CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75136

APPROVAL LETTER

ANDA 75-136

OCT 20 1998

Abbott Laboratories
Attention: Thomas F. Willer, Ph.D.
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, IL 60064-3537

Dear Sir:

This is in reference to your abbreviated new drug application dated May 23, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Verapamil Hydrochloride Injection USP, 2.5 mg/mL, (4 mL fill in a 5 mL plastic syringe).

Reference is also made to your amendments dated February 6, March 6, and October 8, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Verapamil Hydrochloride Injection USP, 2.5 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Isoptin Injection, 2.5 mg/mL, of Knoll Pharmaceutical Company).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253

(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

10/20/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75136

DRAFT FINAL PRINTED LABELING

VERAPAMIL HYDROCHLORIDE Injection, USP

Abboject® Unit-of-Use Syringe
Abboject®-PA Syringe
Ansyr™ Plastic Syringe
Ampul
Fliptop Vial
Protect from light.

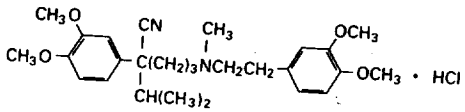
OCT 20 1988

DESCRIPTION

Verapamil hydrochloride is a calcium antagonist or slow-channel inhibitor. Verapamil Hydrochloride Injection, USP is a sterile, nonpyrogenic solution containing verapamil hydrochloride 2.5 mg/mL and sodium chloride 8.5 mg/mL in water for injection. The solution contains no bacteriostat or antimicrobial agent and is intended for single-dose intravenous administration. May contain hydrochloric acid for pH adjustment; pH is 4.9 (4.0 to 6.5).

The chemical name of Verapamil Hydrochloride, USP is benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl] methylamino] propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride. Verapamil hydrochloride is a white or practically white crystalline powder. It is practically odorless and has a bitter

taste. It is soluble in water; freely soluble in chloroform; sparingly soluble in alcohol; practically insoluble in ether. It has the following structural formula:



Molecular weight: 491.07

Molecular formula: $C_{27}H_{38}N_2O_4 \cdot HCl$

Verapamil hydrochloride is not chemically related to other antiarrhythmic drugs.

The plastic syringe is molded from a specially formulated polypropylene. Water permeates from inside the container at an extremely slow rate which will have an insignificant effect on solution concentration over the expected shelf life. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the syringe material.

CLINICAL PHARMACOLOGY

Mechanism of Action: Verapamil inhibits the calcium ion (and possibly sodium ion) influx through slow channels into conductile and contractile myocardial cells and vascular smooth muscle cells. The antiarrhythmic effect of verapamil appears to be due to its effect on the slow channel in cells of the cardiac conduction system. The vasodilatory effect of verapamil appears to be due to its effect on blockade of calcium channels as well as α receptors.

In the isolated rabbit heart, concentrations of verapamil that markedly affect SA nodal fibers or fibers in the upper and middle regions of the AV node have very little effect on fibers in the lower AV

node (NH region) and no effect on atrial action potentials or His bundle fibers.

Electrical activity in the SA and AV nodes depends, to a large degree, upon calcium influx through the slow channel. By inhibiting this influx, verapamil slows AV conduction and prolongs the effective refractory period within the AV node in a rate-related manner. This effect results in a reduction of the ventricular rate in patients with atrial flutter and/or atrial fibrillation and a rapid ventricular response.

By interrupting reentry at the AV node, verapamil can restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardias (PSVT), including PSVT associated with Wolff-Parkinson-White syndrome.

Verapamil does not induce peripheral arterial spasm.

Verapamil has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

Verapamil does not alter total serum calcium levels.

Hemodynamics: Verapamil reduces afterload and myocardial contractility. The commonly used intravenous doses of 5 to 10 mg verapamil hydrochloride produce transient, usually asymptomatic, reduction in normal systemic arterial pressure, systemic vascular resistance and contractility; left ventricular filling pressure is slightly increased. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload, and cardiac index is usually not reduced, but in patients with moderately severe to severe cardiac dysfunction (pulmonary wedge pressure above 20 mm Hg, ejection fraction less than 30%), acute worsening of heart failure may be seen. Peak therapeutic effects occur within 3 to 5 minutes after a bolus injection.

Pharmacokinetics: Intravenously administered verapamil hydrochloride has been shown to be rapidly metabolized. Following intravenous infusion in man, verapamil is eliminated bi-exponentially,

with a rapid early distribution phase (half-life about 4 minutes) and a slower terminal elimination phase (half-life 2 to 5 hours). In healthy men, orally administered verapamil hydrochloride undergoes extensive metabolism in the liver, with 12 metabolites having been identified, most in only trace amounts. The major metabolites have been identified as various N- and O-dealkylated products of verapamil. Approximately 70% of an administered dose is excreted in the urine and 16% more in the feces within 5 days. About 3% to 4% is excreted as unchanged drug.

Aging may affect the pharmacokinetics of verapamil given to hypertensive patients. Elimination half-life may be prolonged in the elderly.

INDICATIONS AND USAGE

Verapamil Hydrochloride Injection, USP is indicated for the following:

- Rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory bypass tracts (Wolff-Parkinson-White [W-P-W] and Lown-Ganong-Levine [L-G-L] syndromes). When clinically advisable, appropriate vagal maneuvers (e.g., Valsalva maneuver) should be attempted prior to verapamil hydrochloride administration.
- Temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation except when the atrial flutter and/or atrial fibrillation are associated with accessory bypass tracts (Wolff-Parkinson-White (W-P-W) and Lown-Ganong-Levine (L-G-L) syndromes).

In controlled studies in the United States, about 60% of patients with supraventricular tachycardia converted to normal sinus rhythm within 10 minutes after intravenous verapamil hydrochloride. Uncontrolled studies reported in the world literature describe a conversion rate of about 80%. About 70% of patients with atrial flutter and/or fibrillation with a faster ventricular rate respond with a decrease in ventricular rate of at least 20%. Conversion of atrial flutter or fibrillation to sinus rhythm is uncommon (about 10%) after

verapamil hydrochloride and may reflect the spontaneous conversion rate, since the conversion rate after placebo was similar. Slowing of the ventricular rate in patients with atrial fibrillation/flutter lasts 30 to 60 minutes after a single injection.

Because a small fraction (<1%) of patients treated with verapamil hydrochloride respond with life-threatening adverse responses (rapid ventricular rate in atrial flutter/fibrillation, and an accessory bypass tract, marked hypotension, or extreme bradycardia/asystole – see CONTRAINDICATIONS and WARNINGS), the initial use of verapamil hydrochloride injection should, if possible, be in a treatment setting with monitoring and resuscitation facilities, including D.C.-cardioversion capability (see ADVERSE REACTIONS, Suggested Treatment of Acute Cardiovascular Adverse Reactions). As familiarity with the patient's response is gained, use in an office setting may be acceptable.

Cardioversion has been used safely and effectively after verapamil hydrochloride injection.

CONTRAINDICATIONS

Verapamil hydrochloride injection is contraindicated in:

1. Severe hypotension or cardiogenic shock.
2. Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker).
3. Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).
4. Severe congestive heart failure (unless secondary to a supraventricular tachycardia amenable to verapamil therapy).
5. Patients receiving **intravenous** beta-adrenergic blocking drugs (e.g., propranolol). **Intravenous** verapamil and **intravenous** beta-adrenergic blocking drugs should not be administered in close proximity to each other (within a few hours), since both may have a depressant effect on myocardial contractility and AV conduction.
6. Patients with atrial flutter or atrial fibrillation and an accessory

bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes) are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil is administered. Therefore, the use of verapamil in these patients is contraindicated.

7. Ventricular tachycardia: Administration of intravenous verapamil to patients with wide-complex ventricular tachycardia (QRS ≥ 0.12 sec) can result in marked hemodynamic deterioration and ventricular fibrillation. Proper pretherapy diagnosis and differentiation from wide-complex supraventricular tachycardia is imperative in the emergency room setting.
8. Known hypersensitivity to verapamil hydrochloride.

WARNINGS

VERAPAMIL HYDROCHLORIDE SHOULD BE GIVEN AS A SLOW INTRAVENOUS INJECTION OVER AT LEAST A TWO-MINUTE PERIOD OF TIME (see DOSAGE AND ADMINISTRATION).

Hypotension: Verapamil hydrochloride injection often produces a decrease in blood pressure below baseline levels that is usually transient and asymptomatic but may result in dizziness. Systolic pressure less than 90 mm Hg and/or diastolic pressure less than 60 mm Hg was seen in 5% to 10% of patients in controlled U.S. trials in supraventricular tachycardia and in about 10% of the patients with atrial flutter/fibrillation. The incidence of symptomatic hypotension observed in studies conducted in the U.S. was approximately 1.5%. Three of the five symptomatic patients required intravenous pharmacologic treatment (norepinephrine bitartrate, metaraminol bitartrate, or 10% calcium gluconate). All recovered without sequelae.

Extreme Bradycardia/Asystole: Verapamil hydrochloride affects the AV and SA nodes and rarely may produce second- or third-degree AV block, bradycardia, and, in extreme cases, asystole. This is more likely to occur in patients with a sick sinus syndrome (SA nodal

disease), which is more common in older patients. Bradycardia associated with sick sinus syndrome was reported in 0.3% of the patients treated in controlled double-blind trials in the U.S. The total incidence of bradycardia (ventricular rate less than 60 beats/min) was 1.2% in these studies. Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less), with spontaneous return to AV nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately. (See ADVERSE REACTIONS and Suggested Treatment of Acute Cardiovascular Adverse Reactions.)

Heart Failure: When heart failure is not severe or rate related, it should be controlled with digitalis glycosides and diuretics, as appropriate, before verapamil is used. In patients with moderately severe to severe cardiac dysfunction (pulmonary wedge pressure above 20 mm Hg, ejection fraction less than 30%), acute worsening of heart failure may be seen.

Concomitant Antiarrhythmic Therapy:

Digitalis: Verapamil hydrochloride injection has been used concomitantly with digitalis preparations without the occurrence of serious adverse effects. However, since both drugs slow AV conduction, patients should be monitored for AV block or excessive bradycardia.

Procainamide: Verapamil hydrochloride injection has been administered to a small number of patients receiving oral procainamide without the occurrence of serious adverse effects.

Quinidine: Verapamil hydrochloride injection has been administered to a small number of patients receiving oral quinidine without the occurrence of serious adverse effects. However, three patients have been described in whom the combination resulted in an exaggerated hypotensive response presumably from the combined ability of both drugs to antagonize the effects of catecholamines on α-adrenergic receptors. Caution should therefore be used when employing this

combination of drugs.

Beta-Adrenergic Blocking Drugs: Verapamil hydrochloride injection has been administered to patients receiving oral beta-blockers without the development of serious adverse effects. However, since both drugs may depress myocardial contractility and AV conduction, the possibility of detrimental interactions should be considered. The concomitant administration of **intravenous** beta-blockers and **intravenous** verapamil has resulted in serious adverse reactions (see CONTRAINDICATIONS), especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Disopyramide: Until data on possible interactions between verapamil and all forms of disopyramide phosphate are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide: A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects reducing myocardial contractility, prolonging AV conduction, and prolonging repolarization.

Heart Block: Verapamil prolongs AV conduction time. While high-degree AV block has not been observed in controlled clinical trials in the United States, a low percentage (less than 0.5%) has been reported in the world literature. Development of second- or third-degree AV block or unifascicular, bifascicular, or trifascicular bundle branch block requires reduction in subsequent doses or discontinuation of verapamil and institution of appropriate therapy, if needed. (See ADVERSE REACTIONS, Suggested Treatment of Acute Cardiovascular Adverse Reactions.)

Hepatic and Renal Failure: Significant hepatic and renal failure should not increase the effects of a single intravenous dose of verapamil hydrochloride but may prolong its duration. Repeated injections of verapamil hydrochloride injection in such patients may

lead to accumulation and an excessive pharmacologic effect of the drug. There is no experience to guide use of multiple doses in such patients, and this generally should be avoided. If repeated injections are essential, blood pressure and PR interval should be closely monitored and smaller repeat doses should be utilized. Verapamil cannot be removed by hemodialysis.

Premature Ventricular Contractions: During conversion to normal sinus rhythm, or marked reduction in ventricular rate, a few benign complexes of unusual appearance (sometimes resembling premature ventricular contractions) may be seen after treatment with verapamil hydrochloride. Similar complexes are seen during spontaneous conversion of supraventricular tachycardias after D.C.-cardioversion and other pharmacologic therapy. These complexes appear to have no clinical significance.

Duchenne's Muscular Dystrophy: Verapamil hydrochloride injection can precipitate respiratory muscle failure in these patients and should, therefore, be used with caution.

Increased Intracranial Pressure: Verapamil hydrochloride injection has been seen to increase intracranial pressure in patients with supratentorial tumors at the time of anesthesia induction. Caution should be taken and appropriate monitoring performed.

PRECAUTIONS

Drug Interactions: (See WARNINGS: Concomitant Antiarrhythmic Therapy.) Verapamil hydrochloride injection has been used concomitantly with other cardioactive drugs (especially digitalis) without evidence of serious negative drug interactions. In rare instances, including when patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction were given **intravenous** beta-adrenergic blocking agents or disopyramide concomitantly with **intravenous** verapamil, serious adverse effects have occurred. Concomitant use of verapamil hydrochloride with ß-adrenergic blockers may result in an exaggerated hypotensive

response. Such an effect was observed in one study, following the concomitant administration of verapamil and prazosin. It may be necessary to decrease the dose of verapamil and/or dose of the neuromuscular blocking agent when the drugs are used concomitantly. As verapamil is highly bound to plasma proteins, it should be administered with caution to patients receiving other highly protein-bound drugs.

Other

Cimetidine: The interaction between cimetidine and chronically administered verapamil has not been studied. In acute studies of healthy volunteers, clearance of verapamil was either reduced or unchanged.

Lithium: Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy with either no change or an increase in serum lithium levels. The addition of verapamil, however, has also resulted in the lowering of serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs must be monitored carefully.

Carbamazepine: Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital: Phenobarbital therapy may increase verapamil clearance.

Cyclosporin: Verapamil therapy may increase serum levels of cyclosporin.

Inhalation Anesthetics: Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists (such as verapamil)

should be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents: Clinical data and animal studies suggest that verapamil may potentiate the activity of depolarizing and nondepolarizing neuromuscular blocking agents. It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Dantrolene: Two animal studies suggest concomitant intravenous use of verapamil and dantrolene sodium may result in cardiovascular collapse. There has been one report of hyperkalemia and myocardial depression following the coadministration of oral verapamil and intravenous dantrolene.

Pregnancy: Teratogenic Effects: *Pregnancy Category C.* Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively, and have revealed no evidence of teratogenicity. In the rat, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: There have been few controlled studies to determine whether the use of verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of verapamil hydrochloride injection in Europe in the treatment of

cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

Nursing Mothers: Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. Also, verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

Pediatric Use: Controlled studies with verapamil have not been conducted in pediatric patients, but uncontrolled experience with intravenous administration in more than 250 patients, about half under 12 months of age and about 25% newborn, indicates that results of treatment are similar to those in adults. **In rare instances, however, severe hemodynamic side effects – some of them fatal – have occurred following the intravenous administration of verapamil to neonates and infants. Caution should therefore be used when administering verapamil to this group of pediatric patients.** The most commonly used single doses in patients up to 12 months of age have ranged from 0.1 to 0.2 mg/kg of body weight, while in patients aged 1 to 15 years, the most commonly used single doses ranged from 0.1 to 0.3 mg/kg of body weight. Most of the patients received the lower dose of 0.1 mg/kg once, but in some cases, the dose was repeated once or twice every 10 to 30 minutes.

ADVERSE REACTIONS

The following reactions were reported with verapamil hydrochloride injection used in controlled U.S. clinical trials involving 324 patients:

Cardiovascular: Symptomatic hypotension (1.5%); bradycardia (1.2%); severe tachycardia (1.0%). The worldwide experience in open clinical trials in more than 7,900 patients was similar.

Central Nervous System Effects: Dizziness (1.2%); headache (1.2%). Although rare, occasional cases of seizures during verapamil injection have been reported.

Gastrointestinal: Nausea (0.9%); abdominal discomfort (0.6%).

In rare cases of hypersensitive patients, broncho/laryngeal spasm accompanied by itch and urticaria has been reported.

The following reactions have been reported at low frequency: emotional depression, rotary nystagmus, sleepiness, vertigo, muscle fatigue, diaphoresis, and respiratory failure.

Suggested Treatment of Acute Cardiovascular Adverse Reactions*

The frequency of these adverse reactions was quite low, and experience with their treatment has been limited.

Adverse Reaction	Proven Effective Treatment	Supportive Treatment
1. Symptomatic hypotension requiring treatment	Dopamine I.V. Calcium chloride I.V. Norepinephrine bitartrate I.V. Metaraminol bitartrate I.V. Isoproterenol HCl I.V.	Intravenous fluids Trendelenburg position
2. Bradycardia, AV block, Asystole	Isoproterenol HCl I.V. Calcium chloride I.V. Norepinephrine bitartrate I.V. Atropine I.V. Cardiac pacing	Intravenous fluids (slow drip)
3. Rapid ventricular rate (due to antegrade conduction in flutter/fibrillation with W-P-W or L-G-L syndromes)	DC-cardioversion (high energy may be required) Procainamide I.V. Lidocaine I.V.	Intravenous fluids (slow drip)

*Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

OVERDOSAGE

Treatment of overdosage should be supportive and individualized. Beta-adrenergic stimulation and/or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been effectively used in treatment of deliberate overdosage with oral verapamil hydrochloride. Verapamil cannot be removed by hemodialysis.

Clinically significant hypotensive reactions or high-degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including isoproterenol hydrochloride, other vasopressor agents, or cardiopulmonary resuscitation (see ADVERSE REACTIONS: Suggested Treatment of Acute Cardiovascular Adverse Reactions).

DOSAGE AND ADMINISTRATION

FOR INTRAVENOUS USE ONLY. VERAPAMIL HYDROCHLORIDE INJECTION SHOULD BE GIVEN AS A SLOW INTRAVENOUS INJECTION OVER AT LEAST A TWO-MINUTE PERIOD OF TIME UNDER CONTINUOUS ELECTROCARDIOGRAPHIC (ECG) AND BLOOD PRESSURE MONITORING. The recommended intravenous doses of verapamil hydrochloride injection are as follows:

Adult:

Initial dose – 5 to 10 mg (0.075 to 0.15 mg/kg body weight) given as an intravenous bolus over at least 2 minutes.

Repeat dose – 10 mg (0.15 mg/kg body weight) 30 minutes after the first dose if the initial response is not adequate. An optimal interval for subsequent I.V. doses has not been determined, and should be individualized for each patient.

Older patients – The dose should be administered over at least 3 minutes to minimize the risk of untoward drug effects.

Pediatric:

Initial dose:

0 to 1 year: 0.1 to 0.2 mg/kg body weight (usual single dose range:

0.75 to 2 mg) should be administered as an intravenous bolus over at least 2 minutes **under continuous ECG monitoring**.

1 to 15 years: 0.1 to 0.3 mg/kg body weight (usual single dose range: 2 to 5 mg) should be administered as an intravenous bolus over at least 2 minutes. **Do not exceed 5 mg.**

Repeat dose:

0 to 1 year: 0.1 to 0.2 mg/kg body weight (usual single dose range: 0.75 to 2 mg) 30 minutes after the first dose if the initial response is not adequate (under continuous ECG monitoring). An optimal interval for subsequent I.V. doses has not been determined, and should be individualized for each patient.

1 to 15 years: 0.1 to 0.3 mg/kg body weight (usual single dose range: 2 to 5 mg) 30 minutes after the first dose if the initial response is not adequate. **Do not exceed 10 mg as a single dose.** An optimal interval for subsequent I.V. doses has not been determined, and should be individualized for each patient.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use only if solution is clear and vial seal is intact. Unused amount of solution should be discarded immediately following withdrawal of any portion of contents.

For stability reasons this product is not recommended for dilution with Sodium Lactate Injection, USP in polyvinyl chloride bags. Verapamil is physically compatible and chemically stable for at least 24 hours at 25°C protected from light in most common large volume parenteral solutions. Admixing intravenous verapamil hydrochloride with albumin, amphotericin B, hydralazine hydrochloride and trimethoprim with sulfamethoxazole should be avoided. Verapamil hydrochloride will precipitate in any solution with a pH above 6.0.

HOW SUPPLIED

Verapamil Hydrochloride Injection, USP 2.5 mg/mL is supplied in single-dose containers as follows:

List No.	Container	Volume	Total Content
4000	Abboject®-PA Syringe	2 mL	5 mg
4011	Ampul	2 mL	5 mg
1143	Abboject® Unit of Use Syringe	4 mL	10 mg
9633	ANSYR™ Plastic Syringe	4 mL	10 mg
1144	Fliptop Vial	2 mL	5 mg
		4 mL	10 mg

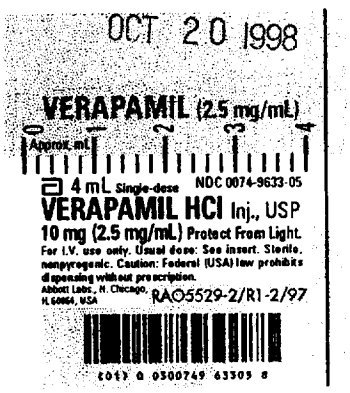
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Protect from light by retaining in package until ready to use.

Caution: Federal (USA) law prohibits dispensing without prescription.

Abboject® – Disposable prefilled syringe, Abbott

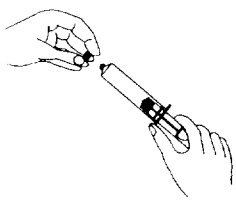
 RAO5752-R2-Rev. Jan., 1998 Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

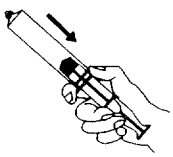

OCT 20 1998
VERAPAMIL (2.5 mg/mL)
Approx. mL
0
1
2
3
4
4 mL Single-dose
NDC 0074-9633-05
VERAPAMIL HCl Inj., USP
10 mg (2.5 mg/mL) Protect From Light.
For I.V. use only. Usual dose: See insert. Sterile, nonpyrogenic. Caution: Federal (USA) law prohibits dispensing without prescription.
Abbott Labs., N. Chicago, IL 60064, USA
RAO5529-2/R1-2/97
(01) 0 0300749 63309 8

USE ASEPTIC TECHNIQUE

1. Remove luer cover.



2. Pull the barrel down until air is expelled from the syringe.



08-8553-2/R1-2/98
 Printed in USA

Abbott Laboratories
North Chicago, IL 60064, USA

VERAPAMIL HYDROCHLORIDE Injection, USP 10 mg

VERAPAMIL HYDROCHLORIDE Injection, USP 10 mg

VERAPAMIL
HYDROCHLORIDE
Injection, USP
10 mg

Ansyr™

LifeShield®

VERAPAMIL HYDROCHLORIDE Injection, USP 10 mg

(01) 1 030074 963305 5

VERAPAMIL
HYDROCHLORIDE Injection, USP
10 mg

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75136

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 75-136 DRUG PRODUCT: Verapamil Hydrochloride

FIRM:Abbott Laboratories DOSAGE FORM: Injection

STRENGTH: 2.5 mg/mL

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP certification is satisfactory (See Page 1-210 and 1-223).
EIR update : Acceptable on June 30, 1997.

BIO STUDY: Satisfactory.
The waiver of in vivo Bioequivalence study for the Verapamil Hydrochloride injection, 2.5 mg/mL, 4 mL in 5mL plastic syringe (lot#21-319-DK) is granted. (see Bio. Review by M. Park on 1-14- 1998).

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not required.This is USP drug. Method validation is acceptable by DE-DO on 5-6-1998.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
Containers used in the stability testing are the same as described in the container section.

Proposed market container/closures:

4 mL fill in 5 mL Plastic Syringe.

LABELING:
Satisfactory per A. Vezza on Aug 7, 1998.

STERILIZATION VALIDATION (IF APPLICABLE): ~~Pending~~ Satisfactory 8/28/98
Microbiology review is ~~pending for review~~ acceptable by J.L. McVey,

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Lot # 21-319-DK

Firm's source of NDS OK : Yes DMF#

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

Executed batch: Lot # 21-319-DK :

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

Proposed production batch:

Manufacturing process is the same as bio.stability.

rievwer: S.Basaran DATE:8-20-1998

Team Leader: U.Venkataram /S/ DATE:8-21-1998

7/25/98

ANDA 75-136

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-136

3. NAME AND ADDRESS OF APPLICANT
Abbott Laboratories
One Abbott Park Road
Abbott Park, IL 60064-3500

4. LEGAL BASIS FOR SUBMISSION
The listed drug is Isoptin® (Verapamil Hydrochloride), 10 mg/4mL single dose vial - Knoll Pharmaceuticals. Abbott Laboratories certifies that the patent has expired and that the drug is not entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Verapamil Hydrochloride

8. SUPPLEMENT(s) PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: May 23, 1997
Amendment February 6, 1998
FDA:
Letter (Plastic Syringes): September 3, 1996
Acknowledgement: July 7, 1997
Deficiency letter: January 8, 1998
Bio. Acceptable letter: January 14, 1998

10. PHARMACOLOGICAL CATEGORY
Calcium antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 70-739 Verapamil HCl 2.5 mg/mL - glass syringe (2 mL)
ANDA 70-740 Verapamil HCl 2.5 mg/mL - glass syringe (4 mL)
ANDA 70-737 Verapamil HCL 2.5 mg/mL - 2 mL & 4 mL vials
ANDA 70-737 Verapamil HCl 2.5 mg/mL - 2 mL & 4 mL ampules
DMF
DMF
DMF
LOAs included for DMFs

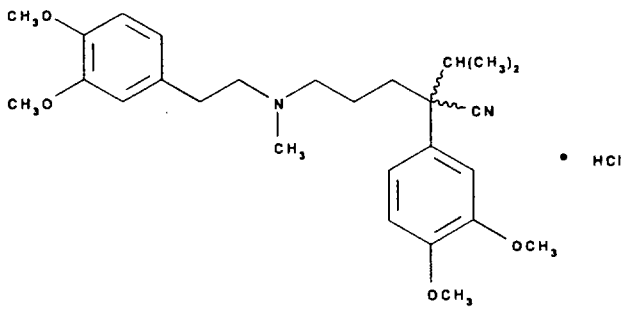
13. DOSAGE FORM
Injection

14. POTENCY
2.5 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Verapamil Hydrochloride USP

$C_{27}H_{38}N_2O_4.HCl$; M.W. = 491.07



(±)-5-[(3,4-Dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile monohydrochloride.
CAS [152-11-4]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. There are four approved ANDA for Abbott for verapamil hydrochloride 2.5 mg/mL in glass syringes, ampules and vials.
b. The microbiological review was found acceptable - J. McVey, HFD-640, ~~9/29/97~~ 8/27/98
c. The labeling review is acceptable as of 8/7/98.
d. The manufacturing process and controls procedures appear satisfactory.
e. The EIR is satisfactory - 6/30/97. Update requested.
f. The bio waiver request is granted on 1/14/98.

18. CONCLUSIONS AND RECOMMENDATIONS

The ANDA can be aproved when microbiological review and updated EIR are found satisfactory.

19. REVIEWER: Sema Basaran, Ph.D. DATE COMPLETED: 8-19-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75136

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD640

Microbiologists Review #1

September 29, 1997

A. 1. ANDA: **75-136**

APPLICANT: Abbott Laboratories
Hospital Products Division
Attention: Mr. Thomas F. Willer
200 Abbott Park Road
D-0389 AP30
Abbott Park, IL 60064-3537

2. PRODUCT NAME: **Verapamil Hydrochloride Injection, 2.5 mg/mL**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 4 mL in 5 mL plastic syringe for injection IV

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Calcium channel blocker. Antiarrhythmic.

B. 1. DATE OF INITIAL SUBMISSION: May 23, 1997.

2. DATE OF AMENDMENT: NA

3. RELATED DOCUMENTS: 18-485 is the innovator product manufactured by Knoll Pharmaceutics as Isoptin® . DMF for the facility may be referenced if the sections reproduced in this ANDA are not sufficient. Abbott refers to ANDA 75-005 for Iopamidol Injection for full data regarding the plastic syringe. 75-005 was reviewed by a Microbiologist and found acceptable on April 24, 1997 but not for parametric release. Fifty mL syringes were used for the Iopamidol. Abbott also references 75-092, 1% and 2% Lidocaine Injection, Plastic Syringes. The lidocaine application is the first generic drug review for parametric release of plastic syringes and a first review was completed on August 15, 1997.

C. REMARKS: Volume 1.2 has sterilization validation information.

D. CONCLUSIONS: The submissions are not recommended for approval on the basis of sterility assurance.

/S/ 9/30/97
James L. McVey

initialed by F. Fang or F. Holcombe 10/8/97

cc:

Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey

OFFICE OF GENERIC DRUGS, HFD640

Microbiologists Review #2

August 27, 1998

A. 1. ANDA: **75-136**

APPLICANT: Abbott Laboratories
Hospital Products Division
Attention: Mr. Thomas F. Willer
200 Abbott Park Road
D-0389 AP30
Abbott Park, IL 60064-3537

2. PRODUCT NAME: **Verapamil Hydrochloride Injection, 2.5 mg/mL**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 4 mL in 5 mL plastic syringe for injection IV

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Calcium channel blocker. Antiarrhythmic.

B. 1. DATE OF INITIAL SUBMISSION: May 23, 1997.

2. DATE OF AMENDMENT: **February 6, 1998. - subject of this review.**

3. RELATED DOCUMENTS: 18-485 is the innovator product manufactured by Knoll Pharmaceutics as Isoptin® . DMF for the facility may be referenced if the sections reproduced in this ANDA are not sufficient. Abbott refers to ANDA 75-005 for Iopamidol Injection for full data regarding the plastic syringe. 75-005 was reviewed by a Microbiologist and found acceptable on April 24, 1997 but not for parametric release. Fifty mL syringes were used for the Iopamidol. Abbott also references 75-092, 1% and 2% Lidocaine Injection, Plastic Syringes. The lidocaine application is the first generic drug review for parametric release of plastic syringes and a first review was completed on August 15, 1997.

C. REMARKS: Sufficient information has been provided to assure sterile manufacturing. Parametric release of 5 mL syringes is included.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance.

/S/ 8/27/98
James L. McVey

initialed by F. Fang or F. Holcombe 9/3/98

cc:

Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75136

BIOEQUIVALENCY REVIEW(S)

Verapamil Hydrochloride Injection USP	Abbott
2.5 mg/mL 4 mL fill in 5 mL Plastic Syringe	Abbott Park, IL
ANDA #75-136	Submission Date: 5/23/97
Reviewer: Moo Park	
Filename: 75136w.597	

Review of a Waiver Request

I. Objectives

Review of Abbott's waiver request for its Verapamil Hydrochloride Injection, 2.5 mg/mL, 4 mL fill in 5 mL plastic syringe. Reference product is Knoll's Isoptin^{R} Injection, 2.5 mg/mL, 4 mL in a single dose glass vial.

II. Comments

1. Verapamil Hydrochloride Injection is a sterile solution for IV injection.

2. Test formulation is identical to the reference formulation. Test formulation is shown in Table 1. The test product is packaged in plastic syringes whereas the reference product is packaged in glass vials.

Table 1. Test Formulation

Ingredients	Amount/mL
Verapamil Hydrochloride USP	2.5 mg
Sodium Chloride	8.5 mg
Hydrochloric Acid	qs
Water for Injection USP	qs to 1 mL

3. OGD chemist should be advised that the firm should submit limited confirmatory testing results on the safety profiles of the test product packaged in the plastic syringes according to the Agency letter to Abbott dated September 3, 1996 regarding applications for products in new plastic syringes.

4. Waiver for the test injection is granted based on 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations.

III. Recommendation

The Division of Bioequivalence agrees that the information submitted by Abbott demonstrate that Verapamil Hydrochloride Injection, 2.5 mg/mL, 4 mL fill in 5 mL plastic syringes falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Knoll's Isoptin^{R} Injection, 2.5 mg/mL, 4 mL in a single dose glass vial.

The firm should be informed of the recommendation.

Moo Park, Ph.D. /S/
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ 12/5/97
Ramakant M. Mhatre, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

Concur: /S/ Date: 1/14/98
~~Rabindra Patnaik, Ph.D.~~
~~Acting~~ Director
Division of Bioequivalence

cc: ANDA #75-136 (original, duplicate), Park, Drug File, Division File, HFD-650 (Director)

File history: Draft (8/12/97); Final (12/4/97)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Verapamil Hydrochloride Injection USP	Abbott
2.5 mg/mL 4 mL fill in 5 mL Plastic Syringe	Abbott Park, IL
ANDA #75-136	Submission Date: 5/23/97
Reviewer: Moo Park	

REF PRODUCT	Knoll's Isoptin[R] Injection, 2.5 mg/mL
BE STUDY DESIGN	n/a
STUDY RESULTS	n/a
WAIVER	Waiver granted.

INITIAL: /S/ DATE: 1/7/98
REVIEWER: Moo Park, Ph.D.
BRANCH: III

INITIAL: /S/ DATE: 1/13/98
TEAM LEADER: Moheb Makary, Ph.D.
BRANCH: III

INITIAL: /S/ DATE: 1/14/98
DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-136 APPLICANT: Abbott

DRUG PRODUCT: Verapamil Hydrochloride Injection, USP, 2.5 mg/mL, 4 mL fill

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

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75136

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: **75-136** Date of Submission: **May 23, 1997**

Applicant's Name: **Abbott Laboratories**

Established Name: **Verapamil Hydrochloride Injection USP, 2.5 mg/mL, 4 mL fill in 5 mL Plastic Syringe**

Labeling Deficiencies:

1. CONTAINER 4 mL fill in 5 mL

   Satisfactory in FPL.

2. CARTON 1s

   a. It is difficult to read the black print on the dark blue background. We encourage you to enhance the readability of your product in this regard, perhaps by using a lighter background color.

   b. Include the following statements on the carton labeling:

      i. Protect from light.

      ii. Do not remove from package until ready for use.

      iii. If the entire amount is not used at one time, the remainder must be discarded.

      iv. DIRECTIONS - Verapamil Hydrochloride Injection USP should be given as a slow intravenous injection over at least a two minute period of time. See package insert for full prescribing information.

3. INSERT

   a. GENERAL COMMENT

      Throughout the insert labeling text, when expressing a range, please replace the hyphen with

the word "to".

b. DESCRIPTION

First sentence - ... is a calcium antagonist or slow-channel inhibitor.

c. CLINICAL PHARMACOLOGY

i. Mechanism of Action

A). First paragraph

1). Last sentence

... cardiac conduction system.

2). Add the following as the last sentence:

The vasodilatory effect of verapamil appears to be due to its effect on blockade of calcium channels as well as α receptors.

B). Relocate the paragraph beginning "In the isolated rabbit heart, ..." to appear as the second paragraph.

C). Third paragraph (Electrical activity ...)

1). First sentence - Electrical activity in the ... to a large degree ...

2). The sentence "By interrupting ..." begins a new paragraph.

D). The new paragraph beginning "By interrupting ..."

1). First sentence - ... (PSVT), including PSVT associated with Wolff-Parkinson-White syndrome.

2). Delete the sentence "Verapamil has no ... bypass tracts".

E). Delete the paragraph

ii. Hemodynamics

Relocate the text "In most patients, ... bolus injection." to immediately follow the sentence ending "... slightly increased.".

d. INDICATIONS AND USAGE

i. First sentence

... indicated for the following: ...

ii. First bullet, last sentence

... to verapamil hydrochloride administration.

iii. Second paragraph

A). ... verapamil hydrochloride ... (2 instances).

B). Third sentence - ... with a decrease in ventricular rate of ...

C). Revise the last sentence to read:

Slowing of the ventricular rate in patients with atrial fibrillation/flutter lasts 30 to 60 minutes after a single injection.

iv. Penultimate paragraph

A). First sentence - ... initial use of verapamil hydrochloride injection should ...

B). Penultimate sentence - ... (See ADVERSE REACTIONS, Suggested Treatment of Acute Cardiovascular Adverse Reactions).

C). Last sentence - ... gained, use in an office setting ...

v. Last paragraph

... after verapamil hydrochloride injection.

e. CONTRAINDICATIONS

i. First sentence - Verapamil hydrochloride injection is ...

ii. Number six

A). ... bypass tract (i.e., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes) are at risk to ...

B). Add the following as the last sentence:

Therefore, the use of verapamil in these patients is contraindicated.

f. WARNINGS

i. Hypotension

A). First sentence - Verapamil hydrochloride injection often ...

B). Penultimate sentence - ... required intravenous pharmacologic ...

ii. Extreme Bradycardia/Asystole

A). First sentence - Verapamil hydrochloride affects ...

B). Last sentence - ... REACTIONS and Suggested ...

iii. Concomitant Antiarrhythmic Therapy

A). This is a subsection. Revise the heading to be of the same prominence as the other subsection headings.

B). The headings "Digitalis", "Procainamide" etc are sub subsection headings and are to be of less prominence than the subsection headings.

C). First sentences of the "Digitalis", "Procainamide", "Quinidine", and "Beta-Adrenergic Blocking Drugs" - Revise "Intravenous verapamil" to read "Verapamil hydrochloride injection".

D). Quinidine - Revise the second sentence to read: "However, three patients have been described in whom the combination resulted in an exaggerated hypotensive response presumably from the combined ability of both drugs to antagonize the effects of catecholamines on α-adrenergic receptors."

E). Beta-Adrenergic Blocking Drugs

1). Second sentence - ... contractility and AV ... (rather than "or").

2). Penultimate sentence - ... and **intravenous** verapamil has ... ("**intravenous**" in bold print).

3). Delete the last sentence (Asymptomatic bradycardia ...).

F). Disopyramide - ... verapamil and all forms of disopyramide phosphate are ...

G). Add the following as the last sub subsection in this subsection:

Flecainide: A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects reducing myocardial contractility, prolonging AV conduction, and prolonging repolarization.

iv. Heart Block

Last sentence - if needed (see ADVERSE REACTIONS, Suggested Treatment of Acute Cardiovascular Adverse Reactions).

v. Hepatic and Renal Failure

A). Second sentence - Repeated injections of

verapamil hydrochloride injection in ...

B). Revise the last sentence to read:

Verapamil cannot be removed by hemodialysis.

vi. Premature Ventricular Contractions

First sentence - ... verapamil hydrochloride.

vii. "Duchenne's Muscular Dystrophy" and "Increased Intracranial Pressure"

Revise the first sentences of these two subsections as follows: Verapamil hydrochloride injection ...

g. PRECAUTIONS

i. Drug Interactions

A). First paragraph

1). First sentence - ... Therapy) Verapamil hydrochloride injection has been used concomitantly with other cardioactive drugs (especially digitalis) without ...

2). Second sentence - ... concomitantly with **intravenous** verapamil, ... (bold print).

3). Revise this paragraph, starting from the third sentence, as follows:

Concomitant use of verapamil hydrochloride with β-adrenergic blockers may result in an exaggerated hypotensive response. Such an effect was observed in one study, following the concomitant administration of verapamil and prazosin. It may be necessary to decrease the dose of verapamil and/or dose of the neuromuscular blocking agent when the drugs are used concomitantly. As verapamil

is highly ...

4). Delete the last two paragraphs of this subsection (Animal experiments ... depression. Clinical data ... concomitantly).

B). Add the following to the end of this subsection:

OTHER

Cimetidine: The interaction between cimetidine and chronically administered verapamil has not been studied. In acute studies of healthy volunteers, clearance of verapamil was either reduced or unchanged.

Lithium: Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy with either no change or an increase in serum lithium levels. The addition of verapamil, however, has also resulted in the lowering of serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs must be monitored carefully.

Carbamazepine: Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital: Phenobarbital therapy may increase verapamil clearance.

Cyclosporin: Verapamil therapy may increase serum levels of cyclosporin.

Inhalation Anesthetics: Animal experiments have shown that inhalation

anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists (such as verapamil) should be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents: Clinical data and animal studies suggest that verapamil may potentiate the activity of depolarizing and nondepolarizing neuromuscular blocking agents. It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Dantrolene: Two animal studies suggest concomitant intravenous use of verapamil and dantrolene sodium may result in cardiovascular collapse. There has been one report of hyperkalemia and myocardial depression following the coadministration of oral verapamil and intravenous dantrolene.

ii. Delete the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection.

iii. Capitalize the nouns found in the subsection headings to be in accord with the other subsection headings (e.g., Labor and Delivery, Nursing Mothers etc.)

iv. Pregnancy: Teratogenic Effects: Pregnancy Category C:

Delete the word in the penultimate sentence.

v. Labor and Delivery

Last sentence - ... use of verapamil hydrochloride injection in Europe ...

vi. Nursing Mothers

Last sentence - ... potential for adverse

reactions ... (delete

vii. Pediatric Use

A). Revise the second sentence as follows:

In rare instances, however, severe hemodynamic side effects - some of them fatal - have occurred following the intravenous administration of verapamil to neonates and infants. (note the bold print)

B). Revise the third sentence (**Caution should** ...) to be in bold print.

C). The sentence beginning "The most commonly used ..." begins a new paragraph.

h. ADVERSE REACTIONS

i. First sentence - ... with verapamil hydrochloride injection used in ... (note the word "used" as well as the other changes).

ii. Central Nervous System Effects

A). Note the capitalization.

B). ... Occasional cases of seizures ...

iii. The following reactions have been reported at low frequency: emotional depression, rotary nystagmus, sleepiness, vertigo, muscle fatigue, diaphoresis, and respiratory failure.

iv. Table

A). Dopamine I.V. [delete

B). Atropine I.V. [delete

C). Lidocaine I.V. [delete

i. OVERDOSAGE

i. First sentence - ... administration of calcium solutions may ...

ii. Last sentence - ... resuscitation (see ADVERSE REACTIONS: Suggested treatment of Acute Cardiovascular Adverse Reactions).

j. DOSAGE AND ADMINISTRATION

i. Second sentence - **VERAPAMIL HYDROCHLORIDE INJECTION SHOULD ... CONTINUOUS ELECTROCARDIOGRAPHIC AND ...**

ii. Third sentence - ... of verapamil hydrochloride injection are ...

iii. Adult

A). Initial dose - ... intravenous bolus over at least 2 minutes.

B). Repeat dose - Add as the second sentence:

... adequate. An optimal interval for subsequent I.V. doses has not been determined, and should be individualized for each patient.

iv. Pediatric

A). Initial dose

1). 0 to 1 year - ... an intravenous bolus over at least 2 minutes **under continuous ECG monitoring.**

2). 1 to 15 years - ... an intravenous bolus over at least 2 minutes. **Do not** ...

B). Repeat dose

1). 0 to 1 year - ... is not adequate **(under continuous ECG monitoring).** An optimal interval for subsequent I.V. doses has not been determined, and should be individualized for each patient.

2). 1 to 15 years - ... **a single dose.** An optimal interval for subsequent I.V. doses has not been determined,

and should be individualized for each patient.

v. Last paragraph

A). Add the following as the second sentence:

Verapamil is physically compatible and chemically stable for at least 24 hours at 25°C protected from light in most common large volume parenteral solutions. Admixing ...

B). Penultimate sentence - ... hydralazine hydrochloride and trimethoprim with sulfamethoxazole should ...

C). Last sentence - Verapamil hydrochloride will ...

k. HOW SUPPLIED

We encourage you to use the NDC numbers for your drug products in this section.

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75136

CORRESPONDENCE

136

Abbott Laboratories
Attention: Thomas F. Willer, Ph.D.
200 Abbott Park Road, D-389 AP30
Abbott Park, IL 60064

JUL 7 1997

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.

NAME OF DRUG: Verapamil Hydrochloride Injection USP, 2.5 mg/mL, 4 mL fill in 5 mL Plastic Syringe

DATE OF APPLICATION: May 23, 1997

DATE OF RECEIPT: May 23, 1997

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:

Tim Ames
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips 7/2/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ABBOTT

Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

May 23, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn
Director

RE: Verapamil HCl Injection, USP, 2.5 mg/mL, 4 mL fill in 5 mL Plastic Syringe

ORIGINAL ABBREVIATED NEW DRUG APPLICATION

Abbott Laboratories hereby submits this original Abbreviated New Drug Application for the subject drug to provide for Verapamil HCl Injection, USP, 2.5 mg/mL, 4 mL fill in a 5 mL polypropylene plastic syringe, in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act. The subject drug is an aqueous, sterilized drug product. The dosage form and manufacturing site may be described as follows:

The dosage forms and manufacturing site may be described as follows:

List Number	Concentration	Fill Volume	Size/ Type Container	Manufacturing Facility
9633	2.5 mg/mL Verapamil HCl	4 mL	5 mL Plastic Syringe	CFN 1021343 Rocky Mount, North Carolina

Abbott Laboratories is filing this original ANDA in accordance with various guidances furnished by CDER concerning packaging changes for established drug products from glass to plastic primary containers. The Agency has determined that the process for submitting currently approved small volume parenteral products in glass containers to be packaged in plastic containers shall be via an abbreviated new drug application. We submit this application in accordance with MAPP 6020.2, "Applications for Parenteral Products in Plastic Immediate Containers," issued September 6, 1996. This application is submitted in accordance with MAPP 6020.2 in that this product duplicates and approved product listed in the current edition of *Approved Drug Products with Therapeutic Equivalence Evaluations*" and studies were not required beyond confirmatory testing.

The subject drug is a prescription drug and not an over-the-counter drug. Abbott Laboratories' Hospital Products Division will manufacture the 4 mL finished dosage form at its currently approved Rocky Mount, North Carolina facility (CFN 1021343). Please refer to Drug Master File for a full description of this Abbott Laboratories, Hospital Products Division facility.

Please refer to the accompanying Table of Contents for a list of the data supporting this newly prepared submission. These data have been presented in four volumes consistent with the Office of Generic Drugs Guidance for Industry, entitled "Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application," dated April, 1997.

We also include in Section XXI of this application the "Certification Requirement for All Applications For Approval of a Drug Product" and "Certification Requirement for All Applications For Approval of a Drug Product Concerning Using Services of Disbarred Persons" as required by the Generic Drug Enforcement Act of 1992.

In compliance with 21 CFR 314.94 covering FDA preapproval inspections of manufacturing sites, Abbott Laboratories has submitted a complete true copy of the CMC section from this application ("designated as the field copy") to the FDA district office (Atlanta, Georgia) with inspection responsibilities for the Abbott Laboratories Hospital Products Division manufacturing site (Rocky Mount, North Carolina) listed in this application. The signed certification follows this letter.

We request twenty-four months expiration dating for this product based on the accelerated stability data enclosed herein. At the request of the Agency, we will provide samples of the bulk drug substance and finished dosage form.

This is the fourth in a series of submissions of drug products to be packaged in plastic syringes. These products were summarized in Dr. Williams' letter (September 3, 1996). The first submission was for 50% Dextrose Injection, USP, 50 mL, Plastic Syringe, as a supplement , to NDA . *Division Of Metabolism And Endocrine Drug Products*, HFD #510. This supplement was accepted for review on May 30, 1996 and the Agency review is underway now. We included the *full data package* for the plastic container in that submission. The second submission, ANDA 75-005 Iopamidol Injection, Plastic Syringe, was submitted on November 14, 1996, and included a full (duplicate) data package for the plastic container. These two submissions contain the same data package for the plastic syringe. We request that the new drug division and OGD reviews of this package cover this submission too. We do not duplicate this previously submitted information again here. The third submission in this series is 1% and 2% Lidocaine Hydrochloride Injection, Plastic Syringe.

Additionally, we include after this cover letter a copy of the "Checklist For Completeness And Acceptability For Filing Abbreviated Applications." This is part of Mr. Douglas Sporn's letter to industry, April 8, 1994, as Attachment A. We added an extra column the OGD checklist in which we included the location (page number) in this ANDA where the specified information can be found. We hope that this aid will permit the Agency to expedite its prereview and acceptance of the ANDA.

We also note that Abbott Laboratories has extensive experience manufacturing 2.5 mg/mL Verapamil HCl Injection products at Rocky Mount, North Carolina. We manufacture many other Verapamil products in small volume containers, including, glass syringes, vials and ampuls. The subject of this ANDA differs from the above products in that it is in a plastic syringe.

We have added the requested CFN (FDA registration) numbers throughout the application where appropriate for the active and inactive drug manufacturers, finished product manufacturing site, and all testing facilities.

We trust that this submission is complete and this abbreviated new drug application can be expeditiously approved. Please contact me if you have any questions or need additional information concerning this submission.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.
Assistant Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETF@hpd.abbott.com

TFW:tw

vera9633.tfw/6
Attachment

ABBOTT

Labeling Review Drafted 7/28/98 A. Vega

Hospital Products Division
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February 6, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG AMENDMENT
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ATTENTION: Douglas Sporn
Director

Re: ANDA: 75-136 Verapamil Hydrochloride Injection, USP, 2.5 mg/mL, Plastic Syringe
MAJOR AMENDMENT

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application for the subject drug. We are responding to the Agency's faxed letter dated January 8, 1998 which made the following comments:

REQUEST: **"Chemistry Deficiencies:**

1. **On p. 4-228 it is stated that stability indicating test data of samples under various stress conditions is included. This data was not submitted. Please submit this data with copies of applicable chromatograms."**

RESPONSE: Degradation studies under stress conditions with acid, base, heat, oxidizer and light were conducted and documented in the Scientific Report #97G-039-AP-97 entitled: Stability Indicating Character of Assay for Verapamil Hydrochloride. As stated in this report, the impurities specified by the USP monograph are (1) Related Compound A, (2) 3,4-dimethoxybenzaldehyde and (3) 3,4-dimethoxybenzyl alcohol. These are the same principal impurities formed in the above-mentioned degradation studies. The USP potency method for Verapamil Hydrochloride Injection is therefore suitable for monitoring chemical stability of the drug product. Please see Exhibit I for the report and copies of applicable chromatograms.

REQUEST: **"2. Please submit USP 23 <661> Physicochemical Tests-Plastics test results for the syringe barrel."**

RESPONSE: The USP Physicochemical test results of the polypropylene used for the syringe barrel were summarized in the Scientific Report # 97G-004-AP-98 entitled: Material Evaluation for Exxon Polypropylene for Use in the Prefilled Plastic Syringe System. We include a copy of this report in Exhibit II.

REQUEST: **"3. The Certificate of Analysis from Recordati for the drug substance was incomplete in that only p. 2 of 2 was submitted (see p. 1-55). Please submit the complete COA."**

RESPONSE: A complete two page of Certificate of Analysis from Recordati for the Verapamil Hydrochloride drug substance is provided in Exhibit III.

REQUEST: **"Microbiology Deficiencies:**

A.1. RM BQA 96.058 page 2-238 in the ANDA, indicates that a) or greater SLR of the indicator organisms is acceptable to assure that a bioburden SAL of 10^6 is achieved. Is this conclusion reached using the data provided in SDT 1595 (Page 2-208)? Please Explain."

RESPONSE: As noted the acceptance criteria for the closure challenge (RM BQA 96.058) in the Rocky Mount, North Carolina, production facility is reached in conjunction with the results from the kinetic inactivation study in a developmental vessel (SDT-1595). However, the original bioburden data in the kinetic study appeared to show an inactivation rate that was similar to the spore forming indicator organisms due to the selected time exposure intervals being too long.

We have revised SDT-1595 to include data from a second short bioburden study that was performed on 5/8/97. This data indicated that the inactivation rate of the bioburden was substantially faster than that of the indicator organisms. Both sets of data are included in the revised report, SDT-1595R, shown in Exhibit IV.

The additional data now demonstrates that sterilization conditions that result in a 3.0 SLR for the indicator organisms will result in a 9.7 microbial inactivation of the bioburden. Hence, the acceptance criteria was met for the enclosure challenge (RM BQA 96.058).

REQUEST: **"2. The Master Solution, List 8183, is referred to as 2.0, 3.0, and 5.0mEq/mL Potassium Acetate at various locations in the PSLR.96.1 and 96.057 reports. Which is it?"**

RESPONSE: Potassium acetate, List 8183, is 2.0 mEq/mL.

REQUEST: **"3. Why are Fo 30 data included in the product release specifications?"**

RESPONSE: The 30 Fo is the absolute upper limit for parametric release of finished product. This is consistent with recent parametric release NDA and ANDA approvals for other sterilized product produced by Abbott Laboratories. Anytime the upper Fo limit in the sterilization specification is exceeded, stability and maintenance of sterility data must still exist to support the excursion. Our commitment to the agency was that we would never release product that exceeds 30 Fo even if there is supporting stability/maintenance of sterility data.

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

1. The above comments are identical to some of the comments asked about the Lidocaine Syringes (75-092)."

RESPONSE: We acknowledge that the above comments are identical to the current pending submission of ANDA 75-092, 1% and 2% Lidocaine Hydrochloride Injection, Ansyr™ Syringe.

REQUEST: **"2. The review of Iopamidol Syringes (75-005) was not for parametric release. A supplemental application will be required for parametric release of this product."**

RESPONSE: We regret that the parametric release information was not apparent in the original submission of Iopamidol (ANDA 75-005). We have included this information in the Scientific Report #97G-041-AP-96 entitled: " Iopamidol Injection, USP, 50 mL Polypropylene Plastic Syringe, Abbott List Nos. 8117 (51%), 8118 (61%) and 8119 (76%) - Manufacturing Controls and Stability Data", on page 7-397, 7-400 and 7-403 of the original submission. In addition, we also provided the parametric release information in the revised drug product specifications and revised marketed product stability protocols shown in the deficiency response letter of August 15, 1997. This amendment superseded information in the original ANDA.

Labeling Deficiencies:

The container labeling was acceptable. The Agency requested changes to the carton and insert. Please note that we did not change the carton as instructed in items 2.b (i to iv). We consulted with OGD - Label Review concerning this decision. As requested, we have lightened the blue ink on the carton and provided the final printed labeling. We made all the requested changes to the insert. We provide twelve copies of final printed labeling in Exhibit V as requested. We include the annotated labeling in Exhibit VI.

We have also updated the insert per the Agency's letter dated January 23, 1996. We will be making the appropriate changes to other verapamil ANDA's in due course.

We trust that this submission is complete and that the ANDA may now be approved. Please telephone me at your earliest convenience if I may of further service.

Sincerely,

ABBOTT LABORATORIES

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