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APPLICATION NUMBER:

20-883

ADMINISTRATIVE DOCUMENTS

Section 13

Patent Information

The Patent which pertains to the product being developed is United States Patent Number 5,214,052 which was issued on May 25, 1993. This patent titled "Method for Dissolving Arginineamides and Pharmaceutical Compositions Containing Them" is held by Mitsubishi Kasei Corporation, Tokyo, Japan and licensed to Texas Biotechnology Corporation, the holder of this New Drug Application. A copy of this patent is included in this section of the NDA. This patent covers the concentrated dosage form of argatroban, which is the product to be marketed by Texas Biotechnology Corporation upon approval of this NDA.

The undersigned declares that Patent No. 5,214,052 covers the formulation, composition, and/or method of use of argatroban. This product is the subject of this application for which approval is being sought.

John McMurdo, MD
Vice President, Clinical Development and Regulatory Affairs

3/11/99
Date

Gary D. Knappenberger
Consultant, Regulatory Affairs

3.3.99
Date

US005214052A

United States Patent [19]

Ofuchi et al.

[11] Patent Number: 5,214,052

[45] Date of Patent: May 25, 1993

[54] METHOD FOR DISSOLVING ARGININEAMIDES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

[75] Inventors: Kunihiko Ofuchi; Tatsuo Nomura, both of Hasaki, Japan

[73] Assignee: Mitsubishi Kasei Corporation, Tokyo, Japan

[21] Appl. No.: 851,248

[22] Filed: Mar. 13, 1992

Related U.S. Application Data

[63] Continuation of Ser. No. 577,042, Aug. 30, 1990, abandoned, which is a continuation of Ser. No. 223,152, Jul. 22, 1988, abandoned.

[30] Foreign Application Priority Data

Jul. 28, 1987 [JP] Japan 62-188484

[51] Int. Cl.[5] A61K 9/08; A61K 31/445; A61K 47/00

[52] U.S. Cl. 514/315; 514/23; 514/53

[58] Field of Search 514/315

[56] References Cited

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4,258,192	3/1981	Okamoto et al.	546/166
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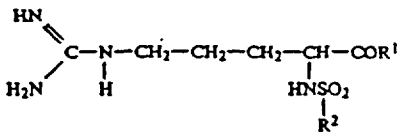
Gstirner F.: "Einfuhrung in die Verfahrenstechnik der Arzneiformung" 1973 pp. 271-272.

Primary Examiner—Shep K. Rose

Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

A method for dissolving an arginineamide of the invention comprising dissolving N^2-arylsulfonyl-L-arginineamide having the general formula (I)



(I)

wherein R^1 represents a (2R, 4R)-4-alkyl-2-carboxypiperizino group and R^2 represents a phenyl group or a condensed polycyclic compound residue which may be substituted with one or more substituents selected from lower alkyl groups, lower alkoxy groups and lower alkyl-substituted amino groups, said condensed polycyclic compound residue including a benzene ring which binds to sulfur atom of the sulfonyl group in the general formula (I) and is condensed with one or more other rings which may be heterocyclic and having 7 to 14 carbon atoms as the ring-constituent atoms;

and/or its salt in a solvent of alcohol and water is disclosed herein.

And, the pharmaceutical composition comprising N^2-arylsulfonyl-L-arginineamide having the general formula (I), an alcohol and water is disclosed herein.

4 Claims, 3 Drawing Sheets

Fig. 1

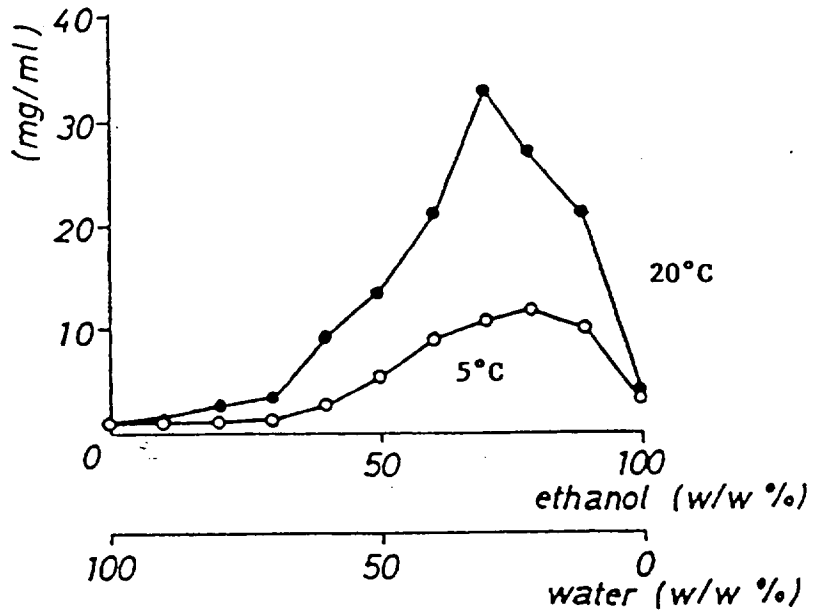

40
30
20
10
(mg/ml)
20°C
5°C
0
50
100
ethanol (w/w %)
100
50
0
water (w/w %)

Fig. 2

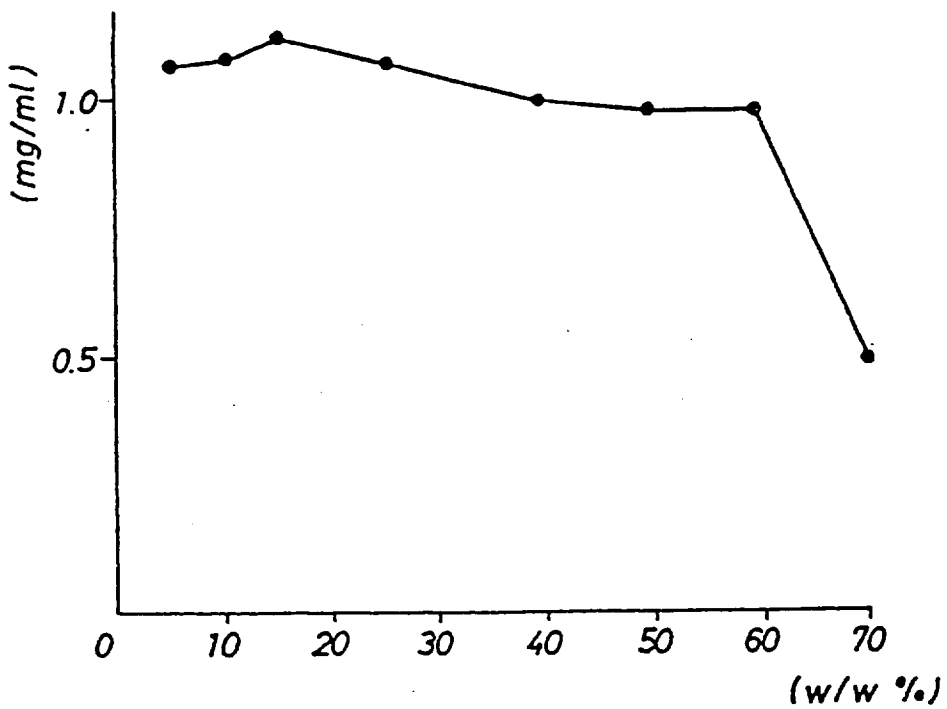

(mg/ml)
1.0
0.5
0
10
20
30
40
50
60
70
(w/w %)

Fig. 4

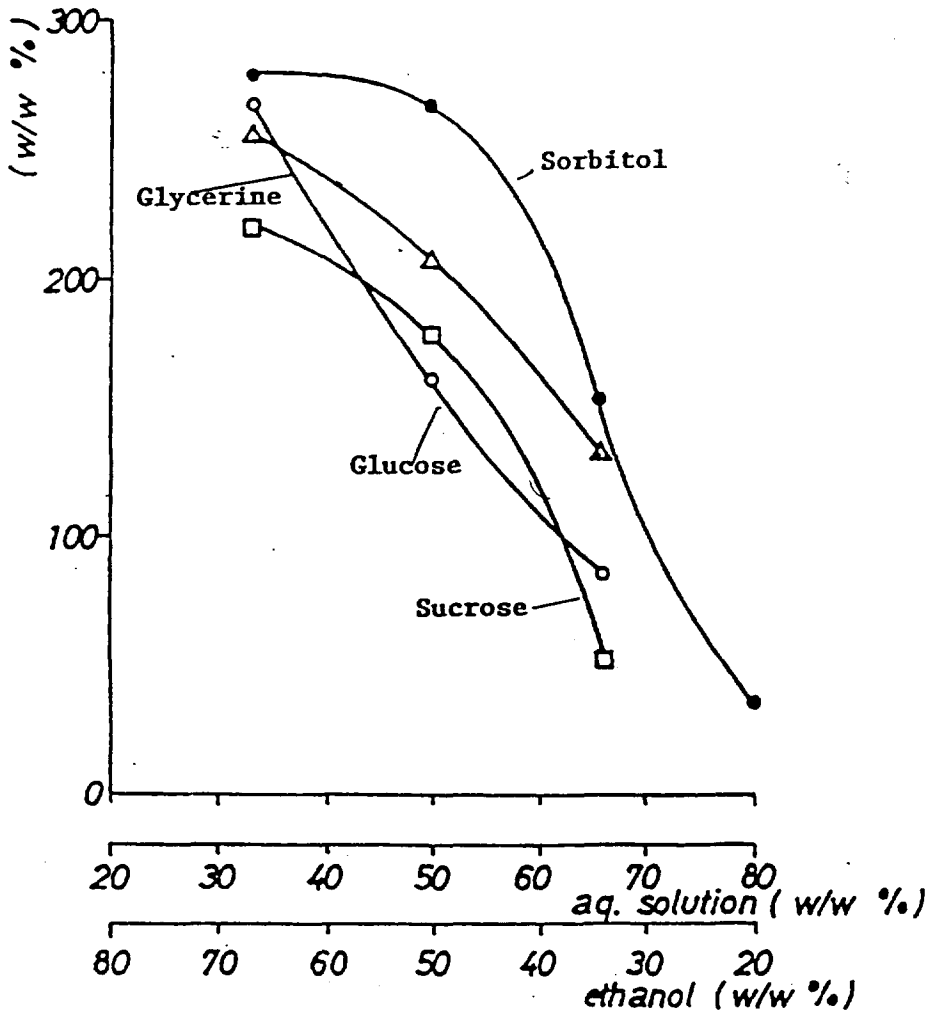
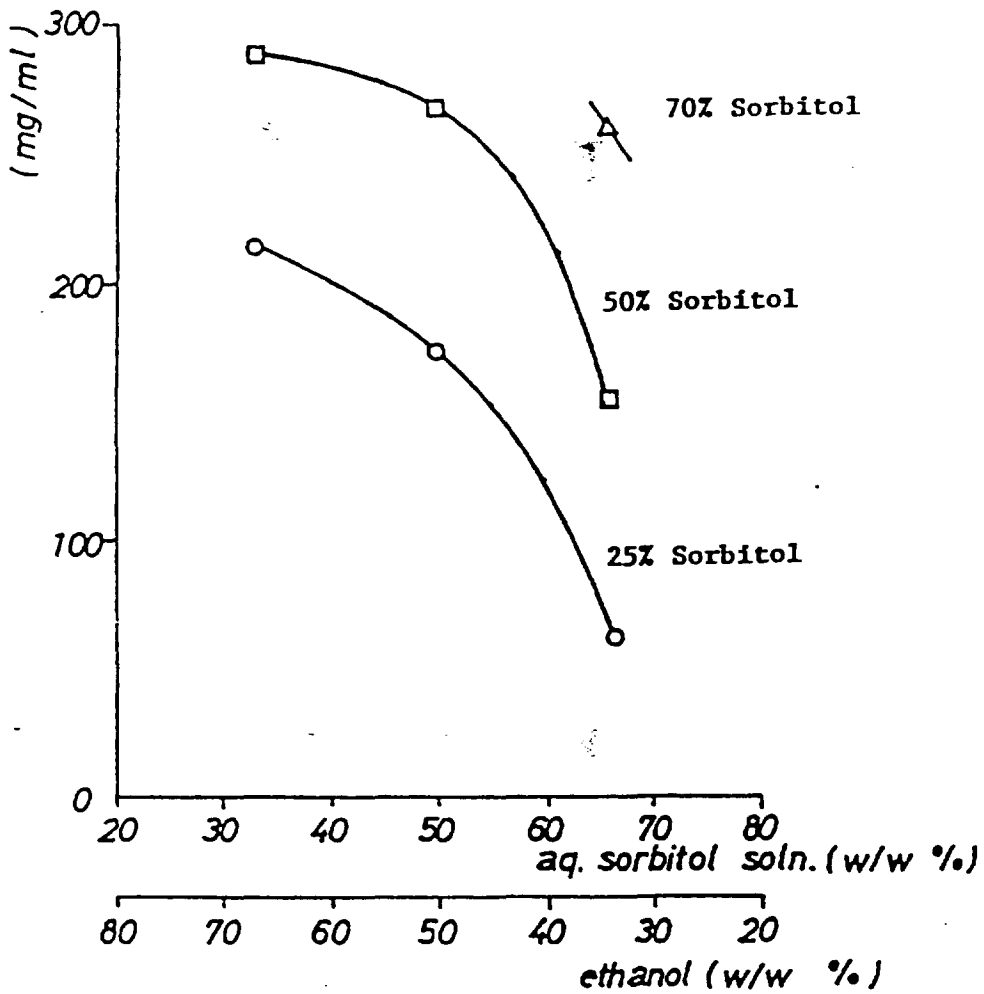

(w/w %)
300
200
100
0
Sorbitol
Glycerine
Glucose
Sucrose
20 30 40 50 60 70 80
aq. solution (w/w %)
80 70 60 50 40 30 20
ethanol (w/w %)

Fig. 3


300
200
100
0
(mg/ml)
70% Sorbitol
50% Sorbitol
25% Sorbitol
20 30 40 50 60 70 80
aq. sorbitol soln. (w/w %)
80 70 60 50 40 30 20
ethanol (w/w %)

METHOD FOR DISSOLVING ARGININEAMIDES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This application is a continuation of application Ser. No. 07/577,042, filed on Aug. 30, 1990, now abandoned, which is a continuation of abandoned application Ser. No. 07/223,152 filed Jul. 22, 1988.

FIELD OF THE INVENTION

The invention relates to a method for dissolving argininеamides and pharmaceutical compositions containing them.

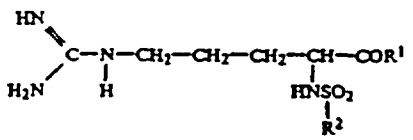
BACKGROUND OF THE INVENTION

Argininеamides are known to have anti-thrombotic activities and are expected to be used as anti-thrombotic agents (please refer to Japanese Patent No. 1382377). However, it is very difficult to obtain a solution containing any of argininеamides at high concentration due to poor solubility in water and therefore any of these compounds is not suitable for applying as the injection containing it at high concentration.

An object of the invention is to provide a method for improving the solubilities of argininеamides so as to apply as the injections containing them at high concentration.

SUMMARY OF THE INVENTION

The invention provides a method for dissolving argininеamide comprising dissolving N^2-arylsulfonyl-L-argininеamide having the general formula (I)



(I)

wherein R^1 represents a (2R, 4R)-4-alkyl-2-carboxypiperidino group and R^2 represents a phenyl group or a condensed polycyclic compound residue which may be substituted with one or more substituents selected from lower alkyl groups, lower alkoxy groups and lower alkyl-substituted amino groups, said condensed polycyclic compound residue including a benzene ring which binds to sulfur atom of the sulfonyl group in the general formula (I) and is condensed with one or more other rings which may be heterocyclic and having 7 to 14 carbon atoms as the ring-constituent atoms;

and/or its salt in a solvent of alcohol and water. Further, the invention provides pharmaceutical compositions containing argininеamides.

BRIEF DESCRIPTION OF THE DRAWINGS

A more complete understanding of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings, wherein:

FIG. 1 is a graph showing the solubility of argipidine in solvent (mg/ml) over a range of ethanol-water solvent mixture:

FIG. 2 shows the solubility of argipidine in aqueous sorbitol solution,

FIG. 3 shows the solubility of argipidine over a range of ethanol-aqueous sorbitol solutions containing different amounts of sorbitol; and

FIG. 4 shows the solubility of argipidine over a range of ethanol-aqueous solutions, wherein the aqueous solutions contain glucose, glycerin, sorbitol or sucrose.

DETAILED DESCRIPTION OF THE INVENTION

R^1 in the general formula (I) represents a (2R, 4R)-4-alkyl-2-carboxypiperidino group. The alkyl herein is a lower alkyl having 1 to 5 carbon atoms such as methyl, ethyl, propyl, isopropyl and butyl. Preferably, R^1 represents a (2R, 4R)-4-methyl-2-carboxypiperidino group.

R^2 in the general formula (I) represents a phenyl group or a condensed polycyclic compound residue. The condensed polycyclic compound residue defines herein that it includes a benzene ring which binds to sulfur atom of the sulfonyl group in the general formula (I) and is condensed with one or more other rings which may be heterocyclic and it has 7 to 14 carbon atoms as the ring-constituent atoms. The benzene ring included in the condensed polycyclic compound residue binds to sulfur atom of the sulfonyl group in the general formula (I), provided that the position on the benzene ring binding to the sulfur atom is not particularly limited. A heteroatom or heteroatoms constituting the heterocyclic ring may be oxygen, nitrogen or sulfur atom.

Preferable condensed polycyclic compound residue is a dicyclic compound residue including benzene ring condensed with one other ring, preferably one five- or six-membered ring which may be heterocyclic or a tricyclic compound residue including benzene ring condensed with two other rings, preferably two five or six-membered rings which may be heterocyclic. The examples of such condensed polycyclic compound residues include anthryl, phenanthryl, benzofuranyl, dibenzothienyl, phenoxthinyl, quinolyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, benzimidazolyl, fluorenyl, 2,3-dihydrobenzofuranyl, thioxathenyl, naphthyl, tetrahydronaphthyl, isoquinolyl, tetrahydroquinolyl and tetrahydroisoquinolyl.

If desired, R^2 can be substituted with one or more substituents selected from lower alkyl groups, lower alkoxy groups and lower alkyl-substituted amino groups. The lower alkyl group is alkyl group having 1 to 5 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert-butyl. The lower alkoxy group is alkoxy group having 1 to 5 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy and butoxy. And, the lower alkyl-substituted amino group is the amino group substituted with the above-mentioned lower alkyl group, such as alkylamino and dialkylamino.

Preferably, R^2 represents 3-methyl-1,2,3,4-tetrahydro-8-quinolyl group.

As the argininеamides used in the invention, the following compounds are exemplified.

(2R, 4R)-1- [N^2-(3-isopropoxybenzenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1- [N^2-(3,5-dimethyl-4-propoxybenzenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1- [N^2-(5,6,7,8-tetrahydro-2-naphthalenesulfon)-yl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N^2-(5-dimethylamino-1-naphthalenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N^2-(3-methyl-1,2,3,4-tetrahydro-8-quinoline-sulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N^2-(2-dibenzothiophenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N^2-(2,4-dimethoxy-3-butoxybenzenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N^2-(3,5-dimethyl-4-propoxybenzenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N^2-(3-ethyl-1,2,3,4-tetrahydro-8-quinoline-sulfonyl)-L-arginyl] 4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N^2-(2-carbazolesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N^2-(2-fluorenesulfonyl)-L-arginyl]-4-methyl2-piperidinecarboxylic acid;

(2R, 4R)-1-[N^2-(2-phenoxthinesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N^2-(2-anthracenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid; and

(2R, 4R)-1-[N^2-(7-methyl-2 -naphthalenesulfonyl)-L-arginyl]-4- methyl-2-piperidinecarboxylic acid: as well as their 4-ethyl analogues, their 4-propyl analogues, their 4-butyl analogues and their 4-pentyl analogues.

The invention can use the salts of argininеamides having the general formula (I). The salts may be acid addition salts prepared by reacting with any inorganic or organic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, citric acid, maleic acid, succinic acid, lactic acid, tartaric acid, gluconic acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid. Further, the salts may be inorganic or organic salts prepared by reacting organic or inorganic bases such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, triethylamine, procaine, dibenzylamine, N, N'-dibenzylethylenediamine and N-ethylpiperidine.

In the method for dissolving an argininеamide according to the invention, the argininеamide and/or its salt is dissolved in the solvent of alcohol and water. As the alcohols used in the invention, monohydric alcohols such as methanol, ethanol and the like; dihydric alcohols such as ethyleneglycol, propyleneglycol and the like; polyhydric alcohols such as glycerine and the like; and ethers of di- and polyhydric alcohols such as polyethyleneglycol and the like are mentioned. Methanol, ethanol, propyleneglycol and polyethyleneglycol are preferable. Ethanol is particularly preferable. If necessary, a mixture of these alcohols can be used.

Water used in the invention is generally distilled water or purified water, but a physiological saline or Ringer's solution may be used.

The mixed ratio (by weight) of alcohol to water in the above solvent is generally 0.1 to 10, preferably 0.2 to 5 and more preferably 0.3 to 3.

If necessary, any saccharides can be admixed with the solvent of alcohol and water in the invention. As the saccharides used in the invention, monosaccharides, oligosaccharides, polysaccharides and their reduced derivatives (for example sugaralcohol) which are soluble in water are mentioned. Among them, glucose, fructose, maltose, saccharose and D-sorbitol each of which has the high solubility in water are preferable. D-sorbitol is particularly preferable. A mixture of these saccharides may be used.

The mixed ratio (by weight) of saccharide (if present) to water is generally 0.1 to 10, preferably 0.4 to 4 and more preferably 0.5 to 2.

The manner how to dissolve the argininеamide having the general formula (I) in the solvent of alcohol and water and optionally saccharide is not particularly limited. Generally, the saccharide is dissolved in water and then the alcohol is added thereto followed by mixing. Next, the argininеamide is slowly added while stirring until complete dissolution.

The temperature on dissolution is not particularly limited. When the saccharide is dissolved in water, however, it is preferable to war water at 40 to 70° C for accelerating the dissolution rate.

Further, when the volatile alcohol such as ethanol and the like is used, it is necessary to take care for preventing the evaporation of alcohol, for example by cooling the solution to room temperature before the dissolution, or dissolving in a closed container.

The concentration of argininеamide in the solution can be selected within the wide range depending on the intended uses. According to the invention, the solution in which the argininеamide is dissolved at high concentration, for example from several times to several thousands times the solubility of argininеamide in water can be obtained.

The solution containing any of the argininеamide having the general formula (I) in the solvent of alcohol and water and optionally saccharide thus obtained can constitute the pharmaceutical composition of the invention.

The pharmaceutical compositions of the invention are useful for treating thrombosis. Accordingly, the pharmaceutical compositions can be used as the antithrombotic agents.

The pharmaceutical composition of the invention may contain antiseptic, anti-oxidant, soothing agent, pH-controlling agent and the like. And, if necessary any pharmaceutical ingredient(S) other than the argininеamides may be added to form the combined preparation.

The pharmaceutical composition of the invention is injectable as the injection. This injectable composition may contain stabilizer, buffer, preservative and the like which are acceptable for the injection may be added in addition to the above-mentioned ingredients. If desired, the injectable composition according to the invention is prepared to contain the argininеamide at very high concentration, which is used by diluting with water, electrolyte, carbohydrate solution, Ringer's solution or the like on the application such as infusion and dialysis.

Alternatively, the pharmaceutical composition of the invention is topically applicable as the solution for topical application, the ointment or the suppository. When the pharmaceutical composition is used as the solution for topical application, the solution prepared above can be used as it is. And, the ointment or the suppository of the invention may be prepared by dissolving the solution prepared above in the base or the like.

EXAMPLES

The invention will now be further described by the following, non-limiting examples.

Example 1

(2R, 4R)-1-[N^2 -(3-methyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid (argipidine) was dissolved in the solvent

of ethanol and water while varying the mixed ratio of ethanol to water at 20° C. ( ) or 5° C. (○).

The results are shown in FIG. 1. In FIG. 1, the ordinate is the solubility of argipidine in the solvent (mg/ml) and the abscissa is the weight percentages of ethanol and water (w/w %).

As shown in FIG. 1, the solubility of argipidine in the solvent comprising 70 % by weight of ethanol and 30 % by weight of water at 20° C. was 33.23 mg/ml and that at 5° C. was 10.73 mg/ml.

COMPARATIVE EXAMPLE 1

Argipidine was dissolved in the aqueous sorbitol solution while varying the sorbitol concentration at 20° C.

The result was shown in FIG. 2. In FIG. 2, the ordinate is the solubility of argipidine in the aqueous sorbitol solution (mg/ml) and the abscissa is the concentration of sorbitol in the aqueous solution (w/w %).

As shown in FIG. 2, the solubility of argipidine in the aqueous sorbitol solution was low and it was the substantially same as the solubility of argipidine in water.

EXAMPLE 2

Argipidine was dissolved in the solvent comprising the aqueous 25 % sorbitol solution (○), the aqueous 50 % sorbitol solution (□) or the 70 % sorbitol solution (Δ) and ethanol while varying the mixed ratio of ethanol to the aqueous sorbitol solution at 30° C.

The results are shown in FIG. 3. In FIG. 3, the ordinate is the solubility of argipidine in the solvent (mg/ml) and the abscissa is the weight percentages of the aqueous sorbitol solution and ethanol (w/w %).

EXAMPLE 3

Argipidine was dissolved in the solvent comprising the aqueous 33% glucose solution (○), the aqueous 50% glycerine solution (Δ), the 50% sorbitol solution ( ) or the aqueous 50% sucrose solution (□) and ethanol while varying the mixed ratio of ethanol to the aqueous solution at 30° C.

The results are shown in FIG. 4. In FIG. 4, the ordinate is the solubility of argipidine in the solvent (mg/ml) and the abscissa is the weight percentages of the aqueous solution and ethanol (w/w %).

EXAMPLE 4

The distilled water for injection (200 g) was placed in a one-litre beaker, to which D-sorbitol (300 g) was added with stirring and dissolved. At this time, if necessary the solution may be heated. Then, ethanol (400 g) was added and mixed with stirring followed by adding argipidine (100 g) with stirring until complete dissolution.

The thus-obtained solution can be used for dialysis after diluting it with the weak acidic solution containing D-sorbitol.

EXAMPLE 5

The distilled water for injection (200 g) was placed in a one-litre beaker, to which glucose (200 g) was added with stirring and dissolved. Then, ethanol (400 g) was added and mixed with stirring followed by adding argipidine (100 g) with stirring. Further, the distilled water for injection was added till the total volume of the solution became 1 litre.

The thus-obtained solution can be used for drip infusion after diluting it with the aqueous sorbitol solution, the aqueous D-sorbitol solution or Ringer's solution on use.

EXAMPLE 6

The distilled water for injection (200 g) was placed in a one-litre beaker, to which -sorbitol (300 g) was added with stirring and dissolved. At this time, if necessary the solution may be heated. Then, glycerine (200g) and ethanol (200 g) were added and mixed with stirring followed by adding argipidine (100 g) with stirring. Further, the distilled water for injection was added till the total volume of the solution became 1 litre.

The thus-obtained solution can be used for dialyses after diluting the weak acidic solution containing D-sorbitol.

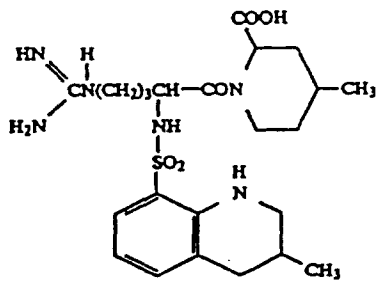
EFFECT OF THE INVENTION

According to the method for dissolving the argininеamide of the invention, the injection containing any of the argininеamides having the general formula (I) and/or their salts, particularly at high concentration can be obtained.

What is claimed is:

1. A method for dissolving an argininеamide, comprising:

dissolving N^2-arylsulfonyl-L-argininamide represented by formula (I):



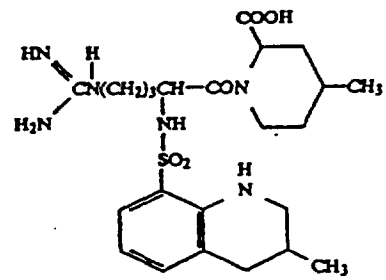
(I)

and/or its salt in a solvent containing ethanol, water and a saccharide.

2. The method according to claim 1, wherein the saccharide is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose.

3. A pharmaceutical composition for injection, comprising:

N^2-arylsulfonyl-L-argininamide represented by formula (I):



(I)

and/or its salt together with ethanol, water and a saccharide.

4. The composition according to claim 3, wherein the saccharide is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose.

* * * * *

Section 13 Patent Information

The Patent which pertains to the product being developed is United States Patent Number 5,214,052 which was issued on May 25, 1993. This patent titled "Method for Dissolving Arginineamides and Pharmaceutical Compositions Containing Them" is held by Mitsubishi Kasei Corporation, Tokyo, Japan and licensed to Texas Biotechnology Corporation, the holder of this New Drug Application. A copy of this patent is included in this section of the NDA. This patent covers the concentrated dosage form of argatroban which is the product to be marketed by Texas Biotechnology Corp. upon approval of this NDA.

The undersigned declares that Patent No. 5,214,052 covers the formulation, composition, and/or method of use of argatroban. This product is the subject of this application for which approval is being sought.

Gary Knappenberger

Gary D. Knappenberger
Senior Director, Clinical and Regulatory Affairs

US005214052A

United States Patent [19]

Ofuchi et al.

[11] Patent Number: 5,214,052

[45] Date of Patent: May 25, 1993

[54] METHOD FOR DISSOLVING ARGININEAMIDES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

[75] Inventors: Kunihiko Ofuchi; Tatsuo Nomura, both of Hasaki, Japan

[73] Assignee: Mitsubishi Kasei Corporation, Tokyo, Japan

[21] Appl. No.: 851,248

[22] Filed: Mar. 13, 1992

Related U.S. Application Data

[63] Continuation of Ser. No. 577,042, Aug. 30, 1990, abandoned, which is a continuation of Ser. No. 223,152, Jul. 22, 1988, abandoned.

[30] Foreign Application Priority Data

Jul. 28, 1987 [JP] Japan 62-188484

[51] Int. Cl.[5] A61K 9/08; A61K 31/445; A61K 47/00

[52] U.S. Cl. 514/315; 514/23; 514/53

[58] Field of Search 514/315

[56] References Cited

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4,870,175	9/1989	Suzuki et al.	544/354
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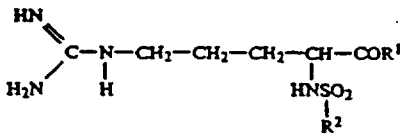
Gstirner F.: "Einfuhrung in die Verfahrenstechnik der Arzneiformung" 1973 pp. 271-272.

Primary Examiner—Shep K. Rose

Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

A method for dissolving an argininеamide of the invention comprising dissolving N^2-arylsulfonyl-L-argininеamide having the general formula (I)



(I)

wherein R^1 represents a (2R, 4R)-4-alkyl-2-carboxypiperizino group and R^2 represents a phenyl group or a condensed polycyclic compound residue which may be substituted with one or more substituents selected from lower alkyl groups, lower alkoxy groups and lower alkyl-substituted amino groups, said condensed polycyclic compound residue including a benzene ring which binds to sulfur atom of the sulfonyl group in the general formula (I) and is condensed with one or more other rings which may be heterocyclic and having 7 to 14 carbon atoms as the ring-constituent atoms;

and/or its salt in a solvent of alcohol and water is disclosed herein.

And, the pharmaceutical composition comprising N^2-arylsulfonyl-L-argininеamide having the general formula (I), an alcohol and water is disclosed herein.

4 Claims, 3 Drawing Sheets

EXCLUSIVITY SUMMARY FOR NDA # ___20-883_____ SUPPL #_____

Trade Name _____ Generic Name ____argatroban_____

Applicant Name __Texas Biotechnology Corporation_____ HFD # _180_____

Approval Date If Known _____

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:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

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?

__No._____

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 /___/ NO /_X__/

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 /_X__/

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.

YES /___/ NO /_X__/

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

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.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____

!

! _____

Investigation #2 !

!

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

__ _____ ! _____

!

!

Investigation #2 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ 6/2/00
Signature Date
Title: Regulatory Health Project Manager

/S/ 6-2-00
Signature of Office/ Date
Division Director

cc: Original NDA 20-883
HFD-180/Division File
HFD-93/Mary Ann Holovac
HFD-180/DuBeau
R/d Init: Talarico
JD/June 2, 2000 (drafted)

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20883	**Trade Name:**	NOVASTAN (ARGATROBAN) INJECTION 100MG/ML
Supplement Number:		**Generic Name:**	ARGATROBAN
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	AP	**Proposed Indication:**	Novastan is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

6/5/00: Requested commitment to conducting P4 peds studies in 2/18/00 AE action letter. Firm committed in writing (4/20/00 submission) to conduct these studies.

6/5/00: Plan to conduct P4 peds studies.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIEANN DUBEAU

Signature /S/ _____ June 5, 2000 Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20883	**Trade Name:**	NOVASTAN (ARGATROBAN) INJECTION 100MG/ML
Supplement Number:		**Generic Name:**	ARGATROBAN
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	AE	**Proposed Indication:**	Novastan is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

[10/30/97 submission]: According to the firm, they have no plans to study this indication in a peds population since there is a very small number of peds patients with HIT.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIEANN DUBEAU

Signature /S/ _____ Date 2/23/00

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

'DA/PLA/PMA # 20-883 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-180 rade and generic names/dosage form: Novastan Injection Action: AP AE (NA)

Applicant Texas Biotech. Therapeutic Class 1P

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate __ inadequate __
Proposed indication in this application Anticoagulant therapy in patients with HIT

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___ Yes (Continue with questions) _X_ No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
__ Neonates (Birth-1month) __ Infants (1month-2yrs) __ Children (2-12yrs) __ Adolecents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
- __ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __ c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing.
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - __ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

_X_ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
*See page 3 of letter from firm dated 10/30/97 (attached).

__ 5. **PEDIATRIC LABELING MAY NOT BE ADEQUATE.**
- __ a. Pediatric studies are needed.
- __ b. Pediatric studies may not be needed but a pediatric supplement is needed.

__ 6. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes _X_ No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/
Signature of Preparer and Title

4/6/98
Date

cc: Orig NDA/PLA/PMA # 20-883
HFD-180/Div File
NDA/PLA Action Package
HFD-006/ KRoberts

(revised 9/15/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Section 16

Debarment Certification

Texas Biotechnology Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

3/11/99

John McMurdo, MD
Vice President, Clinical Development and Regulatory Affairs

Date

3.3.99

Gary D. Knappenberger
Consultant, Regulatory Affairs

Date

Section 16 Debarment Certification

This is to certify that no individuals who have been debarred by HSS or FDA have participated in any way in the development of this product or in the assembly of this New Drug Application.

Gary Knappenberger

Gary D. Knappenberger
Senior Director, Clinical and Regulatory Affairs

*3. Environmental Impact Assessment

In accordance with 21 CFR 25.15(d), a claim for categorical exclusion for the preparation of an Environmental Impact Assessment is made. The Sponsor qualifies for categorical exclusion because the estimated Expected Introduction Concentration (EIC) is less than 1 ppb. To the Sponsor's knowledge, no extraordinary circumstances exist.

*Denotes change.

REQUEST FOR TRADEMARK REVIEW

873

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products		**HFD-180**
Attention: Julieann DuBeau, Project Manager	**Phone:** (301) 443-8423	
Date: September 2, 1997 9/2/97		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product /S/		
Proposed Trademark: Novastan®	**NDA/ANDA#** NDA 20-883	
Established name, including dosage form: Argatroban Injection		
Other trademarks by the same firm for companion products:		
Indications for Use (may be a summary if proposed statement is lengthy): Anticoagulant therapy in patients with heparin-induced thrombocytopenia (HIT).		
Initial Comments from the submitter (concerns, observations, etc.):		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-883; HFD-180/division file; HFD-180/J.DuBeau; HFD-180/Al-Hakim

Rev. December 95

Consult #873 (HFD-180)

NOVASTAN argatroban injection

There were no look-alike/sound-alike conflicts noted or misleading aspects found in the proposed proprietary name.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 1/28/98, Chair
CDER Labeling and Nomenclature Committee

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

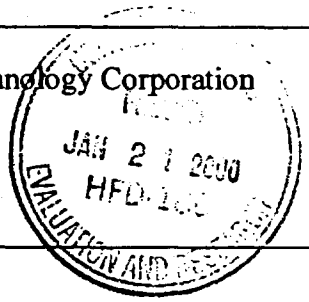
DATE SENT: January 5, 2000	**DUE DATE:** January 10, 2000	**OPDRA CONSULT #:** 99-103

TO (Division): Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
(HFD-180)

PRODUCT NAMES:
Novastan (argatroban) Injection Concentrate

NDA: 20-883

MANUFACTURER: Texas Biotechnology Corporation



CASE REPORT NUMBER(S): N/A

SUMMARY:

In response to a December 6, 1999 request by the Division of Gastro-Intestinal and Coagulation Drug Products, OPDRA conducted a review of the potential name confusion of the proposed proprietary name, Novastan, with other approved proprietary/generic names. This review includes a study conducted within OPDRA with emphasis on the evaluation of the potential medication errors in handwriting and verbal communication of the proposed proprietary name.

OPDRA RECOMMENDATION:

OPDRA does not recommend the use of the proprietary name, Novastan. See review.

/S/ 1/12/2000

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 1/14/00

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research

Proprietary Name Review

DATE OF REVIEW: January 5, 1999

NDA: 20-883

NAME OF DRUG: Novastan (argatroban) Injection Concentrate

NDA HOLDER: Texas Biotechnology Corporation

I. INTRODUCTION

This consult is in response to a request sent on December 6, 1999, from the Division of Gastro-Intestinal and Coagulation Drug Products, to review a proposed proprietary drug name, Novastan, regarding potential name confusion with other proprietary/generic drug names. In addition, container labels and carton labeling were reviewed for possible interventions in minimizing medication errors.

The proposed proprietary name, Novastan, was previously reviewed by the Labeling and Nomenclature Committee (LNC) and was found to be acceptable on January 28, 1998.

PRODUCT INFORMATION

Novastan (argatroban) injection concentrate is a synthetic, direct thrombin inhibitor that binds to the thrombin active site. Argatroban exerts its anticoagulant effects by inhibiting thrombin-catalyzed or induced reactions, including fibrin formation; activation of coagulation factor XIII, factor V, factor VIII, and protein C; and platelet aggregation. Argatroban is also capable of inhibiting the action of clot-associated thrombin. Novastan is indicated as anticoagulant therapy in patients with heparin-induced thrombocytopenia syndrome, who, in opinion of their attending physician, require anticoagulation. Pharmacokinetics of argatroban suggests that Cytochrome P450 3A4/5 mediated metabolism is not an important elimination pathway in vivo. The major route of excretion is via fecal elimination, presumably via biliary secretion. Upon cessation of Novastan infusion, plasma argatroban concentrations rapidly decline with α and β elimination half-lives of approximately 7 and 54 minutes, respectively. Renal dysfunction did not affect the pharmacokinetic or pharmacodynamic parameters of argatroban. Moderate hepatic impairment is associated with a four-folded decreased clearance as well as an increased elimination half-life of 2.5 hours. The recommended initial dose for adult patients without hepatic impairment is 2 ug/kg/min, administered as a continuous infusion. Novastan injection concentrate is supplied in 2.5 ml solution in single-use vials at the concentration of 100 mg/ml. Each vial contains 250 mg of argatroban.

II. RISK ASSESSMENT

In order to predict the potential medication errors and to determine the degree of confusion of the proposed proprietary name, Novastan, with other drug names, the medication error staff of OPDRA searched the MICROMEDEX Healthcare Intranet Series (1999), which includes the following: DrugDex, Poisindex, Martindale, Emergindex, Reprodisk, and Index Nominum. Other references include American Drug Index (43rd Edition), Drug Facts and Comparisons (Monthly Updates), PDR (53rd Edition, 1999), Electronic Orange Book, US Patent and Trademark Office online database, Drug Product Reference File (DPRF), Decision Support System (DSS), EES (Established Evaluation System), and the LNC database for possible sound-alike or look-alike names to approved and unapproved drug products. A focus group discussion was conducted to review all of the findings from the searches. In addition, OPDRA conducted a study of written and verbal analyses of the proposed proprietary name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

A. Study conducted within FDA

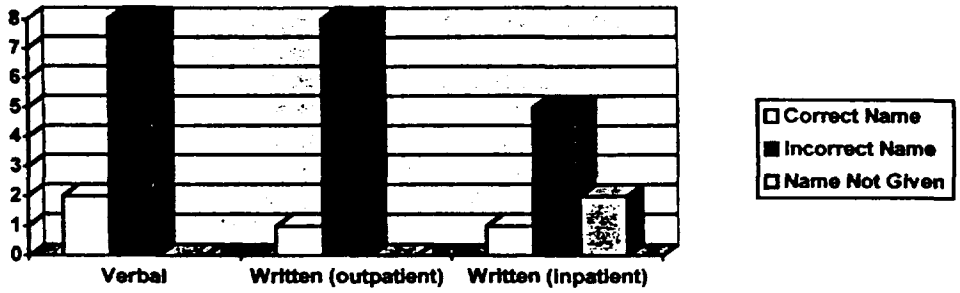
1) Methodology

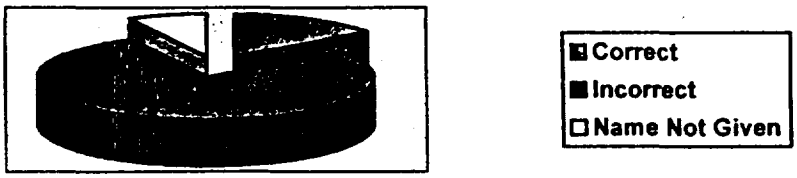
This study involved forty-six health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Novastan with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Random samples of either inpatient or outpatient written orders were delivered to the participating health professionals via e-mail. In addition, verbal orders via voice mail were sent to the participating health professionals for their review. After receiving the prescription orders, the participants sent their interpretations of the prescriptions via e-mail to the medication error staff.

2) Results

Fifteen inpatient written orders, sixteen verbal orders, and fifteen outpatient written orders were sent to the participants. We received responses from twenty-seven participants. Eight interpretations of outpatient written orders, ten interpretations of verbal orders, and nine interpretations of inpatient written orders were received. Four (out of twenty-seven) participants interpreted Novastan correctly. The results are as follows:

Novastan





Incorrect Responses		
Verbal	Written (outpatient)	Written (inpatient)
Novestin	Nevasten	Novastar
Vinostin	Narvastan	Novastar
Novstan	Nevastar	Novastar
Novasten	Navastan	Novastar
Novstan	Norvastan	Novastar
Nosten		Narastar
Nostan		Novostan
Nostan		Novastar

B. Focus Group Findings

1) When scripted, the proposed proprietary name, Novastan, is similar to Novantrone and lovastatin and may cause name confusion. Both Novastan and Novantrone have similar beginnings. Proprietary names with similar beginning syllables are often confused for one another when combined with indistinct physician handwriting of terminal syllables, leading to medication errors. Furthermore, the letter, "L", in lovastatin could look-alike "N" when scripted. If that is the case, lovastatin could appear to have a very similar beginning (same seven letters) as Novastan. Moreover, like Novastan, Novantrone is available as an injectable concentrate that needs to be diluted prior to use. Both Novastan and Novantrone also require patient dependent calculations for determining the doses.

   Despite these similarities, there are differences as well. Lovastatin is available in a tablet formulation and is usually given once daily, whereas Novastan is

administered as a continuous infusion and Novantrone is given as a short intravenous infusion every 21 days. Due to the differences in dosage form and dosage interval, lovastatin could pose less risk of name confusion than Novantrone. On the other hand, Novantrone may be stored separately in pharmacies from the other two drugs since it is an antineoplastic agent. However, it is possible for name confusion and medication errors to occur due to look-alike similarity alone. In addition, medication errors involving these three drugs can be significant because of their indications for use. Novantrone, an antineoplastic agent, in combination with corticosteroids, is indicated in the initial chemotherapy for the treatment of patients with pain related to advance prostate cancer. Novantrone, in combination with other approved drugs, is also indicated in the initial therapy of acute nonlymphocytic leukemia in adults. Novastan is indicated as anticoagulant therapy in patients with heparin-induced thrombocytopenia syndrome, who, in opinion of their attending physician, require anticoagulation. Lovastatin is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia, when the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate. Lovastatin is also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels. Misadventures or substitution of any of these drugs for one another can have significant outcomes, including elevation of creatine phosphokinase, myelosuppression, mucositis, bleeding, and worsening of existing medical conditions.

2) All participants of the focus group commented that in their initial impression, the proposed proprietary name, Novastan, reminded them of an antihyperlipidemic agent (HMG-CoA inhibitor), which has a common suffix, "statin", in the name (i.e. lovastatin).

C. Discussion

The results of the written and verbal analyses demonstrate that majority of the participants (twenty-three out of twenty-seven) interpreted Novastan incorrectly. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health professionals are not familiar with the names. However, in this case, the results of the study in combination with the possibility of name confusion and the associated risks of medication errors are significant to render the proprietary name, Novastan, objectionable. Additional searches in available texts, databases, and the handwriting samples did not produce any significant new information.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels and carton labeling of Novastan, OPDRA has attempted to focus on safety issues relating to possible medication errors. Many of the

items discussed in this consult involve issues normally reviewed by the chemist and/or the medical officer.

OPDRA has reviewed the current labels and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1) Although this product is an injectable concentrate requiring dilution prior to use, the term, "concentrate", should not be a part of the established name. The United States Pharmacopeia (USP) no longer includes "concentrate" in the monograph titles except for potassium chloride injection concentrate. We recommend consulting Dan Boring (of the USAN council & LNC) for the proper designation of the established name.

2) Due to the numerous errors in strength misinterpretations of intravenous drug products, OPDRA recommends that the TOTAL drug strength be the primary designation. We recommend the following presentation:

250 mg/ 2.5 mL
(100 mg/ mL)

3) The statement of ingredients, "Each 2.5 ml ...", should be consistent with the statement on the carton labeling.

4) In order to maximize label space and to be in accordance with Agency policy, the applicant should be informed that the "CAUTION: Federal law prohibits dispensing without prescription," statement should be revised to "Rx Only". This statement is preferred on the center of the label (or the main panel for carton labeling).

B. CARTON LABELING

1) The statement, "DILUTE PRIOR TO USE," should appear immediately beneath the strength. In addition, we recommend eliminating the line that separates the top portion of the panel to the bottom portion.

2) See comments under CONTAINER LABEL.

C. PACKAGE INSERT (DOSAGE AND ADMINISTRATION)

1) The proposed labeling recommends using, "1 vial (for 2.5 ml total) per 250 ml diluent bag, or 2 vials (for 5.0 ml total) per 500 ml diluent bag". We recommend that the total number of **milligrams** be stated instead of using only volume or vial numbers. Thus, the first paragraph under the "Preparation for Intravenous Administration" subsection should read:

Use 250 mg (2.5 ml) per 250 ml of diluent or 500 mg (5 ml) per 500 ml of diluent.

2) The volume, " 5.0 ml" and the infusion rate, "2.0 ug/kg/min" contain terminal zeros. Often times, terminal zeros lead to medication errors. We recommend deleting all terminal zeros in the package insert.

3) In the HOW SUPPLIED section, the manufacturer-distributor relationship is not consistent with the container label and carton labeling. The package insert has listed two distributors, (Texas Biotechnology Corporation and SmithKline Beecham Pharmaceuticals), whereas the only one distributor is listed on the container label and carton labeling. The statement of the distributor relationship should be revised to be in accordance with 21 CFR 201.1 (h) (5).

IV. RECOMMENDATIONS

A. OPDRA does not recommend the use of the proprietary name, Novastan.

B. OPDRA recommends the above labeling revisions which might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at (301) 827-3243.

/S/ 1/12/00

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 1/12/00

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC: NDA# 20-883
HFD-180; DivFiles; Julieann DuBeau, Project Manager, DGCDP
HFD-180; Lilia Talarico, Division Director
Office Files
HFD-400; Lauren Lee, Safety Evaluator, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-2 ; Mac Lumpkin, Acting Director, OPDRA

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 5/8/00	**DUE DATE:** 6/26/00	**OPDRA CONSULT #:** 00-0141

TO:
Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

THROUGH:
Julie DuBeau
Project Manager
HFD-180

PRODUCT NAME: Acova (argatroban) Injection **NDA #:** 20-883	**MANUFACTURER:** Texas Biotechnology Corporation

SAFETY EVALUATOR: Peter Tam, RPh.

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of the proprietary name, Acova. See the checked box below.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

√ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, 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 prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/ 6/20/2000
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 6/21/00
Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 6/15/00

NDA#: 20-883

NAME OF DRUG: Acova
(argatroban) Injection

NDA HOLDER: Texas Biotechnology Corporation

I. INTRODUCTION:

This consult is in response to a request sent on 5/8/00 from the Division of Gastro-Intestinal and Coagulation Drug Products, to review a proposed proprietary drug name, Acova, regarding potential name confusion with other proprietary/generic drug names. The sponsor had previously submitted the name, Novastan, on 1/5/00. OPDRA concluded that the name was unacceptable due to potential name confusions with Novantrone and Lovastatin.

The sponsor subsequently submitted another name for review on 5/8/00. The proposed proprietary name is Acova, and the goal date is 7/5/00.

PRODUCT INFORMATION

Acova (argatroban) injection is a synthetic, direct thrombin inhibitor that binds to the thrombin active site. Argatroban exerts its anticoagulant effects by inhibiting thrombin-catalyzed or induced reactions, including fibrin formation; activation of coagulation factor XIII, factor V, factor VIII, and protein C; and platelet aggregation. Argatroban is also capable of inhibiting the action of clot-associated thrombin. It is indicated as anticoagulant therapy in patients with heparin-induced thrombocytopenia syndrome, who, in the opinion of their attending physician, require anticoagulation.

The recommended initial dose for adult patients without hepatic impairment is 2 mcg/kg/min, administered as a continuous infusion.

Acova injection will be supplied in 2.5 mL solution in single-use vials at the concentration of 100 mg/ml. Each vial contains 250 mg of argatroban.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to Acova to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

The Expert Panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

1. The panel discussion was conducted to gather professional opinions on the safety of the proprietary name, Acova. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The Expert Panel identified several product names considered to have potential for confusion. The identified products are listed in the following table.

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Acova	Injection, argatroban	1 V infusion at 2 mcg/kg/min	
Alora	Transdermal patch, estradiol	Topical application, 0.05/0.075/0.1 mg/24 hr	*SA/LA
Renova	Topical cream, tretinoin 0.05%	Apply once daily	*SA
Acular	Ophthalmic soln, ketorolac 0.5%	One drop qid	*SA

*SA = Sound-alike
*LA = Look-alike

[1] MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

According to the panel, Alora, might pose potential risk with Acova due to name confusion. They sound and look alike. However, Alora is a topical estrogen transdermal product while Acova is an injection indicated for anticoagulant therapy. Confusion of Acova with Alora, hence, seems unlikely given differences in dosage forms, route of administration, and usual dosing schedule.

The panel concluded that the above listed drugs and Acova pose no significant safety risk, and therefore, the proprietary name, Acova, is not objectionable.

2. DDMAC – no objections

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Studies were conducted by OPDRA and involved 92 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Acova with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Acova (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the inpatient verbal orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff. We conducted two inpatient written studies to see if a poorly written script (which is often seen in actual prescription) can result in dramatically different result. We did not conduct the outpatient written study since this drug would not normally be prescribed in that setting.

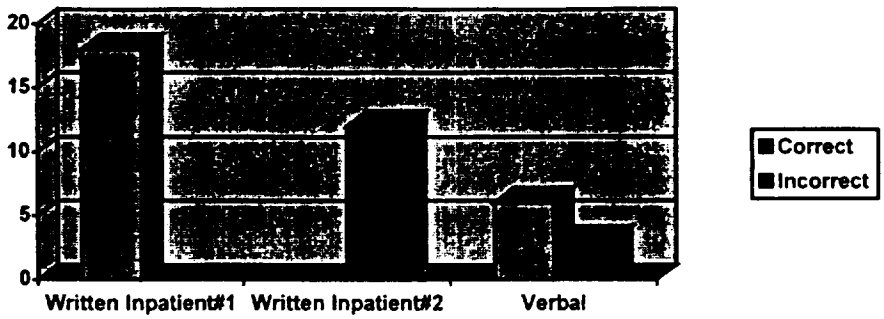
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient RX#1: Increase Acova to 8 mcg/hr	Increase Acova to 8 mcg/hr
Inpatient RX#2: Increase Acova to 8 mcg/hr	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient #1	31	18(58%)	18	0
Written Inpatient #2	31	12(39%)	0	12
Verbal	30	9(30%)	6	3
Total	92	39(42%)	24(61%)	15(39%)



C. SAFETY EVALUATOR RISK ASSESSMENT

A number of proprietary drug names were identified in the Expert Panel discussion that were thought to be similar to Acova. Alora (estradiol transdermal patch) was identified to have the greatest potential for confusion with Acova. They both share three characters "aao" in their name and they both have 5 character lengths. Despite these similarities, Acova and Alora differ in dosing strength, therapeutic class and route of administration and other factors such as to how and when the drug will be used as well as the patient population that will use this drug, Alora is a topical estradiol transdermal system and Acova is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. Considering all the circumstances under which Acova will be used, it is unlikely that Alora would be confused and result in potential medication errors.

The results of the verbal prescription study indicate that three (out of nine) respondents interpreted Acova incorrectly. In the first written study, eighteen (out of eighteen) interpreted Acova correctly while the second written study has no one (twelve out of twelve) interpreted the name correctly. This is possibly due to a poorly written script in the second written study. We conduct two inpatient written studies to see if a poorly written prescription can produce different result. In this case, results were strikingly different.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

We have no comments.

IV. RECOMMENDATIONS:

OPDRA has no objections to the use of the proprietary name, Acova.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam at 301-827-3241.

/S/ 6/16/00

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 6/26/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

NDA – 20-883
Office Files
HFD-180; DivFiles; Julie DuBeau, Project Manager, DGCDP
HFD-180; Lilia Talarico, M.D., Division Director, DGCDP
HFD-042; Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)
HFD-440; Patrick Guinn, Project Manager, DDREII, OPDRA (Electronic Only)
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Sammie Beams, Project Manager, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (Electronic Only)

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20883/000
Stamp: 15-AUG-1997
Regulatory Due: 18-FEB-2000
Applicant: TEXAS BIOTECH
7000 FANNIN STE 1920
HOUSTON, TX 77030
Priority: 1S
Org Code: 180

Action Goal:
District Goal: 09-SEP-1998
Brand Name: NOVASTAN (ARGATROBAN) INJECTION 100MG/ML
Estab. Name:
Generic Name: ARGATROBAN

Dosage Form: (INJECTION)
Strength: 100 MG/ML

Application Comment: THE PROPOSED INDICATION IS ANTICOAGULANT THERAPY IN PATIENTS WITH HEPARIN-INDUCED THROMBOCYTOPENIA (HIT). PDUFA GOAL DATE = FEBRUARY 15, 1998. THIS IS A PRIORITY APPLICATION AND NEW MOLECULAR ENTITY. (on 02-SEP-1997 by J. DUBEAU (HFD-180) 301-827-7310)

FDA Contacts:
J. DUBEAU (HFD-180) 301-827-7310 , Project Manager
A. AL HAKIM (HFD-820) 301-827-7310 , Review Chemist
E. DUFFY (HFD-150) 301-594-5765 , Team Leader

Overall Recommendation: ACCEPTABLE on 14-JAN-1998 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 01-FEB-2000 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: 1925262
ABBOTT LABORATORIES
1776 NORTH CENTENNIAL DR
MCPHERSON, KS 67460

DMF No:
AADA:
Responsibilities: [redacted]

Profile: SVS
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-SEP-1997				DUBEAUJ
SUBMITTED TO DO	05-SEP-1997	PS			DAMBROGIOJ
ASSIGNED INSPECTION	08-SEP-1997	PS			MGARZA
INSPECTION SCHEDULED	08-SEP-1997		09-SEP-1997		MGARZA
DO RECOMMENDATION	09-SEP-1997			ACCEPTABLE	FERGUSONS
				BASED ON FILE REVIEW	
AC BASED ON SATISFATORY GMP AND NO MAJOR FLAWS DETECTS IN THE APPLICATION REVIEW BY THE REVIEW CHEMIST, PER MANUEL GARZA. (KAN-DO SYSTEM NOT WORKING, INFO VIA PHONE).					
OC RECOMMENDATION	10-SEP-1997			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	28-JAN-2000				FERGUSONS
SUBMITTED TO DO	28-JAN-2000	10D			FERGUSONS
DO RECOMMENDATION	31-JAN-2000			ACCEPTABLE	KRODEN
				BASED ON FILE REVIEW	
KAN-DO RECOMMENDED APPROVAL IN SEPTEMBER 1997 FOR THIS APPLICATION. A GMP INSPECTION WAS CONDUCTED 1/10-21/2000, COVERING THIS PROFILE CLASS SVS, AND NO FDA-483 WAS ISSUED. THE INSPECTION IS CLASSIFIED AS NAI. BASED ON THE INSPECTIONAL FINDINGS, KAN-DO CONTINUES TO RECOMMEND APPROVAL OF THIS APPLICATION.					
OC RECOMMENDATION	31-JAN-2000			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-SEP-1997				DUBEAUJ
OC RECOMMENDATION	05-SEP-1997			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	28-JAN-2000				FERGUSONS
OC RECOMMENDATION	28-JAN-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-SEP-1997				DUBEAUJ
OC RECOMMENDATION	05-SEP-1997			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	28-JAN-2000				FERGUSONS
OC RECOMMENDATION	28-JAN-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 9610309
MITSUBISHI CHEMICAL CORP
KASHIMA-GUN IBARKAKI-KEN, , JA
DMF No: [redacted] AADA:
Responsibilities: [redacted]
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-SEP-1997				DUBEAUJ
SUBMITTED TO DO	05-SEP-1997	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	15-SEP-1997	GMP			EGASM
INSPECTION SCHEDULED	16-DEC-1997		10-DEC-1997		EGASM
INSPECTION PERFORMED	14-JAN-1998		09-DEC-1997		EGASM
DO RECOMMENDATION	14-JAN-1998			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	14-JAN-1998			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM
SUBMITTED TO OC	28-JAN-2000				FERGUSONS
OC RECOMMENDATION	01-FEB-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM

FUR

Application: NDA 20883/000
Stamp: 15-AUG-1997 Regulatory Due: 15-MAY-1998
Applicant: TEXAS BIOTECH
7000 FANNIN STE 1920
HOUSTON, TX 77030

Priority: 1P Org Code: 180
Action Goal: District Goal: 11-DEC-1997
Brand Name: NOVASTAN (ARGATROBAN) INJECTION 100MG/ML
Established Name:
Generic Name: ARGATROBAN
Dosage Form: INJ (INJECTION)
Strength: 100 MG/ML

FDA Contacts:

J. DUBEAU	(HFD-180)	301-443-0487	, Project Manager
A. AL HAKIM	(HFD-180)	301-443-0483	, Review Chemist
E. DUFFY	(HFD-180)	301-443-0483	, Team Leader

Overall Recommendation:

ACCEPTABLE on 14-JAN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: 1925262
ABBOTT LABORATORIES
1776 NORTH CENTENNIAL DR
MCPHERSON, KS 67460

DMF No:
AADA No:

Profile: SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 10-SEP-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

Establishment: [redacted] NC [redacted] 00

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 05-SEP-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: [redacted]

Establishment: 9610309
MITSUBISHI CHEMICAL CORP
14, SUNAYAMA HAZAKI-MACHI KA
KASHIMA-GUN IBARKAKI-KEN, , JA

DMF No: [redacted]
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 14-JAN-1998

Responsibilities: [redacted]

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-SEP-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NDA

Application Number: 20-883

SEP 12 1997

Name of Drug: Novastan® (argatroban) Injection

Sponsor: Texas Biotechnology Corporation

Material Reviewed

Submission Date(s): August 11, 1997

Receipt Date(s): August 15, 1997

Background and Summary Description: Texas Biotechnology Corporation submitted this NDA for Novastan® (argatroban) Injection with the following proposed indication: anticoagulant therapy in patients with heparin-induced thrombocytopenia. The Chemistry, Manufacturing, and Controls (CMC) section of the application was submitted and received on June 27, 1997, as a Presubmission to the NDA.

Review

A. Overall Format and Content: All elements listed in the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications" (February 1987) are addressed except for the following:

1. Information Request:

   a. No archival jackets for volumes 2.40-2.49 could be located. The firm was requested on 9/9/97 by telephone to submit volumes 2.40-2.49 in archival jackets.

   b. The overall index does not reference by page number to the summary section. Under 21 CFR 314.50(b), the archival copy of the application is required to contain a comprehensive index by volume number and page number to the summary, to the review sections, and to any supporting information.

   c. The overall index references incorrect page numbers and omits page numbers. For example, the Table of Contents according to the overall index, begins on page 001, however, the Table of Contents actually