CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-392

Administrative/Correspondence Reviews

SECTION 13 – PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

List of Patents

The Diltiazem Hydrochloride Extended-release Capsules, USP formulation is covered by two (2) patents:

- Extended-release form of diltiazem
  Arthur M. Deboeck, Phillippe R. Baudier
  US Patent number: 5,288,505 February 22, 1994.

- Extended-release form of diltiazem
  Arthur M. Deboeck, Phillippe R. Baudier
  US Patent number: 5,529,791 June 25, 1996.

A copy of both patents is enclosed.

SECTION 14 – PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

Certification

This section is not applicable to this New Drug Application.

United States Patent [19]
Deboeck et al.

[11] Patent Number: 5,288,505
[45] Date of Patent: Feb. 22, 1994

[54] EXTENDED RELEASE FORM OF DILTIAZEM

[75] Inventors: Arthur M. Deboeck, Gurabo, P.R.; Philippe R. Bandier, Waterloo, Belgium

[73] Assignee: Galephar P.R., Inc., Ltd., Carolina, P.R.

[21] Appl. No.: 721,396

[22] Filed: Jun. 26, 1991

[51] Int. Cl.[5] A61K 9/16; A61K 9/58
[52] U.S. Cl. 424/497; 424/457; 424/458; 424/462; 424/490; 424/499; 424/502
[58] Field of Search 424/499, 457, 458, 462, 424/490, 493, 498, 497

[56] References Cited

U.S. PATENT DOCUMENTS

3,964,255	6/1976	Catanzarite	60/205
4,263,273	4/1981	Appelgren et al.	424/21
4,556,925	12/1985	Suenaga et al.	360/113
4,600,645	7/1986	Ghebre-Sellasue et al.	428/403
4,623,588	11/1986	Nuwayser et al.	424/31
4,705,695	11/1987	Lehmann et al.	424/19
4,721,619	1/1988	Panoz et al.	424/468
4,784,858	11/1988	Ventouras	424/468
4,808,413	2/1989	Joshi et al.	424/489
4,824,678	4/1989	Lindahl et al.	424/473
4,832,958	5/1989	Baudier et al	424/473
4,839,177	6/1989	Colombo et al	424/482
4,859,469	8/1989	Baudier et al.	424/462
4,891,230	1/1990	Geoghegan et al.	424/461
4,894,240	1/1990	Geoghegan et al.	424/497
4,917,899	4/1990	Geoghehan et al.	424/461
4,938,967	7/1990	Newton et al.	424/458
4,952,402	8/1990	Sparks et al.	424/419
4,960,596	10/1990	Debregeas et al.	424/459
5,000,962	3/1991	Sangekar et al.	424/482
5,002,776	3/1991	Geoghegan et al.	424/497
5,051,262	9/1991	Panoz et al.	424/468
5,175,003	12/1992	Goldman	424/484

FOREIGN PATENT DOCUMENTS

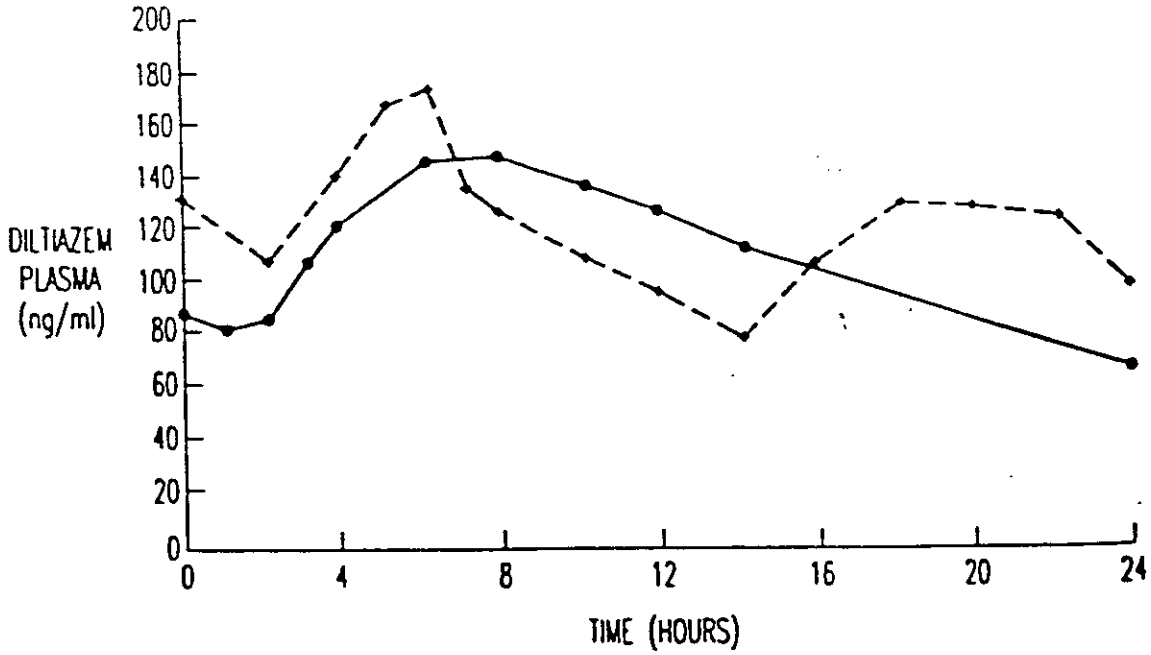
0149920A2	12/1984	European Pat. Off. .
0322277A1	12/1988	European Pat. Off. .
0340105A1	4/1989	European Pat. Off. .
0373417A1	11/1989	European Pat. Off. .

Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

15 Claims, 2 Drawing Sheets



EXTENDED RELEASE FORM OF DILTIAZEM

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an extended release form of Diltiazem, a process for the manufacture thereof and pharmaceutical compositions containing the same.

2. Description of the Background

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties, and, therefore, finds application in the treatment of angina pectoris and hypertension; either alone or in combination with other medications.

Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arteries, peripheral arteries and arterioles are dilated and heart rate may be reduced. Also, myocardial contractibility may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in human is directly related to its blood or plasma concentration.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times render the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate-release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks, a first galenic form of sustained-released of Diltiazem known under the trade name CARDIZEM SR ® was developed and presented in the form of "erodible pellets", U.S. Pat. No. 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not eliminate high Diltiazem blood concentration between successive medication intakes. Hence, the patient is still obliged to take the medication twice daily. The products as described in U.S. Pat. No. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 and 200 layers so as to obtain a core which, thereafter, requires between 20 and 40 layers of coating so as to obtain the membrane. Moreover, the solvent of the polymer solution used to make the membrane is constituted by organic solvents, such as isopropanol, methanol, acetone, and methylene chloride which are dangerous to use due to their flammability and toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are unsuitable in the product which is administered orally.

Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenical form which need be administered only once daily, and from which blood Diltiazem concentrations are not effected by the concomitant intake of food, and, further, which can be made by a process not using organic solvents.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become more apparent in view of the following disclosure are provided by an extended-release galenical form of a pharmaceutically acceptable salt of Diltiazem, which comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration twice daily.

FIG. 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is taken with food.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Diltiazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2,(4-methoxyphenyl)-1,5-benzothiazepin-4(5H) has been known for more than 20 years. The synthesis thereof is described in German patent 1,805,714, corresponding to U.S. Pat. No. 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the active substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentrations peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range while simplifying the administration of the medicine to only once daily.

According to the present invention, the Diltiazem extended release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they may also include the acetate, ci-

trate or lactate salts, for example. It is preferred however, that the hydrochloride salt be used.

In more detail, the microporous membrane whereof the Diltiazem containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer and including at least one adjuvant which may be plastifying agents, pigments, fillers, wetting agent lubricants and antifoam agents.

The active substance containing beads are presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more parucularly be exemplified:

- sugars, for example saccharose, mannitol, sorbitol and lactose;
- lecithins;
- C_{12} to C_{20} fatty acid esters of saccharose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.);
- xylose esters or xylites,
- polyoxyethylenic glycerides;
- esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);
- sorbitan fatty acid esters (Span, Atlas, U.S.A.);
- polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France).

In addition to at least one of the above named wetting agents the beads may contain excipients or carriers, such as Microcrystalline celluloses, such as Avicel products (FMC, U.S.A); methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol, Hercules, U.S.A.), hydroxypropyl celluloses (Klucels, Hercules, U.S.A.); and starches

Among the water-soluble and/or dispersible film forming polymers or copolymers constituting the microporous membrane, may be mentioned parucularly polyacrylates and polymethacrylates of the Eudragit type, such as Eudragit E30D, L30D, RS - 30 D of Rohm Pharma (RFA), ethylcelluloses, such as Ethocels of DOW, U.S.A and such as AquaCoat of FMC, U.S.A., Hydroxypropyl cellulose and hydroxypropylmethylcellulose and their derivations

These polymers or copolymers may be associated into the microporous membrane with at least one adjuvant as exemplified by the following:

- plastifying agents, such as triacetin, dibutylphthalate, dibutylsebacate, citric acid esters, polyethyleneglycols, polypropyleneglycols and polyvinylpyrrolidone,
- pigments, such as iron oxides and titanium oxide;
- fillers, such as lactose and sucrose,
- wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of hexitols derived from sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyethyleneglycols;
- lubricants, such as magnesium stearate and talc;
- antifoaming agents, such as silicone oil.

In addition to the polymer or copolymer, the microporous membrane contains, preferably, talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plastifying agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoa agent.

Generally, the thickness of the microporous brane is expressed by the percentage of the co applied to the uncoated beads.

The weight of the microporous membrane may to 35%, preferably, 5 to 22%, of the weight of microgranules. These beads may contain the Dilti salt in an amount of 20 to 95% by weight, preferab to 85% by weight. The microporous membrane contain 5 to 95% and, preferably, 30 to 90% of mers, polymer mixture or copolymers.

The invention relates also to a medicine conta Diltiazem or salt thereof for extended release, the cine being constituted by beads containing the tiazem or salt, such as the hydrochloride, and at le wetting agent, coated with at least one polymer-b microporous membrane, the coated beads being tained in capsules, little bags or dosage dispensers.

The present invention relates also to a process obtaining novel forms of a Diltiazem or salt the having extended-release in the gastro-intestinal t said process entailing preparing beads and coating salt with a single microporous membrane.

The beads of the Diltiazem or salt thereof may prepared using a conventional technique. A first t nique consists in mixing the Diltiazem or salt the with the wetting agent(s) in a melted or finely divi form, or in solution, in the presence of a solvent, suc water, so as to obtain an extrudable paste or pla mass. Said paste is thereafter extruded in an extru and then rendered spherical. Several extruder types usable, for example the extruder of ALEXAND WERK (RFA) or the apparatus called X-truder FUJI-PAUDAL (Japan). For obtaining microsphe or beads from the extruded product provided in form of spaghetti, an apparatus called "spheroniz (CALEVA Great-Britain) or MARUMERIZI (FUJIU-PAUDAL Japan) type is used.

Another conventional technique for obtaining bea consists in spraying and/or dusting cores obtain through agglomeration of the Diltiazem or salt there such as the chlorohydrate, contingently mixed to least a wetting agent, with a dispersion or solution of least one wetting agent, for example in a known pill turbine or in a granulating apparatus, such as the C granulator system of FREUND INDUSTRIAL C (Japan), or in a known planetary granulator such as t collette (Belgium) type.

The obtained beads are dried by any means, for exar ple in an oven or by means of a gas in a fluidized be

Finally, said beads are calibrated to the necessa diameter by passage through appropriate screens.

A pasty or plastic mixture, appropriate to be gran lated by means of anyone of the above described tec niques, may contain the following weight proportior of the Diltiazem or salt thereof, wetting agents an carriers or excipients:

- 20 to 85%; Diltiazem hydrochloride
- 2 to 20% sucroesters WE 15 (wetting agent);
- 5 to 25% Avicel PH 101 (microcrystalline cellulos of FMC, U.S.A.);
- 2 to 10% Methocel E 5 (hydroxypropylmethyl cellulose of DOW, U.S.A.);
- 1 to 15% polyvinylpyrrolidone and
- 5 to 40% distilled water.

Said microporous membrane may be applied onto said beads by pulverizing an aqueous solution or disper-

sion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pulverization may be carried out by spray-gunning or by pulverizing the above-named dispersion into a turbine or fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient, however, in general, from about 120 mg to about 480 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt, provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients, such as β-adrenoceptor blocking agents or diuretics may be used in the present compositions. However, these are only example and are not intended to be limitative.

As examples of β-adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Prindolol or Sotalol may be used, for example.

As examples of diuretic agents, drugs such as Hydrochlorothiazide, Furosemide, Ethacrynic Acid or Chlorothiazide, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired, however, they need not be

The present invention will now be further illustrated by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative.

According an illustrative embodiment of the present invention, said microporous membrane may be obtained, starting from an aqueous dispersion which contains by weight.

10 to 70 Eudragit E30D (polymer)
0.5 to 15% talc (lubricant)
0.5 to 15% Titanium dioxide (lubricant)
0.5 to 15% Magnesium stearate (lubricant)
0.5 to 15% polyvinylpyrrolidone (plastifying agent)
0.01 to 2% silicone oil (antifoaming agent),
0.05 to 5% polysorbate 80 (wetting agent)
10 to 70% water (carrier)

EXAMPLES

The present invention will now be further illustrated by reference to certain examples, which are provided solely for purposes of illustration and are not intended to be limitative. In particular, examples are provided for Diltiazem Hydrochloride extended release galenic forms, a process for preparing the same, therapeutic applications therefor and pharmacokinetic controls using the present galenic forms.

EXAMPLE 1

Beads Manufacture

Diltiazem hydrochloride	1120 g
Lactose	119 g
Microcrystalline cellulose (Avicel pH 101)	140 g
Povidone k 30	21 g

After introducing the powders into a planetary mixer and granulating same though the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to obtain beads, by means of a spheronizer. After drying at 60° C. for 12 hours the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1,179 g of beads were obtained yield (84%).

EXAMPLE 2

Diltiazem Hydrochloride	560 g
Crodesta F 160	59.5 g
Microcrystalline cellulose (Avicel pH 101)	70 g
Povidone k 30	10.5 g

The ingredients are introduced in a planetary mixer and dry mixed during approximately 15 minutes. There after 100 ml water USP is added and the mixing is pursued during 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spagetties". A spheronizer type caleva is used so as to transform the extruded product in beads. After drying during 12 hours, on trays, in an oven at 60° C the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with size comprised between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

EXAMPLE 3

Beads prepared in Example 1 were a STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technic. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter the coated beads were dried at 50° C. during 16 hours.

Coating suspension composition	
Magnesium stearate	12.5 g
Titanium dioxide	5.0 g
Povidone k 30	5.0 g
Eudragit NE30D	620.0 g
Talc USP	17.5 g
water	338.0 g
Simethicone	1.0 g
Tween 80	0.8 g

"In vitro" dissolution were obtained using the apparatus #2 as described in the United States Pharmacopeia. The 900 ml dissolution medium consisted of a phosphate butter pH 5.8 and the revolution speed 100 rpm.

elapsed time [h]	percent dissolved [%]
1	5
4	34
8	62
12	84

EXAMPLE 4

The beads as in Example 2 were coated using a fluidized bed coater equipped with a "wurster" system. 8 kg of uncoated beads were introduced in an Aeromatic Aerocoater and 2.77 kg of the following coating suspension was applied at a rate of 30–35 g per minute. Thereafter the coated beads were dried during 15 hours at 45° C.

Coating suspension	
Magnesium stearate	0.636 kg
Talc	0.636 kg
Titanium dioxide	0.0909 kg
Hydroxypropylmethylcellulose	0.300 kg
Polysorbate 80 NF	0.007 kg
Simethicone c emulsion	0.018 kg
Eudragit NE 30 D	12.4 kg
purified water	6.7 kg

Dissolution "In Vitro"

The results were obtained using the same equipment as in Example 3. The dissolution medium was composed of 900 ml of water and the temperature was maintained of 37°±0.5° C.

elapsed time [h]	percent dissolved [%]
2	9
4	33
6	54
8	82

Pharmacokinetical Results

The new galenic form of Example 4 was the object of a pharmacokinetical study in comparison with a form in accordance to the prior art as described in U.S. Pat. No. 4,721,619. (Cardizen SR ®) therefore 6 healthy subject received successively in a random order 300 mg of each of the 2 products. The product of Example 4 was administered at a dose of 300 mg once daily while the product on the market was administered twice daily at a dose of 150 mg (300 mg daily total dose) during 7 days. At each of the eight day, 1 samples of blood were withdrawn when product of Example 4 was administered and 15 blood samples where withdrawn after the Cardizen SR ® administration. Diltiazem plasma levels were assayed using a specific high pressure liquid chromatographic method. FIG. 1 shows the results obtained: the continuous line represent the Diltiazem plasma levels obtained with the product of Example 4 and the broken line the Diltiazem plasma levels of Cardizen SR ®.

FIG. 1

Pharmacokinetical parameters	Units	Example 4	Cardizen SR ®
Area under the curve [0-24 h]	mg.h/ml	2782 ± 1037	2864 ± 1222
Maximal concentration	mg/ml	116.3 ± 34.1	192.7 ± 85.3
Time of maximum concentration	h	8.0 ± 1.8	5.2 ± 2.8
Fluctuation	%	83.7 ± 25.7	109.5 ± 25
Time during the concentration is above 75% of the maximum concentration	h	9.8 ± 2.3	6.7 ± 3.7

From these results the following conclusion can be drawn:

First, FIG. 1 shows that the Diltiazem plasma levels obtained after a once daily administration of one of the products of the present invention are comparable to the ones obtained after a twice daily administration of th product of the previous art.

Second, the bioavailability, expressed by the area under the curve of the 2 products, is equivalent (no statistical detectable difference).

Third, the maximal concentration and the fluctuations obtained after a once daily administration of the product of the present invention is lower than the one obtained with Cardizen SR ® after a twice daily administration.

Fourth, the time during the concentration is above 75% of the maximum concentration is 46% longer after the once daily administration of the product of the present invention than with product of the previous art when given twice daily.

Food Effect Study

The product of Example 4 was given to 24 healthy volunteers and the bioavailability was measured after single oral dose of 300 mg given with and without food.

The clinical trial was conducted as an open, single dose, randomized, cross over study. Blood samples were obtained before and until 36 hours after the administration. The experiment was repeated in the same subjects with the other treatment at an interval of 7 days. The plasma concentration of Diltiazem was determined in all available samples using an HPLC method. Pharmacokinetics parameters were derived from the individual plasma concentration versus time profiles and statistically compared for treatment differences and assessment of bioequivalence. FIG. 2 curves shows the mean plasma levels obtained when the product is taken without food and the dotted curve the mean plasma levels obtained when the product is taken with food.

FIG. 2

Pharmacokinetics parameter - product of Example 4	Units	Fasting	Food
Area under the curve (total)	mg h/ml	1988 ± 119	1925 ± 109
Mean residence time	h	21.3 ± 0.7	19.9 ± 0.9
K_e	h^{-1}	0.283 ± 0.024	0.300 ± 0.027
Maximum concentration	mg/ml	100 ± 4.8	112 ± 5.9

No statistical difference was detectable. The product of Example 4 given with food is bioequivalent to the administration without food to within less than 20% regarding area under the curve, mean residence time and maximum concentration. The larger interval obtained for K_e was due to the higher variability of this parameter, the difference between the treatment means remaining small (6.%).

From all the results it appears clearly that the product of the present invention can be administered once a day and that the plasma concentration variations are lower than the one obtained with the conventional product given twice a day.

Having described the present invention, it will now be apparent to one skilled in the art that many changes and modifications may be made to the above-described embodiments while remaining within the spirit and the scope of the present invention.

What is claimed as new and desired to be secured by Letters Patent of the United States is:

1. An extended-release galenical composition of Diltiazem or one or more pharmaceutically-acceptable

salts thereof, which comprises beads, said beads consisting essentially of in admixture together:

a) an effective amount of Diltiazem or said one or more salts thereof as an active ingredient, and

b) an effective amount of a wetting agent, wherein said wetting agent is selected from the group consisting of a sugar, a C_{12}–C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, lecithins and a combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl acrylate, and a pharmaceutically-acceptable adjuvant.

2. The extended-release galenical composition of claim 1, wherein said salt is the hydrochloride salt.

3. The extended-release galenical composition of claim 1, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

4. The extended-release galenical composition of claim 3, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

5. The extended-release galenical composition of claim 1, wherein the weight of the Diltiazem salt is about 20 to 95% by weight.

6. A pharmaceutical composition, comprising an extended-release galenical composition of Diltiazem or one or more pharmaceutically-acceptable salts thereof, which comprises in capsule form

a) beads consisting essentially of an effective amount of each of Diltiazem or said one or more salts thereof and a wetting agent in admixture together, wherein said wetting agent is selected from the group consisting of a sugar, a C_{12}–C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide ester, an alcohol-polyglycide ester, lecithins and a combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, and

b) one or more other pharmaceutically active ingredients which are pharmaceutically compatible with Diltiazem or said one or more salts thereof.

7. The pharmaceutical composition of claim 6, wherein said one or more other pharmaceutically active ingredients comprise-β-adrenoceptor or diuretic compounds or compositions containing the same.

8. The pharmaceutical composition of claim 6, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

9. The pharmaceutical composition of claim 6, wherein said salt is the hydrochloride salt.

10. The pharmaceutical composition of claim 6, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

11. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an extended-release galenical composition consisting essentially of Diltiazem or one or more pharmaceutically-acceptable salts thereof and a wetting agent in admixture together in the form of beads, wherein the wetting agent is selected from the group consisting of a sugar, a C_{12}–C-fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, an alcohol-polyglycide ester, a glyceride-polyglyceride lecithins and a combination thereof, and

wherein the beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable excipient.

12. The method of claim 11, wherein said administration is orally and once per day.

13. The method of claim 11, wherein said mammal is a human.

14. The method of claim 12, wherein from about 120 mg to about 480 mg of said one or more Diltiazem salts are administered in total per day.

15. The method of claim 11, wherein said salt is the hydrochloride salt.

* * * * *

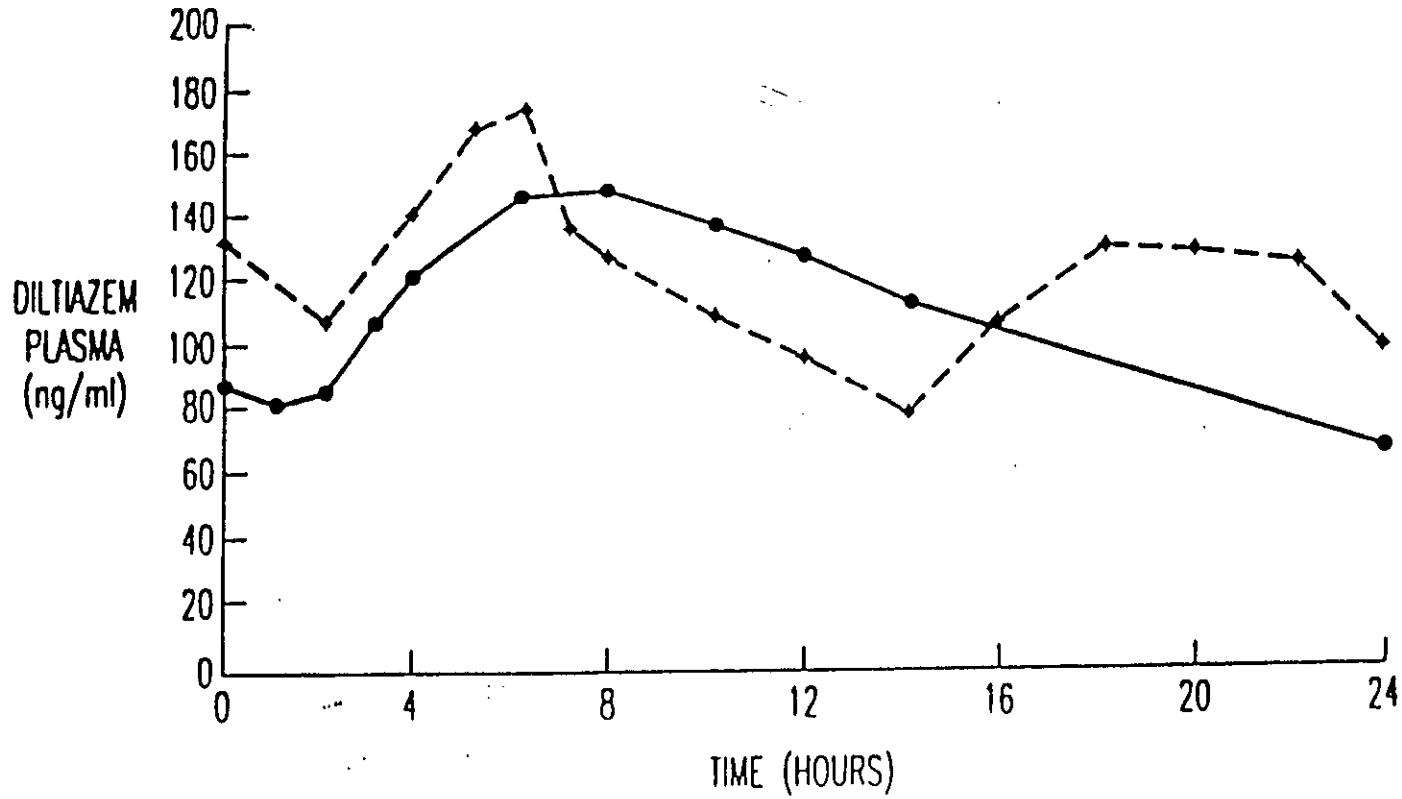

DILTIAZEM
PLASMA
(ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
4
8
12
16
20
24
TIME (HOURS)

FIG. 1

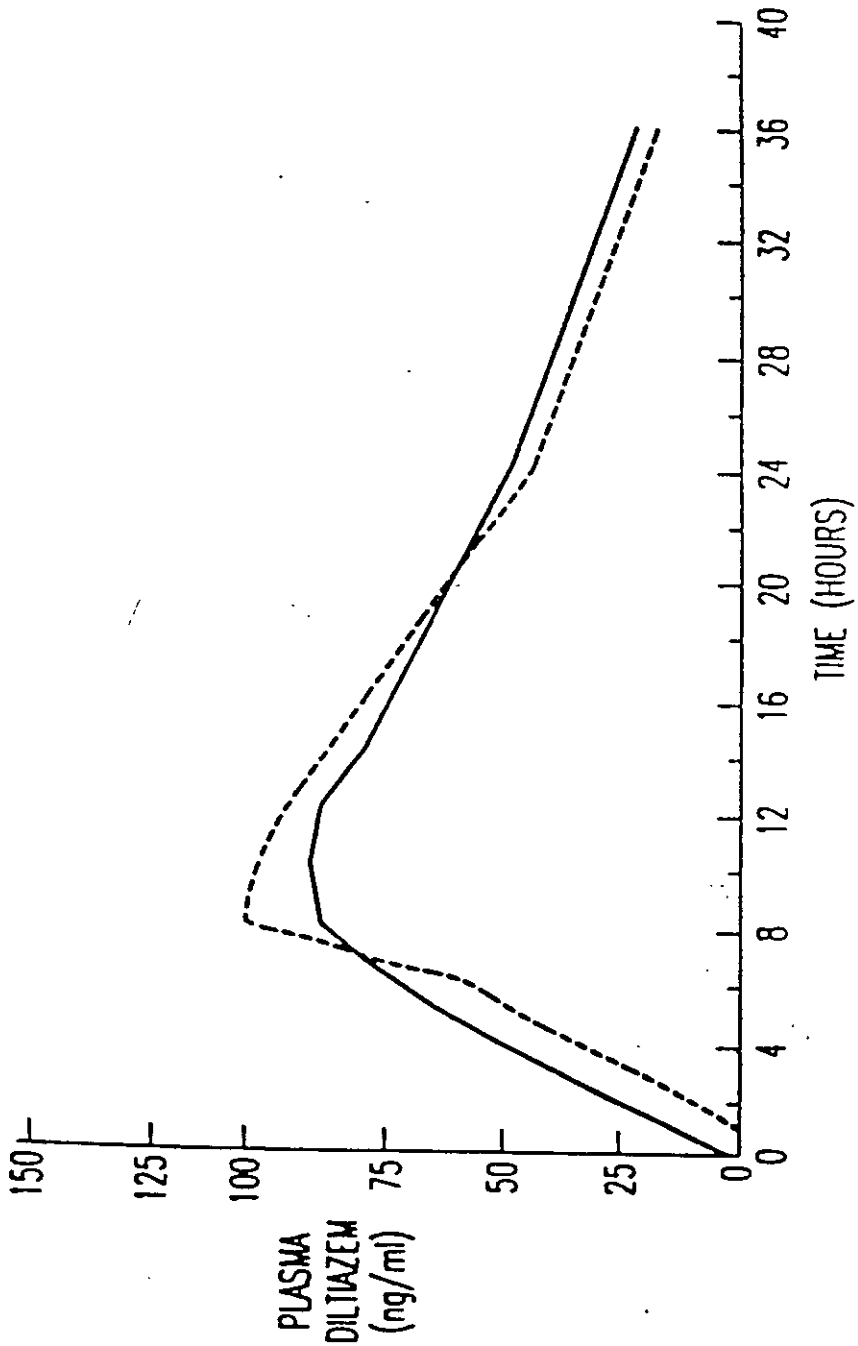

150
125
100
75
50
25
0
PLASMA DILTIAZEM (ng/ml)
0
4
8
12
16
20
24
28
32
36
40
TIME (HOURS)

FIG. 2

Intentionally Left Blank

US005529791A

United States Patent [19]

Deboeck et al.

[11] Patent Number: 5,529,791

[45] Date of Patent: Jun. 25, 1996

[54] EXTENDED RELEASE FORM OF DILTIAZEM

[75] Inventors: Arthur M. Deboeck, Gurabo, Puerto Rico; Philippe R. Baudier, Waterloo, Belgium

[73] Assignees: Galephar P.R., Inc., Ltd., Carolina, Puerto Rico

[21] Appl. No.: 311,722

[22] Filed: Sep. 23, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 68,951, May 28, 1993, abandoned, which is a continuation of Ser. No. 721,396, Jun. 26, 1991, Pat. No. 5,288,505.

[51] Int. Cl.[6] A61K 9/16, A61K 9/58; A61K 9/62

[52] U.S. Cl. 424/494; 424/490; 424/497; 514/777; 514/785; 514/786, 514/970

[58] Field of Search 424/457, 458, 424/462, 490, 493, 497, 498, 499, 494

[56] References Cited

U.S. PATENT DOCUMENTS

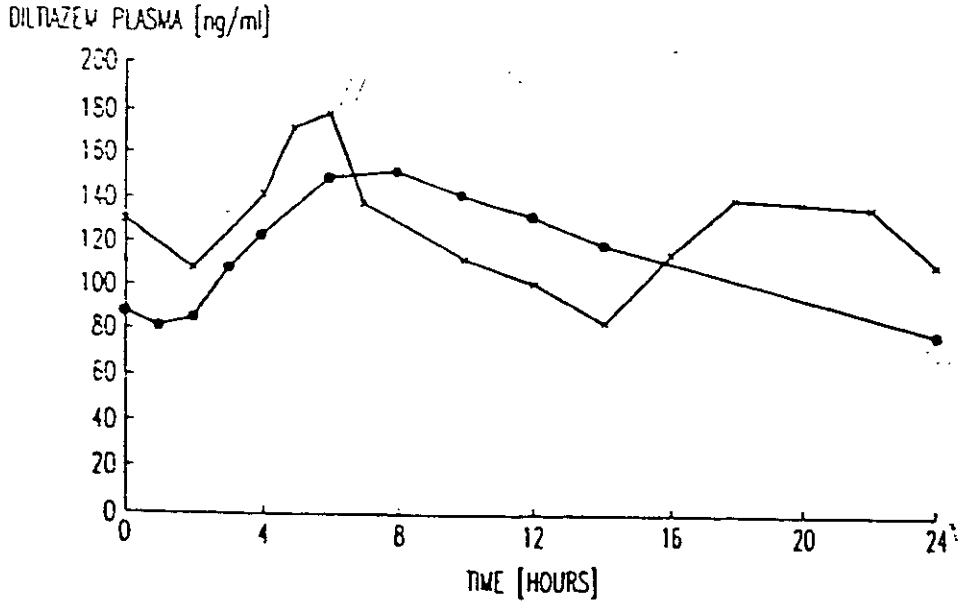
5,112,621	5/1992	Stevens et al.	424/497
5,275,824	1/1994	Curli et al.	424/490

Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

4 Claims, 2 Drawing Sheets



EXTENDED RELEASE FORM OF DILTIAZEM

This application is a continuation of application Ser. No. 08/068,951, filed on May 28, 1993, now abandoned, which is a continuation of application Ser. No. 07/721,396 filed Jun. 26, 1991, now U.S. Pat. No. 5,288,505.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an extended release form of Diltiazem, a process for the manufacture thereof and pharmaceutical compositions containing the same.

2. Description of the Background

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties, and, therefore, finds application in the treatment of angina pectoris and hypertension; either alone or in combination with other medications.

Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arteries, peripheral arteries and arterioles are dilated and heart rate may be reduced. Also, myocardial contractibility may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in human is directly related to its blood or plasma concentration.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times render the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate-release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks, a first galenic form of sustained-released of Diltiazem known under the trade name CARDIZEM SR® was developed and presented in the form of "erodible pellets", U.S. Pat. No. 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not eliminate high Diltiazem blood concentration between successive medication intakes. Hence, the patient is still obliged to take the medication twice daily. The products as described in U.S. Pat. No. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 and 200 layers so as to obtain a core which, thereafter, requires between 20 and 40 layers of coating so as to obtain the membrane. Moreover, the solvent of the polymer solution used to make the membrane is constituted by organic solvents, such as isopropanol, methanol, acetone, and methylene chloride which are dangerous to use due to their flammability and toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are unsuitable in the product which is administered orally.

Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenical form which need be administered only once daily, and from which blood Diltiazem concentrations are not effected by the concomitant intake of food, and, further, which can be made by a process not using organic solvents.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become more apparent in view of the following disclosure are provided by an extended-release galenical form of a pharmaceutically acceptable salt of Diltiazem, which comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration twice daily.

FIG. 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is taken with food.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Diluazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2,(4-methoxyphenyl)-1,5-benzothiazepin-4(5H) has been known for more than 20 years. The synthesis thereof is described in German patent 1,805,714, corresponding to U.S. Pat. No. 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the active substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentrations peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range while simplifying the administration of the medicine to only once daily.

According to the present invention, the Diltiazem extended release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they

may also include the acetate, citrate or lactate salts, for example. It is preferred however, that the hydrochloride salt be used.

In more detail, the microporous membrane whereof the Diltiazem containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer and including at least one adjuvant which may be plastifying agents, pigments, fillers, wetting agent lubricants and antifoam agents.

The active substance containing beads are presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified:

saccharose, mannitol, sorbitol;

lecithins;

polyvinylpyrrolidones;

C_{12} to C_{20} fatty acid esters of saccharose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.);

xylose esters or xylites;

polyoxyethylenic glycerides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France).

In addition to at least one of the above named wetting agents the beads may contain excipients or carriers, such as: Microcrystalline celluloses, such as Avicel products (FMC, U.S.A), methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol, Hercules, U.S.A.), hydroxypropyl celluloses (Klucels, Hercules, U.S.A.); and starches

Among the water-soluble and/or dispersible film forming polymers or copolymers constituting the microporous membrane, may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type, such as Eudragit E30D, L30D, RS-30 D of Röhm Pharma (RFA), ethylcelluloses, such as Ethocels of DOW, U.S.A. and such as AquaCoat of FMC, U.S.A., Hydroxypropyl cellulose and hydroxypropylmethylcellulose and their derivations.

These polymers or copolymers may be associated into the microporous membrane with at least one adjuvant as exemplified by the following:

plastifying agents, such as triacetin, dibutylphthalate, dibutylsebacate, citric acid esters, polyethyleneglycols, polypropyleneglycols and polyvinylpyrrolidone;

pigments, such as iron oxides and titanium oxide;

fillers, such as lactose and sucrose;

wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of hexitols derived from sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyethyleneglycols;

lubricants, such as magnesium stearate and talc;

antifoaming agents, such as silicone oil.

In addition to the polymer or copolymer, the microporous membrane contains, preferably, talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plastifying agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoaming agent.

Generally, the thickness of the microporous membrane is expressed by the percentage of the coating applied to the uncoated beads.

The weight of the microporous membrane may be 2 to 35%, preferably, 5 to 22%, of the weight of said microgranules. These beads may contain the Diltiazem salt in an amount of 20 to 95% by weight, preferably 30 to 85% by weight. The microporous membrane may contain 5 to 95% and, preferably, 30 to 90% of polymers, polymer mixture or copolymers.

The invention relates also to a medicine containing Diltiazem or salt thereof for extended release, the medicine being constituted by beads containing the Diltiazem or salt, such as the hydrochloride, and at least a wetting agent, coated with at least one polymer-based microporous membrane, the coated beads being contained in capsules, little bags or dosage dispensers.

The present invention relates also to a process for obtaining novel forms of a Diltiazem or salt thereof having extended-release in the gastro-intestinal tractus, said process entailing preparing beads and coating the same with a single microporous membrane.

The beads of the Diltiazem or salt thereof may be prepared using a conventional technique. A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Said paste is thereafter extruded in an extruder and then rendered spherical. Several extruder types are usable, for example the extruder of ALEXANDER WERK (RFA) or the apparatus called X-truder of FUJI-PAUDAL (Japan). For obtaining microspheres or beads from the extruded product provided in the form of spaghetti, an apparatus called "spheronizer" (CALEVA Great-Britain) or MARUMERIZER (FUJIU-PAUDAL Japan) type is used.

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersion or solution of at least one wetting agent, for example in a known pilling turbine or in a granulating apparatus, such as the CF granulator system of FREUND INDUSTRIAL CO. (Japan), or in a known planetary granulator such as the colletta (Belgium) type.

The obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed.

Finally, said beads are calibrated to the necessary diameter by passage through appropriate screens.

A pasty or plastic mixture, appropriate to be granulated by means of anyone of the above described techniques, may contain the following weight proportions of the Diltiazem or salt thereof, wetting agents and carriers or excipients:

20 to 85%: Diltiazem hydrochloride

2 to 20% sucroesters WE 15 (wetting agent);

5 to 25% Avicel PH 101 (microcrystalline cellulose of FMC, U.S.A.);

2 to 10% Methocel E 5 (hydroxypropylmethylcelulose of DOW, U.S.A.);

1 to 15% polyvinylpyrrolidone and

5 to 40% distilled water.

Said microporous membrane may be applied onto said beads by pulverizing an aqueous solution or dispersion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pul-

verization may be carried out by spray-gunning or by pulverizing the above-named dispersion into a turbine or fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient, however, in general, from about 120 mg to about 480 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt, provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients, such as β-adrenoceptor blocking agents or diuretics may be used in the present compositions. However, these are only example and are not intended to be limitative.

As examples of β-adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Prindolol or Sotalol may be used, for example.

As examples of diuretic agents, drugs such as Hydrochlorothiazide, Furosemide, Ethacrynic Acid or Chlorothiazide, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired, however, they need not be.

The present invention will now be further illustrated by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative.

According an illustrative embodiment of the present invention, said microporous membrane may be obtained, starting form an aqueous dispersion which contains by weight:

10 to 70 Eudragit E30D (polymer)
0.5 to 15% talc (lubricant)
0.5 to 15% Titanium dioxide (lubricant)
0.5 to 15% Magnesium stearate (lubricant)
0.5 to 15% polyvinylpyrrolidone (plastifying agent)
0.01 to 2% silicone oil (antifoaming agent);
0.05 to 5% polysorbate 80 (wetting agent)
10 to 70% water (carrier)

EXAMPLES

The present invention will now be further illustrated by reference to certain examples, which are provided solely for purposes of illustration and are not intended to be limitative. In particular, examples are provided for Diltiazem Hydrochloride extended release galenic forms, a process for preparing the same, therapeutic applications therefor and pharmacokinetic controls using the present galenic forms.

Example 1—beads manufacture

Diltiazem hydrochloride	1120 g
Lactose	119 g
Microcrystalline cellulose (Avicel pH 101)	140 g
Povidone k 30	21 g

After introducing the powders into a planetary mixer and granulating same though the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to obtain beads, by means of a spheronizer. After drying at 60° C. for 12 hours the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1,179 g of beads were obtained yield (84%).

Example 2

Diltiazem Hydrochloride	560 g
Crodesta F 160	59.5 g
Microcrystalline cellulose (Avicel pH 101)	70 g
Povidone k 30	10.5 g

The ingredients are introduced in a planetary mixer and dry mixed during approximately 15 minutes. There after 100 ml water USP is added and the mixing is pursued during 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spagetties". A spheronizer type caleva is used so as to transform the extruded product in beads. After drying during 12 hours, on trays, in an oven at 60° C. the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with size comprised between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

Example 3

Beads prepared in Example 1 were coated in a STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technic. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter the coated beads were dried at 50° C. during 16 hours.

Coating suspension composition:

Magnesium stearate	12.5 g
Titanium dioxide	5.0 g
Povidone k 30	5.0 g
Eudragit NE30D	620.0 g
Talc USP	17.5 g
water	338.0 g
Simethicone	1.0 g
Tween 80	0.8 g

"In vitro" dissolution were obtained using the apparatus #2 as described in the United States Pharmacopeia. The 900 ml dissolution medium consisted of a phosphate buffer pH 5.8 and the revolution speed 100 rpm.

elapsed time [h]	percent dissolved [%]
1	5
4	34
8	62
12	84

Example 4

The beads as in Example 2 were coated using a fluidized bed coater equipped with a "wurster" system. 8 kg of uncoated beads were introduced in an Aeromatic Aerocoater and 2.77 kg of the following coating suspension was applied at a rate of 30–35 g per minute. Thereafter the coated beads were dried during 15 hours at 45° C.

Coating suspension:

Magnesium stearate	0.636 kg
Talc	0.636 kg

-continued

Titanium dioxide	0.0909 kg
Hydroxypropylmethylcellulose	0.200 kg
Polysorbate 80 NF	0.007 kg
Sucrochlorose e emulsion	0.018 kg
Eudragit NE 30 D	12.4 kg
purified water	6.7 kg

Dissolution "in vitro"

The results were obtained using the same equipment as in Example 3. The dissolution medium was composed of 900 ml of water and the temperature was maintained of 37±0.5° C.

elapsed time [h]	percent dissolved [%]
2	9
4	33
6	54
8	82

Pharmacokinetical results

The new galenic form of Example 4 was the object of a pharmacokinetical study in comparison with a form in accordance to the prior art as described in U.S. Pat. No. 4,721,619. (Cardizen SR®) therefore 6 healthy subject received successively in a random order 300 mg of each of the 2 products. The product of Example 4 was administered at a dose of 300 mg once daily while the product on the market was administered twice daily at a dose of 150 mg (300 mg daily total dose) during 7 days. At each of the eight day, 11 samples of blood were withdrawn when product of Example 4 was administered and 15 blood samples where withdrawn after the Cardizen SR® administration. Diltiazem plasma levels were assayed using a specific high pressure liquid chromatographic method. FIG. 1 shows the results obtained: the continuous line represent the Diltiazem plasma levels obtained with the product of Example 4 and the broken line the Diltiazem plasma levels of Cardizen SR®

FIG. 1

Pharmacokinetical parameters

	Units	Example 4	Cardizen SR ®
Area under the curve (0–24 h)	mg.h/ml	2782 ± 1037	2864 ± 1222
Maximal concentration	mg/ml	116.3 ± 54.1	192.7 ± 85.3
Time of maximum concentration	h	8.0 ± 1.8	5.2 ± 2.8
Fluctuation	%	85.7 ± 25.7	109.5 ± 25
Time during the concentration is above 75% of the maximum concentration	h	9.8 ± 2.3	6.7 ± 3.7

From these results the following conclusion can be drawn:

First, FIG. 1 shows that the Diltiazem plasma levels obtained after a once daily administration of one of the products of the present invention are comparable to the ones obtained after a twice daily administration of the product of the previous art.

Second, the bioavailability, expressed by the areas under the curve of the 2 products, is equivalent (no statistical detectable difference).

Third, the maximal concentration and the fluctuations obtained after a once daily administration of the product of the present invention is lower than the one obtained with Cardizen SR® after a twice daily administration.

Fourth, the time during the concentration is above 75% of the maximum concentration is 46% longer after the once daily administration of the product of the present invention than with product of the previous art when given twice daily.

Food effect study

The product of Example 4 was given to 24 healthy volunteers and the bioavailability was measured after single oral dose of 300 mg given with and without food.

The clinical trial was conducted as an open, single dose, randomized, cross over study. Blood samples were obtained before and until 36 hours after the administration. The experiment was repeated in the same subjects with the other treatment at an interval of 7 days. The plasma concentration of Diltiazem was determined in all available samples using an HPLC method. Pharmacokinetics parameters were derived from the individual plasma concentration versus time profiles and statistically compared for treatment differences and assessment of bioequivalence. FIG. 2 curves shows the mean plasma levels obtained when the product is taken without food and the dotted curve the mean plasma levels obtained when the product is taken with food.

FIG. 2

Pharmacokinetics parameter - product of Example 4

	Units	Fasting	Food
Area under the curve (total	mg. h/ml	1988 ± 119	1925 ± 109
Mean residence time	h	21.3 ± 0.7	19.9 ± 0.9
K_a	h^{-1}	0.283 ± 0.024	0.300 ± 0.027
Maximum concentration	mg/ml	100 ± 4.8	112 ± 5.9

No statistical difference was detectable. The product of Example 4 given with food is bioequivalent to the administration without food to within less than 20% regarding area under the curve, mean residence time and maximum concentration. The larger interval obtained for K_a was due to the higher variability of this parameter, the difference between the treatment means remaining small (6.%).

From all the results it appears clearly that the product of the present invention can be administered once a day and that the plasma concentration variations are lower than the one obtained with the conventional product given twice a day.

Having described the present invention, it will now be apparent to one skilled in the art that many changes and modifications may be made to the above-described embodiments while remaining within the spirit and the scope of the present invention.

What is claimed as new and desired to be secured by Letters Patent of the United States is:

1. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract

or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant,

and wherein the wetting agent is selected from the group consisting of sugars, C_{12}-C_{20} fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

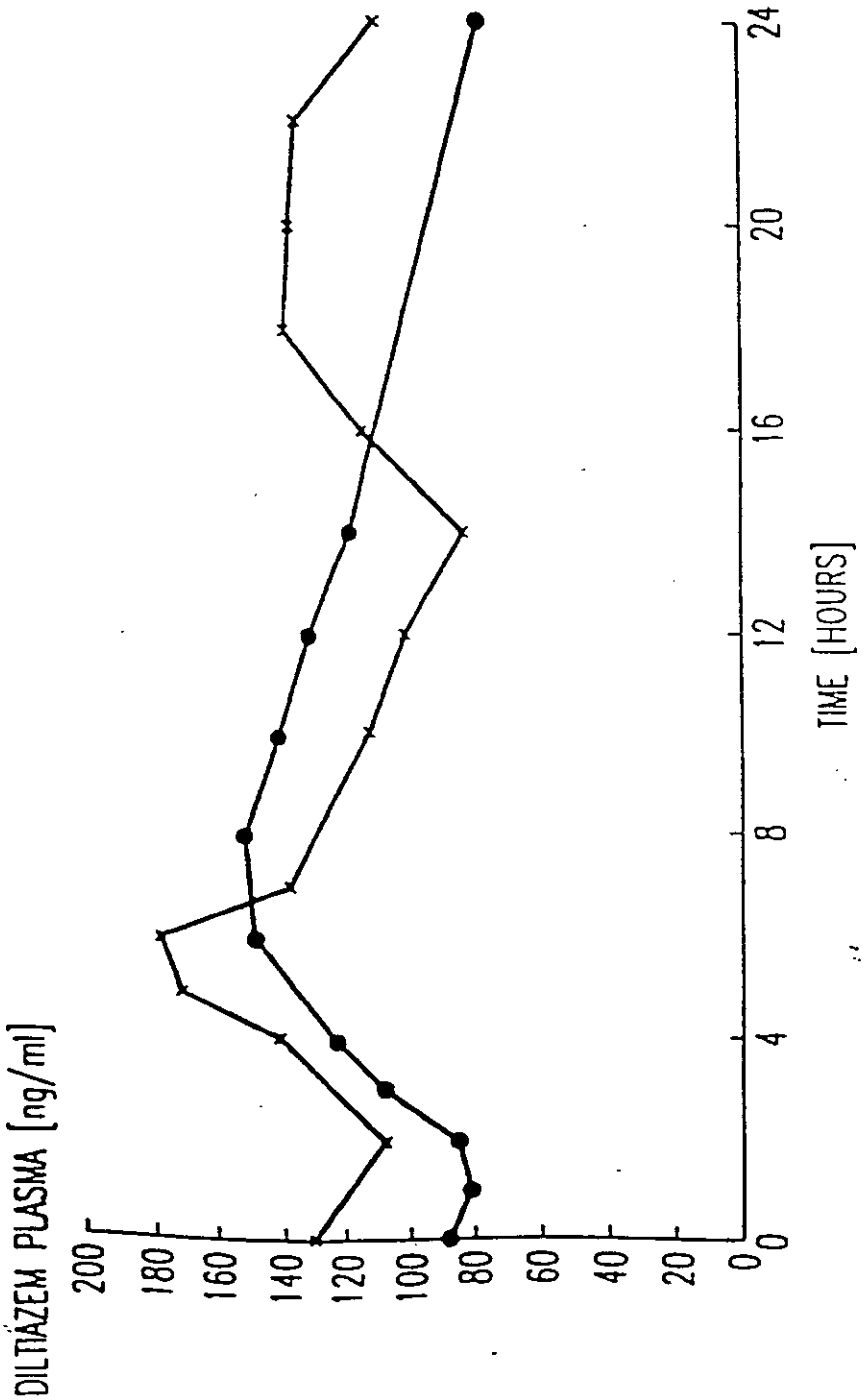
2. The composition of claim 1, wherein the wetting agent is a sugar.

3. The composition of claim 1, wherein the effective amount of the wetting agent is about 8% by weight of the composition.

4. The composition of claim 1, wherein the wetting agent is sucrose stearate, the water-soluble or water-dispersible polymer or copolymer is hydroxypropylmethyl-cellulose and the water, acid- and base- insoluble polymer is an acrylic polymer.

* * * * *

FIG. 1


DILTIAZEM PLASMA [ng/ml]
200
180
160
140
120
100
80
60
40
20
0
0
4
8
12
16
20
24
TIME [HOURS]

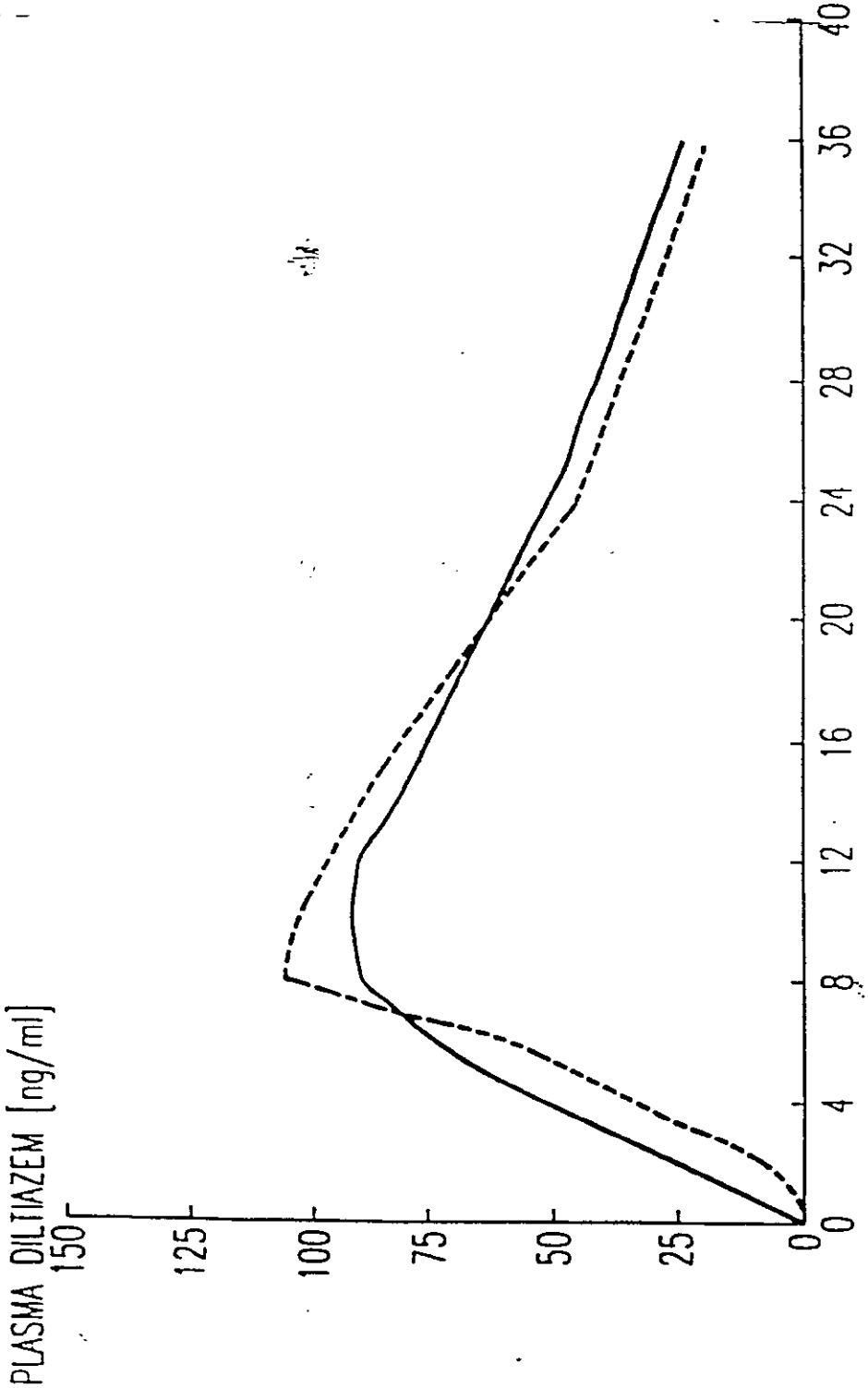

PLASMA DILTIAZEM [ng/ml]
150
125
100
75
50
25
0
0
4
8
12
16
20
24
28
32
36
40
TIME [HOURS]

FIG. 2

EXCLUSIVITY SUMMARY FOR NDA # SUPPL #_____

Trade Name: Cardizem . —— Generic Name: Diltiazem Hydrochloride Extended Release Tablets

Applicant Name: Biovail HFD # 110

Approval Date If Known: N/A

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO / X//

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

The evening dosing in the treatment of hypertension is supported by a single double- blind, parallel clinical study in which subjects with moderate diastolic hypertension were randomized to placebo or 120, 240, 360, or 540 mg of diltiazem hydrochloride once daily in the evening or 360 mg once daily in the morning. Follow-up was at 7 weeks.

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /__X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO- please indicate as such)

YES /_X__/ NO /___/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations

in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

SECTION 2 – SUMMARY

H. Clinical Data Summary

Cross Ref. to Section Vol/Page

The clinical efficacy data for the hypertension indication is referenced from the approved Diltiazem Hydrochloride Extended-release Capsule NDA 20-939. One clinical study was included in that application: 48/0001

Study Number 1003-0001-DILG12: A Double blind, Placebo-Controlled, Parallel Group Fixed-dose study of the efficacy and adverse event profile of Diltiazem Extended-Release (ER) in the Treatment of Essential Hypertension.

This study conducted in 258 patients demonstrated the efficacy of Diltiazem Hydrochloride Extended-release capsules in the treatment of essential hypertension.

Based on the bioequivalence of the Diltiazem Hydrochloride Extended-release Capsule and Diltiazem Hydrochloride Extended Release Tablet formulations, the clinical efficacy data for the Extended-release Capsule formulation is applicable to the Diltiazem Hydrochloride Extended Release Tablet and additional clinical studies are not required (agreed in the August 26, 1999 meeting with the Division of Cardio-Renal Drug Products). Data demonstrating bioequivalence is enclosed in Section 6.

On March 7, 2001 the applicant was granted a full waiver from including pediatric studies in this NDA (under 21 CFR 314.55). A copy of the correspondence from the Division of Cardio-Renal Drug Products is attached in Section 8 of this application. Please note that the letter makes reference to Diltiazem Hydrochloride Extended Release Capsules as the request was submitted under IND 57, 711, but the dosage form referenced in our letter dated December 12, 2000 (copy attached) was the proposed Diltiazem Hydrochloride Extended Release Tablet. Diltiazem Hydrochloride Extended-release Capsules were approved in January, 2000 without the need for pediatric studies and no supplements to this NDA, that would require pediatric studies, are contemplated at this time.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-392 Supplement Type (e.g. SE5): N000 Supplement Number: NA

Stamp Date: June 11, 2001 Action Date: June 11, 2002

HFD 110 Trade and generic names/dosage form: Cardizem CD Diltiazem Hydrocloride Extended Release Tablets, 240, 300, 360 mg for once daily administration

Applicant: Biovail Therapeutic Class: Calcium Channel Blocker

Indication(s) previously approved: Hypertension

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Hypertension

Is there a full waiver for this indication (check one)?

☒ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☒ Other: This product is not suitable for dosing in the pediatric population.
Application granted under 21 CFR 314.55

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval

- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other:_____

Date studies are due (mm/dd/yy): _____

studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ction D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
1-594-7337

BIOVAIL
TECHNOLOGIES LTD.

DEBARMENT CERTIFICATION

Cardizem —
Diltiazem Hydrochloride Extended Release Tablets, 120, 180, 240, 300, 360 and 420 mg

In accordance with the requirements of Section 306 (k) (1) of the Federal Food Drug and Cosmetic Act, I, the undersigned, certify that, Biovail Laboratories Incorporated did not and will not use in any capacity the services of any person debarred under Section 306 (k) of the Federal Food, Drug and Cosmetic Act connection with this application.

Furthermore, I certify that neither the applicant nor its employees nor any affiliated company or its employees has been convicted within the last five years for acts described in subsections (a) and (b) of Section 306.

Eugene Melnyk
President
Biovail Laboratories Incorporated

July 2nd, 2002
Date

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel. (703) 995-2400 Fax: (703) 995-2490

BIOVAIL
LABORATORIES INCORPORATED

DEBARMENT CERTIFICATION

Diltiazem Hydrochloride Extended Release Tablets, 240, 300 and 360 mg

In accordance with the requirements of Section 306 (k) of the Federal Food Drug and Cosmetic Act, I, the undersigned, certify that to the best of my knowledge, Biovail Laboratories Incorporated did not use any person debarred under subsection (a) or (b) of 306 (k) in any capacity in connection with this application, nor will Biovail Laboratories Incorporated use any such person in connection with this application.

Furthermore, I certify that to the best of my knowledge, neither the applicant nor its employees nor any affiliated company or its employees has been convicted within the last five years for acts described in subsections (a) and (b) of Section 306.

Eugene Melnyk
President
Biovail Laboratories Incorporated

June 5th, 2001
Date

BIOVAIL LABORATORIES INCORPORATED
Chelston Park, Building 2, Collymore Rock, St. Michael, BH1, Barbados, W.I.
Tel: (246) 437-7080 Fax: (246) 437-7085

BIOVAIL
LABORATORIES INCORPORATED

REPROCESSING STATEMENT

Diltiazem Hydrochloride Extended Release Tablets

Biovail Corporation confirms in this letter that there will not be any reprocessing of any batch of Diltiazem Hydrochloride Extended Release Tablets.

In the future, if reprocessing is needed, the reprocessing procedures will be submitted to FDA for approval before use.

Eugene Melnyk
President
Biovail Laboratories Incorporated

June 6th, 2001
Date

BIOVAIL LABORATORIES INCORPORATED
Chelston Park, Building 2, Collymore Rock, St. Michael, BH1, Barbados, W.I.
Tel: (246) 437-7080 Fax: (246) 437-7085

BIOVAIL
LABORATORIES INCORPORATED

ENVIRONMENTAL COMPLIANCE CERTIFICATION

Diltiazem Hydrochloride Extended Release Tablets

Biovail Laboratories Incorporated certifies that the manufacturing of Diltiazem Hydrochloride Extended Release Tablets will be in compliance with all federal, state and local environmental laws.

Eugene Melnyk
President
Biovail Laboratories Incorporated

June 6th 2001
Date

BIOVAIL LABORATORIES INCORPORATED
Chelston Park, Building 2, Collymore Rock, St. Michael, BH1, Barbados, W.I
Tel: (246) 437-7080 Fax: (246) 437-7085

RHPM Overview
February 4, 2003

NDA 21-392	Cardizem LA (diltiazem hydrochloride extended release) Tablets
Sponsor:	Biovail Technologies
Classification:	3S
Date of Application:	June 8, 2001
Date of Receipt:	June 11, 2001
User Fee Goal Date:	June 11, 2002
Class 2 Resubmission:	October 24, 2002
Class 2 Goal Date:	April 24, 2003

Background:

Diltiazem hydrochloride, a calcium ion cellular influx inhibitor intended for use as an antihypertensive, is currently marketed as once-a-day extended release capsules for daytime administration. [redacted] The basis of approval is a double blind clinical study demonstrating the efficacy of 120 mg to 420 mg diltiazem capsules administered at nighttime compared to placebo and 360 mg daytime administration. The related IND is 51,711.

Review

Medical Review

Reviewer:	Norman Stockbridge, Ph.D.
Labeling:	See Dr. Stockbridge's revised labeling dated January 3, 2003
Conclusion:	There are no clinical barriers to approval of Cardizem LA as an antihypertensive for use once daily in the morning or evening. The various chemistry and biopharmaceutics have been resolved and as a result, an "approval" letter should be issued.

Statistical Review:

Reviewer:	John Lawrence, Ph.D. (HFD-710)
Labeling:	None
Conclusion:	All studied doses of the drug appear to be safe after 7 weeks of treatment for reduction of hypertension. The level of evidence required to establish efficacy in a single study was reached only for the highest dose studied (540 mg PM). (See Dr. Lawrence's 2/13/02 review)

Chemistry Review

Reviewer:	Ramshara Mittal, Ph.D.
Labeling:	The labels and package insert are satisfactory. (See page 23 of the June 6, 2002 review).
Conclusion:	The deficiencies noted regarding reference standards, drug substance from two manufacturers, and stability protocols (See Dr. Mittals April 17, May 22, and June 6, 2002 reviews) have been resolved. The sponsor withdrew references to [redacted]. As a result, Dr. Mittal states that the application may be approved from the CMC perspective.

Pharmacology Review:

Reviewer:	Charles Resnick, Ph.D.
Labeling:	Statements regarding animal and *in vitro* studies are the same as in the approved labeling for Biovail's Diltiazem HCL Extended Release Capsule (NDA 20-939).
Conclusion:	Approval

Biopharmaceutics Review:

Reviewer:	Lydia Velazquez, Pharm.D.
Labeling:	See Dr. Velazquez's 12/30/02 review for labeling recommendations.
Conclusion:	The sponsor demonstrated bioequivalence of the 420 mg strength extended-release tablet. A biowaiver is granted for the 120, 180, 240 and 360 mg diltiazem hydrochloride. The dissolution timepoints used by the sponsor for dissolution-stability testing are acceptable on an interim basis in addition to the pending submission of further stability and lot-release data on the primary stability lots as well as the first three post-marketing production lots as part of the initial Annual Report. Final dissolution specifications will be set a later time based on the review to the additional one-year stability and lot release data (see Dr. Velazquez's 12/30/02 review). Approval should be granted based on the proposed draft labeling attached to the approval letter.

Safety Update:	No safety concerns identified.
Patent Information:	Included in package
Pediatric Information:	Waiver granted.
EER:	The overall EER recommendation, dated July 19, 2001, was acceptable.
DSI:	No DSI audits conducted.

Debarrment Certification: Included in package

ODS Tradename Review: The Office of Drug Safety, Division of Medication Errors and Technical Support has no objection to the use of the tradename Cardizem LA (see 8Nov03 review).

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

12/24/02

Office of Drug Safety

MEMO

To: Douglas Throckmorton, M.D.
Director, Division of Cardio-Renal Drug Products
HFD-110

From: Jennifer Fan, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Denise P. Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

CC: Denise Hinton
Project Manager, Division of Cardio-Renal Drug Products
HFD-110

Date: November 5, 2002

Re: NDA 21-392/Cardizem — (Primary) and Cardizem LA (Alternate)
(Diltiazem Hydrochloride Extended-Release Tablets) 120 mg,
180 mg, 240 mg, 300 mg, 360 mg, and 420 mg (ODS Consult 02-0081-3)

This is in response to the October 17, 2002 request from the Division of Cardio-Renal Drug Products (DCRDP) to review the proposed proprietary name *Cardizem* — and an alternate proposed proprietary name, *Cardizem LA*. The sponsor previously submitted the proprietary names Cardizem —, Cardizem —, and Cardizem — However, DMETS found Cardizem — and Cardizem — unacceptable because the proposed modifiers sounded and looked similar to currently marketed products (see ODS consults 02-0081-1 and 02-0081-2). DMETS did not identify any safety concerns related to Cardizem —, however, the Division found the proposed name unacceptable because — could be interpreted as — 'ill' which, would potentially be misleading to practitioners [

]

The sponsor now submits *Cardizem* — as its new proprietary name. According to the Division, the sponsor stated that the abbreviation — stands for " —— ." However, the Division believes that — ' could represent — dosing, which will not be a part of the recommended dosing schedule. Given that the Division does not approve of the name *Cardizem* —DMETS will not evaluate the name *Cardizem* —

As an alternative to *Cardizem* —, the sponsor submitted *Cardizem LA*. The only proprietary names currently on the market that utilizes 'LA' as a modifier are Detrol LA, Inderal LA, and Ritalin LA. The modifier 'LA' does not look or sound similar to the existing Cardizem modifiers (i.e., XR, XT, CD, and SR). Therefore, DMETS believes that there will be a low risk of confusion between these names and *Cardizem LA*. DMETS has some concern that the diltiazem product line contains several products that use modifiers (Dilacor XR, Cartia XT. Cardizem CD, and Cardizem SR) to distinguish the products. The addition of the Cardizem LA product may increase the potential for confusion among the extended-release products; however, the new formulation needs to be distinguished from the other Cardizem formulations because they are not bioequivalent and cannot be used interchangeably. For this reason, DMETS has no objection to the use of the tradename *Cardizem LA*.

DMETS considers this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the Medication Errors Project Manager, Sammie Beam, at 301-827-3242.

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

/s/

Alina Mahmud
11/8/02 12:16:46 PM
PHARMACIST

Carol Holquist
11/8/02 02:30:36 PM
PHARMACIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7/11/02

NDA 21-392

Biovail Laboratories Incorporated
Attention: Mr. John B. Dubeck
c/o Keller and Heckman
1001 G Street, N.W., Suite 500 West
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your June 8, 2001 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for diltiazem hydrochloride 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg extended release tablets.

Your proposed dissolution specifications of 2, 8, 14, and 24 hours at NMT — NLT —, and NLT — respectively, are not acceptable, and we recommend on an interim basis the following specifications:

Time (hours)	Interim Dissolution Specifications
2	NMT %
8	
14	%
24	NLT

The final dissolution specification will be set at a later time following collection of dissolution data at 2, 6, 8, 12, 14, 16, and 24 hours and will be based on the review of the additional one-year stability and lot release data provided.

If you have any questions, please call:

Ms. Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5312

Sincerely,

{See appended electronic signature page}

Douglas C.Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
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/

Doug Throckmorton
7/11/02 02:54:40 PM

Hinton, Denise

From: Dorantes, Angelica
Sent: Friday, June 07, 2002 4:58 PM
To: Throckmorton, Douglas C; Hinton, Denise
Cc: Robbie, Gabriel J; Dorantes, Angelica
Subject: NDA 21-392 for Diltiazem Extended Release Tablets

Hello Doug & Denise:

I am enclosing my comments for this NDA.

Diltiazem ActionLetter1.doc

Regarcs, Angelica

1. Your proposed dissolution method [USP Apparatus 2 (paddle), 100 rpm, and 900 ml of phosphate buffer pH 5.8 at 37°C] is acceptable. However, the proposed dissolution sampling time points of 8, 14, and 24 hours, are not appropriate. We consider that sampling at 2, 6, 12, and 16 hours will provide more adequate information on the dissolution/release characteristics of your product.

   Taking into account that your dissolution-stability data were generated using 2, 8, 14, and 24 hours, we will accept on an interim basis your dissolution time points, provided that further stability and lot-release data (i.e., data collected during the first year from date of approval), includes both sets of dissolution time points (i.e., 2, 6, 8, 12, 14, 16, and 24 hours).

2. We consider that your proposed dissolution specifications are not acceptable, and we recommend on an interim basis the following specifications:

Time (hours)	Interim Dissolution Specifications
2	NMT —
6	—
8	—
12	—
14	—
16	NLT —
24	NLT —

   Please note that final dissolution specification will be set at a later time and they will be based on the review of the additional — stability and lot release data that you will provide.

3. For extended release products, a bio-waiver based on dissolution profile comparison for strengths higher that the one tested in the bioequivalence study cannot be granted. Therefore, the proposed 420 mg extended release tablet is not acceptable. To get the approval of this higher 420 mg strength, you should provide acceptable bioequivalence data.

4. Your comment indicating that you did not perform comparative dissolution studies in 0.1N HCl, because Diltiazem degrades substantially in this medium is not acceptable. Please note that your NDA for CARDIZEM® CD capsules included dissolution data in this medium. Therefore, before a bio-waiver for the 240 and 300 mg extended release tablets could be granted, you should provide additional dissolution profile comparison data in 0.1N HCl under the same dissolution conditions (i.e., USP Apparatus 2 and 100 rpm).

5. In order to obtain a waiver for the requirement of the submission of in vivo bioequivalence data for the lower strengths 120 and 180 mg extended release tablets, you should provide dissolution profile comparisons in the application dissolution medium (phosphate buffer pH 5.8) and in the following three dissolution media; 0.1N HCl, buffer pH 4.2, and buffer pH 6.8. The dissolution profiles should be generated using 12 units/lot of the test and reference products and same dissolution conditions.

6. Before a bio-waiver for the proposed manufacturing site changes for the 300 and 360 mg extended release tablets can be granted, you should provide additional comparative dissolution profile data in 0.1N HCl. To obtain a manufacturing-site change bio-waiver for the 120, 180, and 240 mg extended release tablets, you should provide comparative dissolution profile data from these sites in the following dissolution media: 0.1N HCl, buffer pH 4.2, buffer pH 6.8, and application dissolution medium (phosphate buffer pH 5.8).

7. Additionally, we noted that you decided to change the scored extended release tablets that were used to generate all the bioequivalence and dissolution data, for unscored tablets. In lieu of this change, you should provide additional comparative dissolution profile data in the application dissolution medium (phosphate buffer pH 5.8), showing that this change is not affecting your product (i.e., 120, 180, 240, 300, and 360 mg extended release tablets).

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Hinton, Denise

From: Robbie, Gabriel J
Sent: Tuesday, May 28, 2002 1:40 PM
To: CDER-CPBBRIEFING
Cc: Stockbridge, Norman L; Hinton, Denise
Subject: Optional Inter-Division Briefing for NDA 21-392 (Diltiazem)

Category:	Optional Inter-Division CPB Briefing
Date & Time:	Wednesday, May 29, 2002, 4:00 p.m.
Location:	WOC II, Conference Room 'A'
NDA:	21-392
Drug name:	Diltiazem Extended Release Tablets —— 240mg, 300mg and 360mg
Drug Category:	3-S
Sponsor:	Bioavail Laboratories
Primary Reviewer:	Gabriel Robbie, Ph.D.
Team Leader:	Patrick J. Marroum, Ph.D
Clinical Division:	Cardio-Renal Drug Products (HFD-110)

Diltiazem hydrochloride, a calcium ion cellular influx inhibitor intended for use as an antihypertensive, is currently marketed as once-a-day extended release capsules for daytime administration. The basis of approval of this NDA is a double-blind clinical study demonstrating the efficacy of 120 mg to 540 mg diltiazem capsules administered at nighttime compared to placebo and 360 mg daytime administration.

The results of the clinical pharmacology/biopharmaceutics review are as follows. Bioequivalence of the highest proposed strength of 360 mg tablet to capsule was demonstrated for both daytime and nighttime administration under single-dose fasted/fed conditions and under multiple dose fasting conditions. Comparison of daytime and night time administration of diltiazem tablet in a single dose and multiple dose study in the fasted state indicated lower exposures of diltiazem Cmax (10-15%) and AUC (15-22%) following daytime administration. The rationale for greater bioavailability of the bead tablets during night time administration is not clear.

The Sponsor is requesting a waiver for in-vivo bioequivalence studies for the lower strengths - 240mg and 300mg of Diltiazem Hydrochloride extended release tablets. The 240mg, 300mg and 360mg strengths are similar with respect to composition and proportion. Comparative dissolution data was submitted at pH 4.2 acetate buffer, pH 5.8 phosphate buffer, pH 6.8 phosphate buffer and water comparing 240mg, 300mg vs. 360mg tablet. Furthermore, dissolution profiles of half tablet and full tablet for the 240mg and 360mg strengths were generated because the tablets are scored. However, the dissolution in 0.1 N HCl was not performed. The biowaiver can be granted provided that the sponsor provide acceptable dissolution profiles in 0.1 N HCl.

The proposed dissolution method: USP Apparatus 2 (Paddle) at 100 rpm in 900 ml of pH 5.8 phosphate buffer at 37°C is acceptable. The sponsor proposed dissolution specification was not acceptable. The Office of Clinical Pharmacology and Biopharmaceutics has proposed alternate dissolution specifications of: 2 h - NMT —— 6 h - —— , 12 h - —— and 16 h - NLT ——

There are no significant issues.

Attached to this email is the draft review.

Thanks,

Gabriel Robbie

Appears This Way
On Original

RHPM Overview
June 7, 2002

NDA 21-392	Cardizem — (diltiazem hydrochloride extended release) Tablets
Sponsor:	Biovail Technologies
Classification:	3S
Date of Application:	June 8, 2001
Date of Receipt:	June 11, 2001
User Fee Goal Date:	June 11, 2002

Background:

Diltiazem hydrochloride, a calcium ion cellular influx inhibitor intended for use as an antihypertensive, is currently marketed as once-a-day extended release capsules for daytime administration. [illegible] The basis of approval is a double blind clinical study demonstrating the efficacy of 120 mg to 420 mg diltiazem capsules administered at nighttime compared to placebo and 360 mg daytime administration. The related IND is 51,711.

Review

Medical Review

Reviewer:	Norman Stockbridge, Ph.D.
Labeling:	See Dr. Stockbridge's for labeling revisions
Conclusion:	There are no clinical barriers to approval of Cardizem — as an antihypertensive for use once daily in the morning or evening. The various unresolved chemistry and biopharmaceutics issues should result in an "approvable action (See June 7, 2002 review).

Statistical Review:

Reviewer:	John Lawrence, Ph.D. (HFD-710)
Labeling:	None
Conclusion:	All studied doses of the drug appear to be safe after 7 weeks of treatment for reduction of hypertension. The level of evidence required to establish efficacy in a single study was reached only for the highest dose studied (540 mg PM). (See Dr. Lawrence's 2/13/02 review)

Chemistry Review

Reviewer:	Ramshara Mittal, Ph.D.
Labeling:	The labels and package insert are satisfactory. (See page 23 of the June 6, 2002 review).
Conclusion:	Deficiencies were noted regarding reference standards, drug substance from two manufacturers, and stability protocols. (See Dr. Mittals April 17, May 22, and June 6, 2002 reviews). The application is approvable pending resolution of the deficiencies listed.

Pharmacology Review:

Reviewer:	Charles Resnick, Ph.D.
Labeling:	Statements regarding animal and *in vitro* studies are the same as in the approved labeling for Biovail's Diltiazem HCL Extended Release Capsule (NDA 20-939).
Conclusion:	Approvable.

Biopharmaceutics Review:

Reviewer:	Gabriel Robbie, Ph.D.
Labeling:	See Dr. Robbie's 5/31/02 review for labeling recommendations.
Conclusion:	The rationale for greater bioavailablity of the bead tablets during nighttime administration is not clear. The sponsor requested a waiver for in-vivo bioequivalence studies for the lower strengths (240 mg and 300 mg of Diltiazem hydrochloride Extended Release Tablets. The biowaiver can be granted provided that the sponsor provide acceptable dissolution profiles in 0.1 N HCl for the 420 mg tablet. The sponsor needs to provide stability data, final specifications, and Biopharm recommended timepoints. (See Dr. Robbie's May 31, 2002 review).

Safety Update: No safety concerns identified.

Patent Information: Included in package

Pediatric Information: Waiver granted.

EER: The overall EER recommendation, dated July 19, 2001, was acceptable.

DSI: No DSI audits conducted.

Debarrment Certification: Included in package

ODS Tradename Review: Division of Medication Errors and Technical Support (DMETS) does not recommend the use of the modifier ‾‾ in conjunction with the proprietary name, "Cardizem. DMETS recommends implementation of the labeling revisions outlined in section III of the May 1, 2002 Proprietary Name Review. (See review located in Advertising section). Biovail has proposed two alternate product tradenames of Cardizem ‾ and Cardizem — for FDA review and consideration.

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

3/27/02

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-392	Efficacy Supplement Type SE-	Supplement Number
Drug: Cardizem LA (diltiazem hydrochloride) Extended- Release Tablets		Applicant: Biovail
RPM: Denise M. Hinton	HFD-110	Phone # (301) 594-5333
Application Type: (x) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): 51,711	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates/Class 2 resubmission	April 24, 2003
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE-June 11, 2002
• Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	3Feb03-Dr. Stockbridge Attached to AP letter
• Most recent applicant-proposed labeling	7Oct02
• Original applicant-proposed labeling	21Aug02
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	8Nov02 27Feb02 24Dec02 12Jun02 4Jun02
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Enclosed
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	21Aug02
• Reviews	R. Mittal N. Stockbridge L. Velazquez
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Enclosed
❖ Memoranda and Telecons	Enclosed
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	26Aug99
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Dr. Throckmorton 11June01
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	7Jun02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	27Dec01, 7Jun02
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	NA
❖ Statistical review(s) *(indicate date for each review)*	13Feb02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	31May02, 30Dec02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	None
• Bioequivalence studies	No inspection per Dr. Lipicky
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	6Jan03, 6Jun02
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	6Jan03
• Review & FONSI *(indicate date of review)*	6Jan03
• Review & Environmental Impact Statement *(indicate date of each review)*	6Jan03
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: 22May02 (x) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (x) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	9Aug01
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	13Feb02
❖ CAC/ECAC report	NA

423-989-8055 Division of Cardio-Renal Drug Products
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	703-995-2444
Attention:	Mr. Wayne Kreppner
Company Name:	Biovail
Phone:	703-995-2280
Subject:	Meeting Minutes
Date:	March 21, 2002
Number of pages including this cover sheet:	4
From:	Sandy Birdsong
Phone:	301-594-5334
FAX:	301-594-5494

Dear Mr. Kreppner:

The minutes of our February 27, 2002 meeting accompany this fax. You are responsible for notifying us of any differences perceived in meeting outcomes. Please let me know you received this fax. Thank you.

Sandy

Minutes of a Meeting

Application:	NDA 21-392 Cardizem — (diltiazem hydrochloride) Extended Release Tablets
Sponsor:	Biovail Technologies, Ltd.
Date:	February 27, 2002
Subject:	Labeling Discussion
Meeting Chair:	Raymond Lipicky, M.D.
Meeting Recorder:	Sandra Birdsong

FDA Participants

Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Douglas C. Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Medical Team Leader, HFD-110
Sandra Birdsong	Regulatory Project Manger, HFD-110

Biovail Participants

Dr. Paul Desjardins	Vice-President, Product Development Operations
Dr. Kenneth Albert	Vice-President, Clinical Development
Dr. Theo Gana	Director, Clinical Research
Dr. Okpo Eradiri	Senior Director, Pharmacokinetics and Toxicology
Mr. Paul Maes	Vice-President, Pharmaceutics
Mr. Wayne Kreppner	Director, Regulatory Affairs and Technology Transfer
[	] Consultant

Background

In a meeting with the sponsor on April 21, 2000, the design of the clinical studies and evening dosing were discussed and — clinical studies were proposed: one study in hypertensive patients [ ]

NDA 21-392 was submitted on June 8, 2001. The study in hypertensive patients has been completed. The sponsor requested this meeting to discuss inclusion of the study results in the labeling.

Meeting

Dr. Lipicky said that it seemed appropriate for the sponsor to have this meeting before we take an action. With regard to the reviews, Dr. Stockbridge said the Clinical and Statistical reviews are completed and no problems have been identified. The Biopharmaceutics review is outstanding. The Division's current view is that the labeling should state only that this product can be administered in the morning or evening. The sponsor argued that they had reached an agreement with Dr. Temple in a previous meeting about the conduct of the trials, and their and inclusion of the trials, into labeling if successful, into the labeling, and that the current stance of the Division was apparently inconsistent with this agreement.

Dr. Lipicky said he could not disagree with that statement. However, [redacted] inappropriate for the public health, as the inclusion of the information could be seen as an implied claim of clinical benefit, despite the absence of strong evidence for such a benefit. Despite the epidemiologic data linking the early morning rise in BP to the timing of stroke, death and myocardial infarction, there is no clinical evidence linking prevention of the morning rise in BP to a reduction in these events. He believes there is a conflict between the sponsor's desire for [redacted] and the interests of the public health. The labeling should say that blood pressure is controlled over the 24-hour period. Dosing once in the morning or once in the evening would be acceptable.

The sponsor said that the data showed a difference in bioavailability between morning and night. However, Dr. Lipicky stated that bioavailability is not a pertinent consideration with regard to the clinical benefit [redacted]

Dr. Lipicky suggested that something in the Clinical Trials section indicating that blood pressure is controlled over the dosing interval regardless of time of administration, [redacted] A second option would be a relatively compact description of what happened in the nighttime dosing trial, similar to what is now in the label for daytime dosing. Dr. Stockbridge stated the view that the importance of a trial in the label is in some way correlated to on the amount of space taken up in the label, such that we should give equal space to the description of the trials using daytime and nighttime administration . Finally, the Division raised the possibility of placing language in the labeling about the trial along with a disclaimer saying that no data indicating that a particular time of day is better than another are available.

The sponsor asked [redacted]? Dr. Lipicky said that our experience is that when data are included in the label a benefit is implied. The sponsor asked [redacted]

[ ] would be permitted? Dr. Stockbridge asked if the sponsor is suggesting something such as: the peak effect for the drug, irrespective of when it is given, is time given, occurs a certain number of hours after dosing? In any case, the Division is concerned that including such information in the label implies that the differences demonstrate clinical value.

The sponsor asked for an explanation for what happened between the last meeting with the Division and this one. Dr. Lipicky acknowledged that while he was not present at the last meeting, he believes Dr. Temple is guided heavily by saying "if you do trials, we will put something in the label." He stated that Dr. Throckmorton would make the final decision for the Division regarding the product labeling. Should the sponsor choose to appeal that decision, Dr. Temple would obviously be involved in the response.

[ ]

Dr. Stockbridge replied that an outcome trial should be done. The firm stated [ ] and asked what effect they might have on this question. Dr. Lipicky said they would have no effect.

Trade Name

Dr. Lipicky informed the sponsor that he doesn't believe the Office of New Drug Safety (ONDS), formerly the Office of Post-Marketing Drug Risk Assessment (OPDRA) would accept — in the trade name. The sponsor noted that there is a precedent for the use of — would that be acceptable? Dr. Lipicky said that precedent was decided at a time when input from OPDRA was not required, but this would not be possible in the future.

Conclusion

Dr. Lipicky stated more thought should be given to these issues by both the Division and the sponsor. The Division would send a draft package insert to the sponsor when it is completed. That would be the appropriate time for the sponsor to request a meeting with Dr. Temple.

/S/

Sandra Birdsong

/S/

Douglas C. Throckmorton, M.D.

RD: slb/18 Mar 02
DCT/20 Mar 02
NS/20 Mar 02

Final: slb/21 Mar 02

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

/s/

Sandra Birdsong
3/29/02 10:46:31 AM
Faxed to sponsor on 21 March 2002

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attached	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Paul DesJardins	Vice President Product Development Operations
FIRM/ORGANIZATION: Biovail Technologies Ltd.	
SIGNATURE	DATE: November 2, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(703) 995-2444
Attention:	Wayne Kreppner
Company Name:	Biovail
Phone:	(703) 995-2400
Subject:	meeting notice
Date:	2-15-02
Pages including this sheet:	3
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Wayne,

The notice for our upcoming meeting regarding NDA 21-392 accompanies this cover sheet. This serves as confirmation of the meeting. I should note that I will not attend this meeting, as it has been reassigned to another Project Manager (Sandra Birdsong).

With respect to your voicemessage, the primary goal date for this NDA is now July 11, 2002 and the secondary goal date is June 11, 2002. (The CMC amendment extended the primary, but not the secondary, goal date.) We will try to meet the earliest goal date, which is now the secondary goal date (June 11, 2002). I will look into your question [ ] and its affect on the goal dates and get back to you. Also, the "Change of Sponsor" letters are drafted by someone other than

myself and I did not see them. I will look into the discrepancy in the Sponsor name that you mentioned and follow up with the necessary corrective actions.

Regards,
Colleen

Notice of Forthcoming Meeting

Application:	NDA 21-392
Product:	Diltiazem extended-release tablets
Sponsor:	Biovail
Purpose:	to discuss labeling issues
Internal pre-meeting:	**Wednesday, February 27, 2002 @ 1:00 p.m. in conference room "F", 5th floor, WOC II**
Meeting:	**Wednesday, February 27, 2002 @ 1:30 p.m. in conference room "F", 5th floor, WOC II**

Participants:

FDA

Sandra Birdsong	Regulatory Health Project Manager, Division of Cardio-Renal Drug Products (HD-110)
Raymond Lipicky, M.D.	Director, HFD-110
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Douglas Throckmorton, M.D.	Deputy Director, HFD-110

Biovail

To be announced

Meeting arranged by: Colleen LoCicero Phone: (301) 594-5332

ape

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(703) 995-2444
Attention:	Wayne Kreppner
Company Name:	Biovail
Phone:	(703) 995-2400
Subject:	Statistician's requests
Date:	12-17-01
Pages including this sheet:	2
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Wayne,

Dr. Lawrence, the Statistician reviewing NDA 21-392 has requested the following to assist him in his review:

A data set with the following variables:

a. Patient ID
b. Randomized treatment assignment
c. Indicator variable for ITT population (1= in ITT, 0= not in ITT)
d. Baseline trough DBP
e. Endpoint trough DBP

f. Baseline mean DBP measured between 6:00 am and 12:00 noon
g. Endpoint mean DBP measured between 6:00 am and 12:00 noon
h. Center
i. Gender
j. Age
k. The values of any covariates used in any primary analysis, if there were any.

Please provide these in a SAS transport file that can be opened without using "proc cimport".

If you have any questions, please let me know.

Regards,
Colleen

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Biovail Laboratories Incorporated

DATE OF SUBMISSION
November 2, 2001

TELEPHONE NO. (Include Area Code)
(703) 995-2400

FACSIMILE (FAX) Number (Include Area Code)
(703) 995-2444

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
Chelston Park, Building 2
Collymore Rock
St. Michael, BHI
Barbados, WI

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
John Dubeck, Agent for Biovail Laboratories Inc.
Keller and Heckman
1001 G Street, N.W., Suite 500 West
Washington, D.C. 20001

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-420

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Cardizem — PROPRIETARY NAME *(trade name)* IF ANY N/A

CHEMICAL BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* 1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-5-(2-(dimethylamino)ethydro)-2, 3-dihydro-2-(4-methoxyphenyl)-monohydrochloride (+)cis- | CODE NAME *(If any)*

DOSAGE FORM: Tablet | STRENGTHS: 240 mg, 300 mg, 360 mg | ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE: Hypertension

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to FDA Request

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 | THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please See Attachment "A"

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Please See Attachment "B"

RECEIVED
NOV 13 2001
CDR/CDER

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (k)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Clinical Data

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
John B. Dubeck	John B. Dubeck (U.S. Agent)	November 2, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Keller and Heckman LLP, 1001 G Street, NW, Ste 500-W, Washington, DC 20001	(202) 434-4125

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h (4/00)

Minutes of a teleconference

Date of teleconference:	Tuesday, October 16, 2001
Product:	Cardizem — (Diltiazem Hydrochloride Extended Release Tablets)
Sponsor:	Biovail Laboratories Incorporated
Purpose:	to discuss administrative management of application, dated August 22, 2001, submitted as an original new drug application
Teleconference Chair:	Raymond Lipicky, M.D.
Teleconference Recorder:	Colleen LoCicero
Participants:	
FDA	
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
Biovail	
Paul Desjardins, Ph.D.	Vice President, Product Development Operations
Wayne Kreppner, M.Sc.	Manager, Regulatory Affairs

Background

Dr. Lipicky requested this teleconference to discuss the management of the sponsor's August 22, 2001 submitted new drug application (NDA) for Cardizem — (Diltiazem Hydrochloride Extended Release Tablets).

The teleconference

Discussion Point #1: Management of August 22, 2001 submission

The drug formulation in the application the sponsor submitted on August 22, 2001 for Cardizem — appears to be identical to the formulation in pending NDA 21-392, submitted June 8, 2001. It appears that the only difference between these two applications is [redacted] Provided this is the case, the Division plans to convert the August 22, 2001 Cardizem — submission from an NDA to an amendment to pending NDA 21-392.

While the sponsor found the Division's plan acceptable, they noted that they submitted the Cardizem — application as an NDA, based on their interpretation of the draft Guidance on submitting marketing applications for purposes of assessing user fees (*Guidance for Industry- Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*). It was their understanding that a submission that supports a new claim or indication should be submitted as a new NDA and not an amendment to a pending NDA. Dr. Lipicky noted that the August 22, 2001 submission does not support a new claim, but rather a change in the time of day the drug is administered.

The Division plans to convert the August 22, 2001 Cardizem — submission to an amendment to pending NDA 21-392, eliminating NDA —— The goal date for NDA 21-392, including the

August 22, 2001 amendment, will remain the same (i.e. a 10-month goal of April 11, 2001 and a 12-month goal of June 11, 2002).

Discussion Point #2: Refund of user fee

The sponsor paid user fees for both NDA 21-392 and NDA — and asked whether they would be eligible for a refund of one of the fees. Ms. LoCicero will consult with those who manage the user fees and get back to the sponsor on this.

Discussion Point #3: Labeling

Noting that the review of the Cardizem — submission is not complete or near completion and that his comments are preliminary, Dr. Lipicky stated [ ] in labeling. He does not believe the application will go to an Advisory Committee, but noted that it is possible, depending on how aggressively the [ ] labeling issue is pursued.

If the sponsor wishes to discuss further the labeling issues, [ ] it would be best to do so once the review is further along. The review should be well underway by mid-December. To ensure a spot on the calendar for such a labeling discussion, Ms. LoCicero will schedule a meeting/teleconference for sometime during the first two weeks of December, if possible. If, as the time nears, it is apparent that a discussion is not needed or that the Division is not ready for such a discussion, the discussion can be cancelled or rescheduled at that time.

Discussion Point #4: Safety data for higher doses

With respect to the adequacy of the safety data for the higher doses (420 and 540 mg) the sponsor describes in their September 18, 2001 submitted pre-NDA meeting briefing document, Dr. Lipicky's preliminary bias is that the safety data for these doses are adequate. However, this is a review issue and a final decision on this cannot be made at this time.

Signature, Teleconference Recorder:_____ Colleen LoCicero

Concurrence, Teleconference Chair:_____Raymond Lipicky, M.D.

drafted: 10/19/01 finaled: 10/25/01

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

/s/

Colleen LoCicero
11/8/01 11:03:59 AM
These final minutes were signed by Dr. Lipicky and faxed to the sponso
r on 11/8/01.

BIOVAIL
TECHNOLOGIES LTD.

DATE: 23 October 2001

TO: Colleen Locicero
COMPANY: Division of Cardio-Renal Drug Products
Food and Drug Administration

FAX: (301) 594-5494

FROM: Wayne Kreppner

FAX: (703) 995-2444

PAGES: 1 (including cover page)

SUBJECT: Cardizem — NDA 21-392
October 16, 2001 Teleconference

Colleen,

I'm sorry I missed your call this afternoon. The Biovail participants from the Oct 16/01 teleconference were:

Paul Desjardins, Ph.D. - Vice-President Product Development Operations
Wayne Kreppner, M.Sc. – Manager, Regulatory Affairs

The proposed December 11, 2001 meeting date to discuss the Cardizem — labeling is acceptable for Biovail. I have notified our team members to clear this date form their calendars. Do you require any correspondence from Biovail in the form of an official request for this meeting?

Lastly thank you for your help win dealing with the User Fess for NDA 21-392. I will call Mike Jones directly to clarify our requirements prior to making the formal refund request.

Sincerely,

Wayne Kreppner
Manager, Regulatory Affairs
Biovail Technologies Limited

3725 Concorde Parkway, Suite 1500, Chantilly, Virginia 20151 • (703) 995-2400

TOTAL P.01

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Numbers:	703.995.2444
Attention:	Wayne Kreppner
Company Name:	Biovail
Phone:	703.995.2280
Subject:	Decision to cancel the September 26, 2001 Meeting
Date:	09/21/01
Pages including this sheet:	1
From:	**John Guzman**
Phone:	**301-594-5312**
Fax:	**301-594-5494**

Dear Wayne,

This FAX serves as notice of the Division's decision to cancel the September 26, 2001 meeting scheduled with Biovail. Due to the recent NDA submission for Cardizem — (NDA 21-420), Dr. Lipicky has reviewed the meeting package submitted for the September 26, 2001 meeting and concluded that the questions posted in the meeting package will be addressed during the review of NDA ——

If you have any further questions, please do not hesitate to contact me at 301.594.5312.

Best Regards,

John Guzman

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

/s/

John Guzman
9/21/01 05:15:14 PM
CSO

FAX telling the company that we are canceling their scheduled meeting

Filing Meeting

Date of meeting:	October 16, 2001
Application:	NDA 21-420
Product:	Cardizem — (Diltiazem Hydrochloride Extended Release Tablets)
Sponsor:	Biovail Laboratories Inc.
User Fee Goal Dates:	June 23, 2002 (10-month) August 23, 2001 (12-month)
Type of application:	3S
Participants:	
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Stephen Fredd, M.D.	Deputy Director, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, Division of New Drug Chemistry (HFD-810)
James Hung, Ph.D.	Team Leader, Statistical, Division of Biometrics I (HFD-710)
Gabriel Robbie, Ph.D.	Clinical Pharmacologist and Biopharmaceutist, Division of Pharmaceutical Evaluation I (HFD-860)
Christine Benton	Management Specialist, HFD-110
Zelda McDonald	Regulatory Health Project Manager, HFD-110
Edward Fromm	Regulatory Health Project Manager, HFD-110
Sandra Birdsong	Regulatory Health Project Manager, HFD-110
Quynh Nguyen	Regulatory Health Project Manager, HFD-110
Daryl Allis	Regulatory Health Project Manager, HFD-110
Colleen LoCicero	Regulatory Health Project Manager, HFD-110

Background

As there was no record of a filing meeting for this application and the filing date (October 22, 2001) was approaching, Dr. Lipicky decided during the October 16, 2001 Supervisors' meeting to conduct an impromptu, informal filing meeting for this application.

The meeting

Dr. Srinivasachar confirmed that the extended-release tablet formulation in pending NDA 21-392 (submitted June 8, 2001) is identical to the extended-release tablet formulation in NDA [ ] The difference between the two applications is [

] Therefore, the Division concluded that the August 22, 2001 Cardizem —

submission would not be filed as an NDA, but accepted as an amendment to pending NDA 21-392.

Dr. Lipicky and Ms. LoCicero will telephone the sponsor prior to the filing date to inform them of this administrative decision. Ms. LoCicero will request that NDA NDA 21-392 in COMIS

Signature, Meeting Recorder:_____Colleen LoCicero

Concurrence, Meeting Chair:_____Raymond Lipicky, M.D.

drafted: 10/18/01 finaled: 3/12/02

rd:
K Srinivasachar/12/13/01
G Robbie/1/14/02
Z McDonald/1/14/02
S Birdsong/1/15/02
Q Nguyen/1/15/02
E Fromm/1/15/02
A Karkowsky/1/15/02
N Stockbridge/1/24/02

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

/s/

Colleen LoCicero
3/12/02 11:44:55 AM
These final meeting minutes were signed by Dr. Throckmorton for Dr. Lipicky on 3/12/02.

Memo to the file

Date: October 11, 2001

From: Colleen LoCicero, RHPM

To: [ ]

Subject: Response to sponsor's October 3, 2001 correspondence

On October 3, 2001, the sponsor submitted to the Division correspondence concerning the cancelled pre-NDA meeting for this application and the questions the sponsor included in the briefing document for the cancelled meeting. The sponsor noted a September 21, 2001 facsimile from John Guzman that stated that Dr. Lipicky, after reviewing the briefing document, indicated that the questions would be addressed during the review of the NDA. The sponsor asked whether Dr. Lipicky could answer some or all of the questions at this time, or provide an estimate of when the questions could be answered, noting that the answers to these questions are very crucial to their sales and marketing efforts.

On October 12, 2001, I telephoned Dr. Paul Desjardins of Biovail to inform him that I discussed with Dr. Lipicky the sponsor's October 3, 2001 correspondence. Dr. Lipicky indicated that we did not respond to the questions previously because we do not and will not know the answers until the review of the application is complete, and not because we did not have adequate time to review the questions.

Furthermore, Dr. Lipicky indicated that the application might go to the Advisory Committee. Dr. Desjardins asked when the Advisory Committee Meeting would be. If (it has not been decided yet) the application goes to the Committee, the date will be determined by several factors that might include the application's goal date, other applications going to the Committee, etc. The next scheduled meeting is in January of 2002.

I concluded the conversation by providing Dr. Desjardins with Dr. Lipicky's responses to the four questions in the sponsor's September 18, 2001 submitted briefing document, as follows:

Question #1: Based on the positive efficacy results for the Cardizem — bead tablet evening administration study versus both placebo and a comparable AM dose, Biovail has incorporated the following description of the study in the CLINICAL PHARMACOLOGY section of the proposed labeling:

[ ]

[

]

Is this acceptable?

Dr. Lipicky's response: We do not know and may not know until there is an Advisory Committee Meeting, but we doubt it.

Question #2: Furthermore, based on the study results, Biovail has included the following specific wording in the DOSAGE AND ADMINISTRATION section of the proposed labeling:

[

]

Is this acceptable?

Dr. Lipicky's response: We do not know, but we doubt it.

Question #3: Biovail intends to add additional dosage strengths to the Cardizem — product line post-approval. At present tablet doses of 420 mg [ ] contemplated. Numerous studies have been performed in hypertensive patients demonstrating the safety of diltiazem extended release [ ] Biovail intends to submit a supplement for these dosage strengths based on the existing safety database.

Is this acceptable?

Dr. Lipicky's response: No.

Question #4: The submitted Cardizem — application contains the results of the Evening administration clinical study, [ ] Does the Division agree that this application meets all of the requirements as outlined in 21 CFR 314.108(b)(4) and upon approval Cardizem — should be granted three years of market exclusivity as provided for under section 505(c)(3)(D) of the Federal Food Drug and Cosmetic act?

Dr. Lipicky's response: No.

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

/s/

Colleen LoCicero
10/12/01 01:19:58 PM
CSO

See Dr. Lipicky's comments in marked-up copy of sponsor's pre-NDA briefing document in the file.

Teleconference minutes between Biovail and the FDA

NDA:	21-392
Drug:	Diltiazem Hydrochloride Extended Release Tablets
Date of meeting request:	September 6, 2002
Meeting package received:	September 20, 2002
Date of meeting:	September 25, 2002
Type:	C
Meeting chair:	Douglas C. Throckmorton, M.D.
Meeting recorder:	Denise Hinton

FDA Participants:

Douglas C. Throckmorton, M.D.	Division Director Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D.	Team Leader Medical Officer
Ramsharan Mittal, Ph.D.	Chemist
Kasturi Srinivasachar, Ph.D.	Team Leader Chemist
Patrick Marroum, Ph.D.	Team Leader Biopharmaceutist
Lydia Velazquez, Pharm. D.	Biopharmaceutist
Cheryl Cropp, R.Ph.	Safety Reviewer, DDMAC
Jennifer Fan, Pharm.D.	Safety Evaluator, Office of Drug Safety
Denise Toyer, Pharm.D.	Director of Regulatory Affairs, Office of Drug Safety
Kim Dettelbach, J.D.	General Attorney, Office of the Chief Counsel
Denise Hinton	Project Manager

Biovail Participants:

Mr. Eugene Melnyk	Chief Executive Officer, Biovail Corporation
Dr. Paul Desjardins	VP, Product Development Operations
Dr. Ken Albert	VP, Clinical Development
Dr. Okpo Eradiri	Senior Director, Pharmacokinetics and Toxicology
Mr. James Petrilla	General Manager, Diltiazem Products
Mr. Wayne Kreppner	Director, Technology Transfer and Regulatory Affairs
Mr. John Dubeck	Legal Counsel
Ms. Shannon Woodall	Project Manager

Background:

Biovail received an Approvable letter on June 11, 2002 for NDA 21-392 (diltiazem hydrochloride extended release tablets). In addition to addressing the eight issues listed in the letter, Biovail was asked to submit final printed labeling identical to the Division's enclosed labeling for the package insert, and immediate container and carton labels. Biovail sent in a revised draft for review and agreement with the Division before submitting final printed labeling.

Teleconference:

Biovail requested a teleconference to discuss the following questions with the Division:

1. *On August 21, 2002, Biovail amended its response to the June 11, 2002 Approvable letter to include revised product labeling. This revised labeling included a "redline" version that included justifications for changes made that differed from those suggested by the Division. Is the submitted labeling acceptable for approval?*

2. *In the July 16, 2002 response to the Approvable Letter Biovail submitted additional stability information to support an 18 month shelf life for the product. Included in this request was a notification that Biovail intends to* [redacted] *Does the Division agree with the assignment of an 18-month shelf life for this product?*

Dr. Throckmorton advised Biovail to send a complete response letter to the June 11, 2002 Approvable letter. The remaining deficiencies to be addressed are bioequivalence data on the 420mg strength, complete dissolution data, labeling, and chemistry issues regarding the reference standard, stability data and impurity profile comparison tests. Biovail stated that they would send a complete response letter after all the issues have been addressed and submitted to the Agency.

Dr. Throckmorton conveyed that this teleconference would focus on labeling agreements. It was noted that Biovail deleted portions of the labeling changes recommended by the Division in the Approvable letter without identification of the particular items. Biovail was advised to submit a line by line copy of the label issued by the Division with their comments and justifications for the proposed changes inclusive of line changes for future discussions.

Biovail stated that they made revisions based on what they believed should be in the label and that any deletions were not intentional. Dr. Throckmorton informed them that the submission is not acceptable as final printed labeling. The description of the effects [redacted] t should not be included in the labeling because it gives information that can be misleading to the prescriber. The information should reflect antihypertensive efficacy of the product as stated in the language that was sent in the Approvable letter.

Biovail stated that the Agency's comment that the information could be potentially misleading has not been established and noted the results were from the pivotal study. They agreed to amend the text with a disclaimer so it would not be misleading. The Division stated that a disclaimer would not be an attractive option and the idea of the measurements being prespecified primary endpoints carries no additional weight. Division does not believe Biovail's proposed statement provides any clinical benefit as it was not needed for an adequate description of safety and efficacy for the label.

Biovail stated that in a previous meeting, Dr. Temple asked them to include an AM arm. During that meeting, Biovail said they asked if they could include data as a result of such a trial and design a study with variables as discussed. Their expectation was that, with positive results, the data could be included in the label. The Division stated that Biovail was asked to do AM dose administration, not parameters to compare AM vs. PM dosing. The issue of interest is — observed differences in the AM and PM dose.

Biovail stated that the design of the study included a variable and data was collected at trough. They expressed that knowing the affects of early morning dosing was desirable and would allow providers to decide how to manage patients in the AM or PM. The Division reiterated their disagreement that an adequate disclaimer could be written in the label. Labeling is to reflect clinical benefit of a drug, not to describe where no utility has been demonstrated. Given the Division 's position to include data from the clinical trial, Biovail proposed including all treatments from the AM and PM trough.

The Division advised Biovail to write language with the results of the trial in the labeling and submit it for review excluding the PK differences for AM/PM administration because they are not necessary for labeling. The Division also recommended that Biovail consider using the Division's proposals listed on page 5 and 6 of the Approvable letter in addition to the bioequivalence of administration language and the dose increase from 120-300 mg, excluding the description of day and night administration. Biovail agreed to draft a label based on AM/PM data for all troughs to be consistent with the results of the study.

The Division is resistant to promotion of false implications to any benefit of efficacy with the drug being administered in the AM or PM. All advertising materials will be submitted to DDMAC. Biovail asked for clarification regarding the PK section of the label. The Division stated that Biovail's language needed to be

amended with the above comments in mind. Insertion of potentially misleading information in labeling should not be encouraged, including such language in the PK section. The Division recommended that Biovail keep the language that the Division recommended throughout the label. If Biovail desires to include the [ ] in the label, they are advised to submit their rationale supporting the relevance to use of such a small difference.

Conclusions:

Biovail stated that they would submit new draft labeling to the Division for review and comment. After the Division reviews the submission, if necessary, a follow up meeting will be scheduled.

Minutes preparation: _____
Denise M. Hinton

Meeting Concurrence: _____
Douglas C. Throckmorton, M.D.

Draft: 25Oct02
RD:

Velazquez	31Oct02
Mittal	1Nov02
Srinivasachar	1Nov02
Stockbridge	1Nov02
Throckmorton	5Nov02
McDonald	7Nov02
Final:	7Nov02

Filing Summary

Meeting Date:	July 17, 2001
NDA Number:	21-392
Drug Name:	Diltiazem Hydrochloride Extended Release Tablets
Indication:	Treatment of Hypertension
Sponsor:	Biovail
Subject:	45-Day Filing Meeting
Meeting Chair:	Raymond Lipicky, MD
Meeting Recorder:	John Guzman

FDA Attendees

Raymond Lipicky, MD	Director, Division of Cardio Renal Drug Products, HFD-110
Norman Stockbridge, MD, PhD	Team Leader, Medical, HFD-110
Patrick Marroum, PhD	Team Leader, Clinical Pharmacology and Biopharmacology, HFD-860
Charles Resnick, PhD	Team Leader, Pharmacology, HFD-110
Kasturi Srinivasachar, PhD	Team Leader, Division of New Drug Chemistry, HFD-810
Ram Mittal, PhD	Chemist, Division of New Drug Chemistry, HFD-810
Jorge Rios, MD	Medical Officer, DSI, HFD-47
Martin Yow, MD	Medical Officer, DSI, HFD-47
John Guzman	Regulatory Health Project Manager, HFD-110

Background

Biovail has submitted a new NDA (NDA 21-392) for Diltiazem Hydrochloride Extended Release Tablets 240, 300, and 360 mg for the treatment of hypertension. This NDA provides for an extended release tablet that is bioequivalent to the Biovail's once-daily Diltiazem Hydrochloride Extended Release Capsule approved for the treatment of hypertension on January 28, 2000 (NDA 20-939).

On August 26, 1999, a pre-NDA meeting was conducted to discuss the requirements and the format of the NDA submission. Meeting Minutes are attached.

Submission Information

Therapeutic Classification:	3S
Date of Application:	June 8, 2001
Date of Receipt:	June 11, 2001
10-Month User Fee Goal Date:	April 11, 2002
12-Month User Fee Goal Date:	June 11, 2002
User Fee Status:	Paid
Submission Complete As Required by 21 CFR 314.50?	Yes (?)
Patent Information Included?	Yes
Exclusivity Requested?	No
Debarment Statement Included?	Yes
Financial Disclosure Certification?	No (*)
Pediatric Rule Addressed?	No

* PM will contact Sponsor regarding obtaining this information.

Assigned Reviewers

Discipline	Reviewer	Review Completion Date
Medical	Norman Stockbridge MD, PhD	NA
Biostatistics	James Hung, PhD	NA
Chemistry	Ram Mittal, PhD	November 1, 2001
Pharmacology	Charles Resnick, PhD	TBA
Biopharmaceutics	Gabriel Robbie, PhD	September 17, 2001
Project Management	John Guzman	TBA

Meeting Minutes

- Dr. Lipicky stated that no DSI audit would be needed.
- Dr. Stockbridge noted that no primary medical review is needed due to the fact that the NDA is supported by bioequivalence studies.
- Dr. Mittal noted that the Sponsor needed more stability data [ ] and more information regarding the drug substance (multiple suppliers of the drug substance). Dr. Lipicky noted that all the reviews should just review the submissions as is, and if there are deficiencies, then those deficiencies will be communicated in the action letter.
- No tradename was found in the submission. Until the Sponsor submits one, the tradename will be considered "Diltiazem tablets."

Signature, Meeting Recorder: *{See appended electronic signature page* John Guzman

Signature, Meeting Chair: *{See appended electronic signature page* Raymond Lipicky, MD

Drafted: July 18, 2001

Reviewed:

Mittal	7/13/01
Srinivasachar	7/17/01
Resnick	7/19/01
Marroum	7/20/01
Stockbridge	7/23/01
Morgenstetn	7/25/01
Lipicky	7/31/01

Cc: HFD-110
HFD-110/Guzman

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Biovail Laboratories Incorporated
c/o Biovail Technologies Limited
3725 Concorde Parkway
Chantilly, VA
20151
USA

2. TELEPHONE NUMBER *(Include Area Code)*
(703) 995-2400

3. PRODUCT NAME
Diltiazem Hydrochloride Extended Release Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N021-392

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4157

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	MANAGER, REGULATORY AFFAIRS	June 8, 2001

FORM FDA 3397 (3/01)

Created by: PSC Media Arts (301) 443-2454 EF

BIOVAIL
LABORATORIES INCORPORATED

VIA FACSIMILE: (617) 624-7607

Ref: 0245/01

June 6, 2001

Mr. Greg Yong
The Bank of Nova Scotia
Boston Branch
28 State Street, Floor 17
Boston, Massachusetts 02109

Dear Mr. Yong,

Please accept this letter as your authorization to issue the following wire transfer:

To:	Mellon Bank
Address:	Pittsburgh, U.S.A
ABA No:	043000261
FDA Demand Deposit Account No:	9116309
Account Name:	Food and Drug Administration
Currency:	**United States Dollars**
Amount:	**USD154,823.00** (One Hundred and Fifty Four Thousand Eight Hundred and Twenty Three 00/100 United States Dollars)
Reference:	User Fee ID number (4517) and the NDA number (N021-392)

The test no: is [ ] Please quote the reference on the wire transfer. Please debit our Chequing Account No. [ ]

Sincerely,
BIOVAIL LABORATORIES INCORPORATED

Eugene N. Melnyk
President & Chief Executive Officer

Arlene Fong, CA
Manager, Finance and Administration

00008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,711

3/7/01

Biovail Laboratories Incorporated
c/o Keller and Heckman
Attention: Mr. John B. Dubeck
1001 G Street, N.W.
Suite 500 West
Washington, D.C. 20001

Dear Mr. Dubeck:

Reference is made to your correspondence dated December 12, 2000 (received on December 13, 2000), requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Diltiazem Hydrochloride Extended Release Capsules USP (120, 180, 240, and 300 mg) for the treatment of Hypertension [ ] for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have any questions, please contact

Mr. John Guzman
Regulatory Health Project Manager
(301) 594-5312.

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Raymond Lipicky
3/7/01 11:47:58 AM

Memo to the file

Date: January 15, 2002

From: Colleen LoCicero, RHPM

To: IND 51,711
Diltiazem HCl Extended Release Capsules
Biovail Laboratories Incorporated

Subject: Serial # 014, dated October 27, 2000

This submission contains a proposal for a pediatric study for FDA review and comment. The cover letter of the submission does not designate the submission a proposed pediatric study request, nor does the accompanying FDA Form 1571. (The submission is designated general correspondence on the accompanying FDA Form 1571.) The Sponsor states in the cover letter of the submission that they are proposing the study to meet the requirements of the pediatric final rule. However, the submission was coded a proposed pediatric study request by the Division Document Room.

Upon review of the proposed study and the medical and clinical pharmacology/biopharmaceutics reviews of the proposal, Dr. Lipicky concluded that if the purpose of the proposed study was to fulfill the requirements of the pediatric rule, the Sponsor should request a full waiver of the pediatric study requirement. He indicated that he would grant a full waiver because the product is sustained-release and therefore not suitable for dosing in the pediatric population. Dr. Lipicky indicated, however, that if the Sponsor were truly interested in studying this product in pediatric patients, they would need to talk to the Division as there are problems with the proposed study. This was communicated to the Sponsor on December 1, 2000.

On December 12, 2000, the Sponsor submitted a request for a waiver of the pediatric study requirement for the anticipated NDA for this product. In the request, the Sponsor noted that the study included in the October 27, 2000 submission was designed specifically to meet the requirements of the pediatric final rule and not for the purposes of obtaining pediatric exclusivity. On March 7, 2001, the Division granted a full waiver of the pediatric study requirement for the anticipated NDA for this product.

In conclusion, the October 27, 2000 pediatric study proposal (serial #14) was not intended as a proposed pediatric study request and should be recoded as general correspondence.

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

/s/

Colleen LoCicero
1/15/02 01:34:13 PM
CSO

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Minutes of a Meeting Between Biovail and the FDA

MAY 2 2000

Date of Meeting: April 21, 2000

Application: NDA 20-939
Diltiazem Extended Release Capsules

Applicant: Biovail

Subject: —

Meeting Chair: Robert Temple, M.D.

Participants:

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
Shaw Chen, M.D., Ph.D., HFD-110, Medical Group Leader
Cristobal Duarte, M.D., HFD-110, Medical Officer
Janet Norden, HFD-040, Acting Branch Chief
Emmanuel Fadiran, Ph.D., HFD-860, Clinical Pharmacologist/Biopharmaceutist
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
David Roeder, HFD-110, Regulatory Health Project Manager

Biovail

Dr. David Tierney, President, Biovail Technologies Limited
Mr. Kenneth Cancellara, Senior Vice President and General Counsel
Dr. Kenneth Albert, Vice President and Chief Scientific Officer
Dr. Theo Gana, Director, Clinical Research
Mr. Wayne Kreppner, Manager, Corporate Regulatory Affairs
Dr. Sury Sista, Director, Pharmacokinetics
[ ]

Background

NDA 20-939 is an approved NDA for a once-daily sustained release diltiazem capsule (G99) approved for the treatment of hypertension. G99 is bioequivalent to Cardizem CD and has an AB rating in the Orange Book. Biovail also has an approved ANDA for the same product (ANDA 75-116). The applicant requested a meeting with the Agency to discuss the development of this product [ ] for the treatment of hypertension [ ]

Meeting

Dr. Temple noted that other once-daily products currently on the market do not differentiate between a.m. and p.m. dosing. The labeling of these products merely instructs the patient to take the product once daily. [ ]
He said that [ ] It would seem potentially misleading to imply that [ ] He would prefer to

describe the data in the CLINICAL PHARMACOLOGY section. He also pointed out that once-daily dosing formulations are not approved unless they provide adequate effectiveness throughout the 24-hour period, generally assessed at the end of the interval. There are no data to show a clinical benefit to having the peak plasma levels in the morning. Biovail's [ ] does not address this question. He also pointed out that the optimal pharmacokinetic profile of a once-daily dosage would have a broad, flat peak, not what is seen with G99. Biovail's [ ] could make what is in reality a weakness of this product (low blood levels at the end of the dose interval) appear to be an advantage.

Another product, Covera-HS (verapamil) Tablets, was approved with a nighttime dosing regimen. This product, however, was designed to have no drug release at all in the first hours after administration. It made more sense to limit it to a nighttime dosing regimen. Biovail's product begins to release drug slowly shortly after dosing. Since their product has already been shown to be safe and effective when dosed in the morning, it would be hard to justify limiting the dosing to the evening.

[ ] Dr. Temple recommended that they compare evening dosing with morning dosing [ ] The labeling that would result [ ] would depend on our review of the data. He also recommended [ ]

The firm said that [ ]

They also said that they plan to study G99 up to 420 mg. Dr. Temple said that since the currently approved diltiazem labeling mentions dosing up to 540 mg, Boivail would probably not get marketing exclusivity for the 420 mg dose.

The firm said that it is important to them [ ] Dr. Temple said that we would have to discuss that question internally with the Office of Generic Drugs. After this internal meeting, the firm should request a follow-up meeting with the Agency to continue the discussion. He also recommended that the firm revise their protocols based on discussions at this meeting and submit them for Agency review.

Minutes Preparation: David Roeder

Concurrence Chair: Robert Temple, M.D.

dr/4-26-00/5-1-00

RD: EFadiran/4-27-00
CDuarte/4-28-00
SChen/4-28-00

cc: NDA 20-939
HFD-110
HFD-110/DRoeder/SMathews

Minutes of a Meeting Between Biovail and the FDA

Date of Meeting: August 26, 1999

Subject: Pre-NDA
Diltiazem Extended Release Tablets

Sponsor: Biovail

Participants:

FDA

Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Florian Zielinski, Ph.D., HFD-110, Chemist
Ram Mittal, Ph.D., HFD-110, Chemist
Patrick Marroum, Ph.D., HFD-860, Clin Pharm/Biopharmaceutics Team Leader
David Roeder, HFD-110, Regulatory Health Project Manager

Biovail

Dr. Kenneth Albert, Vice President and Chief Scientific Officer
Paul Maes, Director, Technology Transfer & Manufacturing Liaison
Wayne Kreppner, Manager Corporate Regulatory Affairs

Background

Biovail requested a meeting to discuss the requirements for the submission of an NDA for a once-daily diltiazem tablet that is bioequivalent to their once-daily diltiazem capsule, Tiazac.

Meeting

Question #1: Biovail plans to conduct one *in-vivo* pharmacokinetic study to demonstrate that the highest strength bead-tablet dosage form is bioequivalent to the corresponding capsule dosage from. Since all strengths are [redacted] a bio waiver will be requested for the lower strengths. Is this program sufficient to gain approval for the bead-tablet dosage form as a line extension?

Dr. Marroum said that a food effect study would be required, even though they have added only on inactive excipient to the currently approved Tiazac formulation. They would also have to show bioequivalence in a single and multiple dose study. This could all be done in a single study. In order to get a waiver for the lower strengths, they would have to submit dissolution data in three media.

Question #2: According to ICH Q1A batches of the finished product should be manufactured using identifiably different batches of the drug substance. Based on Biovail's experience with numerous lots of diltiazem hydrochloride drug substance from the supplier (for Tiazac and other diltiazem products), Biovail will be manufacturing all of the bead-tablet batches for submission using the same lot of drug substance. Is this acceptable?

This is acceptable, but Biovail should justify their use of just one lot of drug substance. They should supply certificates of analysis for old batches of drug substance.

Dr. Mittal noted that since the sponsor plans to use more than one supplier of drug substance, they need to justify it on the basis of impurity profile.

Question #3: Biovail plans to manufacture three exhibit batches of the bead-tablet formulation for submission. As a common bead blend can be split to manufacture the 240 mg, 300 mg and 360 mg strengths of the bead-tablet, the applicant has defined the following stability program:

Batch description	Batch size of bead blend	Tablet strength(s) manufactured	Approximate number of tablets produced	Packaging configuration
Pilot	—	240 mg	—	Bottles 30 tablets 1000 tablets
Pre-exhibit	—	240 mg, 360 mg	— (240mg) — (360mg)	Bottles 30 tablets 90 tablets 1000 tablets
Exhibit	—	300 mg, 360 mg	— (300mg) —) (360mg)	Bottles 30 tablets 1000 tablets

Is this acceptable?

Dr. Zielinski said that the sponsor's proposal is acceptable.

Questions #4: According to ICH Q1C there is a provision for a reduced stability database for a new dosage form containing the same active ingredient as an already existing approved product. Based on the stability history of the Tiazac capsule formulation (C , Biovail wishes to submit — , of room temperature and accelerated stability at the time of submission with the additional accelerated and room temperature stability data to be supplied during the review process. Is this acceptable?

Dr. Zielinski said that the firm needs to submit [ ] of stability data from three batches at the time of NDA submission. An additional [ ] should be submitted during the NDA review process. Thus, at the time of approval, they would have submitted a total of [ ] data.

Question #5: Biovail wishes to file this dosage form as a 505(b)(1) line extension to [redacted] This submission will contain full CMC information, appropriate *in-vitro* dissolution data to support a bio waiver and data from on *in-vivo* pharmacokinetic study. Is this sufficient for approval?

Mr. Roeder advised them that they would need a right of reference for the pharmacology/toxicology section. He also noted that they may need to submit pediatric information to be in accordance with the 1998 Pediatric Rule, but this question would have to be discussed with Dr. Lipicky. The firm agreed to submit a proposal for a pediatric study. They suggested using the precursor beads that are used for the manufacture of both the Tiazac Capsule that their once-daily tablet.

Minutes preparation: /S/
David Roeder

Concurrence chair: /S/
Abraham Karkowsky, M.D., Ph.D.

dr/9-1-99/9-13-99

cc: Orig
HFD-110
HFD-110/DRoeder

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

/s/

John Guzman
7/31/01 03:17:01 PM