 patent, but was not sued within the 45-day period. However, Osmotica's ANDA may not be approved at this time because Martec has not triggered its 180-day generic drug exclusivity for this drug product (90 mg) under its approved ANDA 75-414. There are no other unexpired patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDa is recommended for tentative approval.

9. Gary Buehler Date 12/28/06
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Esther Chuh Team 2 Date 12/28/2006

Review Support Branch Initials EC
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

10:25 AM Time notified of approval by phone
10:25 AM Time approval letter faxed

FDA Notification:
12/28/2006 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/28/2006 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Esther Chuh
12/28/2006 01:31:19 PM

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-410 Applicant Osmotica Pharmaceutical Corp.
Drug Nifedipine Extended-release Tablets USP Strength(s) 90 mg

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 27 Sept 07 Date 10/3/07
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = _____ NDA# 19-684 (003)
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked N/A
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval
Comments: Firm filed PIV cert to the '446 notified and was not sued within 45 days. ANDA was TA'd on 12/28/2006. No changes to patent or exclusivity status for the RLD, Procardia XL 90 mg. Martec the sponsor of ANDA 75414 has relinquished their eligibility for 180 day exclusivity for this drug product. This ANDA is eligible for Full Approval.

2. Project Manager, Esther Chuh Team 2 Date 9/20/2007 Date 10/2/2007
Review Support Branch Initials ec Initials ec

Original Rec'd date 12/1/2004
Date Acceptable for Filing 12/1/2004
Patent Certification (type) IV
Date Patent/Exclus.expires Martec relinquished their 180 days exclusivity
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 12/14/2006
Date of Office Bio Review 12/1/2006
Date of Labeling Approv. Sum 10/1/2007
Date of Sterility Assur. App. n/a
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date 10/2/2007 Date 10/3/07
Name/Initials Adolph Vezza Name/Initials rlw/for

Comments:
FPL is acceptable for approval.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 10/1/07
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DTR
Comments: Changes to AP ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date rmp
Chemistry Div. I Initials 10/2/07

Comments: It was previously TAed by the DCII. The CMC section as amended is satisfactory for AP.

6. Frank Holcombe **First Generics Only** Date 10/3/07
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. This ANDA was granted tentative approval on December 28, 2006. Martec's ANDA 75-414 for this drug product was approved on March 23, 2004. Upon approval, Martec was granted 180-day generic drug exclusivity for the 90 mg extended-release tablet. Martec did not "trigger" its exclusivity. Martec provided a letter to the agency dated September 20, 2007, whereby Martec relinquishes its eligibility for 180-day exclusivity for the 90 mg tablet strength.

7. Vacant Date _____
Deputy Dir., DLPS Initials _____
RLD = Procardia XL Extended-release Tablets 90 mg
Pfizer Laboratories NDA 19-684 (003)

8. Peter Rickman Date 10/3/06
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: This ANDa was granted tentative approval on December 28, 2006. Final approval was blocked at that time by Martec's eligibility for 180-day generic drug exclusivity under ANDA 75-414. Refer to the administrative sign-off form completed at that time. On September 20, 2007, Osmotica submitted a minor amendment to request final approval of this ANDA based upon Martec's relinquishment of its entitlement to 180-day generic drug exclusivity for the 90 mg tablet strength. Minor CMC updates were also proposed at that time. On September 25, 2007, Osmotica submitted a minor CMC amendment in response to a telephone inquiry from the review chemist. On September 28, 2007, Osmotics submitted updated final-printed labeling.

FPL found acceptable for approval 10/1/07 (in DFS), as endorsed 10/2/07, above.

CMC found acceptable for final approval (Chemistry Rev iew #3) in DFS.

OR

8. Robert L. West Date 10/3/07
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EEs dated 12/14/06 (Verified 10/3/07). No "OAI" Alerts noted.

Refer to the information provided above my M.Shimer as the regulatory basis for the approval of this ANDA. Martec has relinquished its previously granted eligibility for 180-day generic drug exclusivity for this drug procuct (90 mg strength).

There are no other patents or exclusivity listed in the current "Orange Book" for this drug product.

With the relinquishment of 180-day generic drug exclusivity by Martec, this ANDA is recommended for final approval.

9. Gary Buehler Date 10/3/07
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

Press Release Acceptable ☐

10. Project Manager, Esther Chuh Team 2 Date10/3/2007

Review Support Branch Initials ec

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

1:09 PM Time notified of approval by phone

1:18 PM Time approval letter faxed

FDA Notification:

10/3/2007 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

10/3/2007 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Esther Chuh
10/3/2007 01:24:26 PM