# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-478**

## ADMINISTRATIVE DOCUMENTS

# Time Sensitive Patent Information

**Patent Information Pursuant to 21 C.F.R. § 314.53**
**for**

**ZOVIRAX CS® (acyclovir 5% cream)**

**NDA Submitted Concurrently Herewith**

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The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

| | |
|---|---|
| **Trade Name:** | ZOVIRAX CS® |
| **Active Ingredient:** | acyclovir |
| **Strength(s):** | 5% active |
| **Dosage Form:** | topical cream |

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| U.S. Patent | Expiration Date | Type of Patent | Patent Owner | U.S. Agent |
|---|---|---|---|---|
| 4,963,555 | 16 October 2007 | Drug Product Composition/ Formulation Method of Use | Glaxo Wellcome Inc. | Glaxo Wellcome Inc. |

The undersigned declares that U.S. Patent 4,963,555 covers the formulation, composition and method of use of ZOVIRAX CS® (acyclovir 5% cream). This product is the subject of this application for which approval is being sought.

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Respectfully submitted,

Date: 12 February, 1999

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# United States Patent [19]

**Jones et al.**

[11] **Patent Number: 4,963,555**

[45] **Date of Patent: Oct. 16, 1990**


[54] **FORMULATIONS OF HETEROCYCLIC COMPOUNDS**


[75] Inventors: Trevor M. Jones, Sanderstead; Alan R. White, Meopham, both of England

[73] Assignee: Burroughs Wellcome Co., Research Triangle Park, N.C.



[21] Appl. No.: 317,129

[22] Filed: Mar. 1, 1989

**Related U.S. Application Data**

[63] Continuation of Ser. No. 825,956, Feb. 4, 1986, abandoned, and a continuation of Ser. No. 279,861, Jul. 2, 1981, abandoned, which is a continuation-in-part of Ser. No. 202,339, Oct. 30, 1980, abandoned.

[30] **Foreign Application Priority Data**

Jul. 18, 1980 [GB] United Kingdom ..... 8023645

[51] Int. Cl.[5] ..... A61K 31/52

[52] U.S. Cl. ..... 514/262

[58] Field of Search ..... 514/262



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[57] **ABSTRACT**

A topical pharmaceutical formulation for use in treating virus infections of the skin or mucosa and containing 9-(2-hydroxyethoxymethyl) guanine or a salt or ester thereof which comprises a dispersed oil phase and a continuous aqueous phase containing therein water, at least 30% of a polyhydric alcohol (by weight of the formulation) and solublized acyclovir.


**15 Claims, No Drawings**

# FORMULATIONS OF HETEROCYCLIC COMPOUNDS

This is a continuation of co-pending application Ser. No. 823,956 filed on Feb. 4, 1986 which is a continuation of of Ser. No. 279,861, filed July 2, 1981, which is a continuation-in-part of Ser. No. 202,339, filed Oct. 30, 1980, all now abandoned.

This invention relates to a topical pharmaceutical formulation suitable for use in treating virus infections of the skin and mucosa, and in particular it relates to topical formulations containing 9-(2-hydroxyethoxymethyl)guanine, otherwise known as acyclovir, and hereinafter referred to as such.

Acylovir and pharmaceutically acceptable salts and esters thereof are known to have antiviral activity against various classes of DNA and RNA viruses both in vitro and in vivo, see UK patent No. 1 523 865. In particular the compound is active against herpes simplex virus which causes herpetic keratitis in rabbits, herpetic encephalitis in mice, and cutaneous herpes in guinea pigs.

Acyclovir suffers from the disadvantage that it has a low solubility in water and is almost totally insoluble in hydrophobic solvent systems. It is accordingly difficult to produce a topical formulation containing a sufficient dissolved concentration of active ingredient for it to exert its full effect and also to optimise the flux of the compound into the skin. In addition to ease of release it is also important that any formulation of a pharmaceutically active compound should be stable for long periods of time, should not lose its potency, should not discolour or form insoluble substances or complexes, and also should not be unduly irritating to the skin or mucosa.

In example 26 of UK patent No. 1 523 865 there are listed the constituents of an oil-in-water cream containing 5% w/w acylovir, amongst which constituents is 5% w/w propylene glycol. The function of the propylene glycol in the formulation of example 26 is to act as an humectant, i.e. a hygroscopic ingredient, which should improve the cosmetic feel of the product and also limit dehydration during storage. In animal experiments this formulation and a formulation of aqueous cream B.P. (British Pharmacoepia) containing acylovir did not provide a particularly rapid cure probably because of insufficient active ingredient in solution and poor penetration of the active ingredient into the skin.

In view of the lipid nature of the skin surface, especially the stratum corneum, it has long been thought that to achieve good transdermal penetration the active ingredient in an emulsion should be located in the oil phase so that it can partition into the lipid components of the skin.

It has now been found that, in order to optimise the release of acyclovir from topical formulations, the maximum solubilised concentration of drug should be in the external phase of an oil-in-water emulsion preparation, i.e. in the aqueous phase. Further it has been found that by using a high concentration of a polyhydric alcohol as a cosolvent in the aqueous phase, for example at least 50% v/v of that phase, an increased concentration of solubilised acyclovir can be attained, leading to enhanced activity and efficacy of such formulations. Such a high concentration of a polyhydric alcohol also dispenses with the necessity of including a preservative as an additional ingredient in the formulation.



Such topical formulations also satisfy the criteria of adequate stability, maintenance of potency and are not unduly irritating to the skin or mucosa and have the advantages over the prior art formulation of penetrating skin more effectively and in greater concentration with the result that a rapid, complete cure of the infection is achieved.

According to the present invention there is provided an oil-in-water topical pharmaceutical formulation for the treatment of virus diseases of the skin or mucosa of a mammal comprising a dispersed oil phase and a continuous aqueous phase containing therein water, at least 30% of a water miscible polyhydric alcohol (by weight of the formulation) and solubilised acyclovir. Preferably the formulation contains a maximum of 50% water.

Such a topical formulation may contain 0.075% to 10% w/w acyclovir or a salt or an ester thereof, from 30% to 60% w/w of a polyhydric alcohol, from 15% to 50% w/w water and an oil phase. Hereafter references to acyclovir should be understood to include also its pharmaceutically acceptable salts and esters unless the context clearly indicates otherwise.

In a preferred aspect the formulation comprises from 1% to 10% w/w acyclovir, from 30% to 50% w/w of a polyhydric alcohol, from 20% to 40% w/w water together with an oil phase, whilst the most preferred formulation comprises from 2% to 5% w/w acyclovir, from 35% to 45% w/w of a polyhydric alcohol, from 25% to 40% w/w water together with an oil phase. The formulation should preferably contain about 40% w/w of a polyhydric alcohol.

A polyhydric alcohol is an alcohol having two or more hydroxyl groups. Polyhydric alcohols suitable for incorporation into the topical formulation of the present invention include glycols and macrogols such as propylene glycol, butane 1,3-diol, polyethylene glycol and glycerol, propylene glycol being the preferred alcohol.

When at least 50% v/v of a polyhydric alcohol is used in the aqueous phase of a formulation of the present invention, the maximum concentration of acyclovir at ambient temperature rises from 0.15% w/w, that being the maximum aqueous solubility of acyclovir, to 0.3% w/w. Thus if aqueous phase concentrations of greater than 0.3% acyclovir are incorporated into a formulation the amount of active ingredient in excess of 0.3% will be in suspension and act as a reservoir of drug. The amount of acyclovir present in the formulation should be at least sufficient to be antivirally effective and to be non-toxic. The water used in the formulation is preferably purified water, purified that is according to the standards of the British Pharmacopoeia.

The oil phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it is desirably comprised of a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, as explained in more detail below, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so called emulsifying ointment base which forms the oil dispersed phase of the emulsions.

Oil-in-water topical formulations may be formulated in a number of ways, all of which depend primarily on the alignment of the emulgent or emulsifying agent and

emulsion stabiliser at the oil/water interface, with the non-polar or lipophilic groups soluble in the oil phase and the polar or hydrophilic or lipophilic groups in the aqueous or continuous phase. Thus the more polar hydrophilic emulgents result in oil-in-water emulsions. This principle has been systemised in the idea of a 'hydrophilic-lipophilic balance' (H.L.B.) Griffen, W. C. *J. Soc. Cos. Met. Chem.*, 1954, 5, 249 and the various emulgents have been allocated H.L.B. numbers from which their behaviour with constituents of the aqueous and oil phases (to which are applied theoretical required H.L.B. figures) may be predicted.

It is a well established theory of oil-in-water emulsion formulation that the combination of a lipophilic emulgent with a hydrophilic emulgent of the same chemical type may be used in varying proportions to give the required H.L.B. value. With the high concentration of polyhydric alcohol required to maximise acyclovir release from the formulation of the present invention an H.L.B. value of from 3.5 to 10.0, preferably 4.0 to 8.0, most preferably about 5.5, is desirable, compared with the accepted H.L.B. range for mineral oil-in-water emulsions of 8 to 18.

Emulgents and emulsion stabilisers suitable for use in the formulation of the present invention include polyoxyethylene sorbitan monostearate (polysorbate 60), sorbitan monostearate, sorbitan mono-oleate, cetostearyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulphate. One preferred combination of emulgents is cetostearyl alcohol and sodium lauryl sulphate in a ratio of from 3:1 to 30:1 preferably from 6:1 to 20:1, most preferably from 9:1 to 15:1.

In addition, the formulation may optionally contain other emulgents such as poloxamers in an amount of from 0.1 to 3% w/w, preferably 0.3 to 2% w/w, most preferably about 1% w/w of the formulation.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of acyclovir in most oils likely to be used in pharmaceutical emulsion formulations in very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a mixed ester of 2-ethyl hexanoic acid with a blend of cetyl or stearyl alcohols known as Crodamol CAP may be used, the last three being the preferred esters. These may be used singly or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

The present invention further provides a method for the preparation of a topical pharmaceutical formulation, as hereinbefore defined, which comprises mixing the combination of acyclovir, polyhydric alcohol and water with the oil phase.

The manner of formulating the emulsion will of course vary according to the amount and nature of the constituents, but nevertheless follows known techniques in emulsion technology (see The Pharmaceutical Codex, London, The Pharmaceutical Press, 1979). For example the acyclovir may be initially incorporated wholely in the aqueous portion where it may form a solution alone, or a mixed solution/suspension, and then emulsified with the ointment base. Alternatively where high concentrations of acyclovir are being used, a part of the aqueous portion may be formulated as an emulsion, and the balance of the water, polyhydric alcohol and acyclovir added to and dispersed into the emulsion. In another technique the acyclovir may be included in the emulsifying ointment prior to emulsification with the aqueous portion. In using these procedures, it is preferable to heat the aqueous portion and the ointment base to about 40° to 80° C., preferably 50° to 70° C., prior to emulsification which may be achieved by vigorous agitation using for example a standard laboratory mixer. Finer dispersions of the oil phase may be obtained by homogenising or milling in a colloidal mill.

A topical formulation of the present invention may be used in the treatment or prevention of viral infections caused for example by Herpes zoster, Herpes varicella and Herpes simplex types 1 and 2, which cause diseases such as shingles, chicken pox, cold sores and genital herpes. The formulation should desirably be applied to the affected area of skin from 2 to 6 times daily, preferably from 3 to 4 times.

The following are examples of the invention.

## EXAMPLE 1

### 2% w/w Aqueous Cream

An aqueous cream was prepared from the following ingredients:

1. Acyclovir: 20.0 g
2. Cetostearyl alcohol, B.P.: 67.5 g
3. Sodium lauryl sulphate, B.P.: 7.5 g
4. White soft paraffin, B.P.: 125.0 g
5. Liquid paraffin, B.P.: 50.0 g
6. Propylene glycol, B.P.: 400.0 g
7. Purified water, B.P. to: 1000.0 g.

A part of the acyclovir (2 g) was dissolved in the water and propylene glycol at ambient temperature to produce an aqueous solution. The paraffins (4,5) and emulsifiers (2,3) were mixed together and heated to 60° C., and emulsified with the aqueous solution, also at 60°C., using a laboratory mixer at 8000 r.p.m.. The remaining acyclovir was added, the mixture dispersed, allowed to cool, and filled into lacquered aluminium tubes.

## EXAMPLE 2

### 5% w/w Aqueous Cream

In the manner described above, an aqueous cream was prepared containing 5% w/w acyclovir.

## EXAMPLE 3

### 0.2% w/w Aqueous Cream

1. Acyclovir: 2.0 g
2. Isopropyl myristate, B.P.: 100.0 g
3. 2-Ethylhexyl palmitate: 50.0 g
4. Light liquid paraffin, B.P.: 50.0 g
5. Cetostearyl alcohol, B.P.: 30.0 g
6. Glyceryl monostearate, B.P.: 16.0 g
7. Polysorbate 60, B.P.C.: 4.0 g
8. Propylene glycol, B.P.: 400.0 g
9. Purified water, B.P. to: 1000.0 g.

The cream was prepared in the manner described in Example 1 except that all the acyclovir was initially dissolved in the propylene glycol/water ingredients (8,9).

EXAMPLE 4

2% w/w Aqueous Cream

An aqueous cream was prepared from the following ingredients by the method described in Example 1.

1. Acyclovir: 20.0 g
2. Cetostearyl alcohol, B.P.: 67.5 g
3. Sodium lauryl Sulphate, B.P.: 7.5 g
4. White soft paraffin, B.P.: 125.0 g
5. Liquid paraffin, B.P.: 50.0 g
6. Butane 1,3-diol, B.P.: 400.0 g
7. Purified water, B.P. to: 1000.0 g.

We claim:

1. An oil-in-water topical formulation of an effective antiviral non-toxic amount of 9-(2-hydroxyethoxymethyl)guanine or a pharmaceutically acceptable salt thereof, having a dispersed oil phase and a continuous aqueous phase, said aqueous phase containing therein water, 30% to 50% w/w of a water miscible polyhydric alcohol, and an effective antiviral non-toxic amount solubilised 9-(2-hydroxyethoxymethyl)guanine or said salt thereof.

2. A formulation according to claim 1 comprising from 1% to 10% w/w 9-(2-hydroxyethoxymethyl)guanine or said salt thereof, from 30% to 50% w/w of said propylene glycol, from 20% to 40% w/w water together with said oil phase.

3. A formulation according to claim 1 wherein said polyhydric alcohol is a glycol or macrogol.

4. A formulation according to claim 3 wherein said glycol or macrogol is selected from a group consisting of propylene glycol, butane 1,3-diol, glycerol and polyethylene glycol.

5. A method of treating or preventing viral infections of the skin or mucosa of a mammal comprising applying the topical an effective amount of the formulation according to claim 1 to the selected area of skin or mucosa from 2 to 6 times daily.

6. A method of treating or preventing Herpes simplex infections of the skin or mucosa of a mammal comprising applying the topical an effective amount of the formulation according to claim 1 to the selected area of skin or mucosa from 2 to 6 times daily.

7. A method for treating or preventing Herpes zoster infections of the skin or mucosa of a mammal comprising applying the topical an effective amount of the formulation according to claim 1 to the selected area of skin or mucosa from 2 to 6 times daily.

8. A method for treating or preventing Herpes varicella infections of the skin or mucosa of a mammal comprising applying the topical an effective amount of the formulations according to claim 1 to the selected area of the skin or mucosa from 2 to 6 times daily.

9. A topical cream comprising about 2% to about 5% w/w of microsized acyclovir or a pharmaceutically acceptable salt thereof and greater than about 30% w/w of propylene glycol.

10. A topical cream comprising about 5% w/w micronized acyclovir or a pharmaceutically acceptable salt thereof and about 40% w/w of propylene glycol.

11. An oil in water emulsion topical formulation of an effective antiviral acntoxic amount of 9-(2-hydroxyethoxymethyl)guanine or a pharmaceutically acceptable salt thereof comprising about 5% w/w of 9-(2-hydroxyethoxymethyl)guanine or a pharmaceutically acceptable salt thereof and about 40% w/w of propylene glycol in an aqueous phase thereof.

12. A method of treating a herpes viral infection of the skin or mucosa of a mammal which comprises applying to the skin or mucosa an effective herpes antiviral treatment amount of an oil in water topical formulation comprising about 5% w/w of solubilized 9-(2-hydroxyethoxymethyl)guanine or a pharmaceutically acceptable salt thereof and about 40% w/w of propylene glycol in an aqueous phase thereof.

13. An oil in water emulsion topical formulation of an effective antiviral amount of 9-(2-hydroxyethoxymethyl)guanine or a pharmaceutically acceptable salt thereof comprising about 5% w/w of 9-(2-hydroxyethoxymethyl)guanine or a pharmaceutically acceptable salt thereof and about 30 to 50% w/w of propylene glycol in an aqueous phase thereof.

14. A method of treating a herpes viral infection of the skin or mucosa of a mammal which comprises applying to the skin an effective herpes antiviral treatment amount of an oil in water topical formulation comprising about 5% w/w of solubilized 9-(2-hydroxyethoxymethyl) or a pharmaceutically acceptable salt thereof and about 30 to 50% w/w of propylene glycol in an aqueous phase thereof.

15. An oil in water emulsion topical formulation comprising 5 to 10% of 9-(2-hydroxyethoxymethyl)guanine or a pharmaceutically acceptable salt thereof and about 30 to 50% w/w of propylene glycol.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 4,963,555

DATED : October 16, 1990

INVENTOR(S) : Trevor M. Jones; Alan R. White

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 1, line 8, (Claim 1), DELETE "solubillised", and insert therefor — of solubilized--.

Col. 5, line 3, (claim 5), delete "the topical" and before "formulation" insert --topical--.

line 3, (claim 6), delete "the topical" and before "formulation" insert --topical--.

line 3, (claim 7), delete "the topical" and before "formulation" insert --topical—.

Col.6, line 3, (claim 8), delete "the topical" and before "formulation" insert -- topical--.

line 3-4,(claim 12), delete "herpes antiviral"; insert --anti-herpes virus—.

line 3, (claim 14), delete "herpes antiviral", and insert therefor --anti-herpes virus—.

Signed and Sealed this

Twenty-sixth Day of January, 1993

*Attest:*

STEPHEN G. KUNIN

*Attesting Officer*

*Acting Commissioner of Patents and Trademarks*

EXCLUSIVITY SUMMARY for NDA # 21-478 SUPPL # N/A

Trade Name: Zovirax® Cream 5% Generic Name acylovir

Applicant Name GlaxoSmithKline HFD-530

Approval Date December 24, 2002

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 questions 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?

YES /___/ NO /_X_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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 9.**

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 9 (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 / X / NO /___/

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

NDA # 18-603 Zovirax Injection

NDA # 18-604 Zovirax Ointment

NDA # 18-828 Zovirax Capsules

NDA # 19-909 Zovirax Suspension

NDA # 20-089 Zovirax Tablets

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 / X /

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 9. 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 /_X_/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /__X__/ 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 9:**

_____

_____

(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 /__X__/ 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 /__X__/

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 /_X_/

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:

Investigation #1, Study # ZOVA 3003

Investigation #2, Study # ZOVA 3004

Investigation #3, Study # _____

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 /_X_/ |
| Investigation #2 | YES /___/ | NO /_X_/ |
| Investigation #3 | 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #_1_, Study # ZOVA 3003

Investigation #_2_, Study # ZOVA 3004

Investigation #___, Study # _____

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 /_X_/ ! NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /_X_/ ! 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 /_X_/

If yes, explain: _____

_____

_____

Sean J. Belouin
Signature of Preparer
Sean J. Belouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

December 24, 2002
Date

Jeff Murray for Debra Birnkrant
Signature of Office or Division Director
Debra Birnkrant, M.D.
Division Director
Division of Antiviral Drug Products

December 24, 2002
Date

cc:
Archival NDA 21-478
HFD-530/Division File
HFD-530/RPM/Belouin
HFD-530/CRPM/DeCicco
HFD-530/DivDir/Birnkrant
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

/s/

Jeffrey Murray
12/24/02 12:06:31 PM

# PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA# : 21-478 Supplement Type (e.g. SE5): N/A Supplement Numbers: N/A

Stamp Date: April 1, 2002 Action Date: December 24, 2002

HFD-530 Trade and generic names/dosage form: Zovirax® (acyclovir) Cream 5%

Applicant: GlaxoSmithKline Therapeutic Class: Antiviral Agent, Topical, Herpes Labialis

Indication(s) previously approved: None

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

Number of indications for this application(s): One

Indication #1: Treatment of Recurrent Herpes Labialis

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: Not Applicable

☐ 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: Safety has been established for children ages 12 to 17 years. Because recurrent herpes labialis in children of less than 12 years of age is rarely treated in clinical practice, the pediatricians in the Division agreed that the requirement of a safety study in children <12 years old is not warranted.

*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: Not Applicable**

| | | | | | |
|---|---|---|---|---|---|
| **Min**____ | **kg**____ | **mo.**____ | **yr.**____ | **Tanner Stage**____ |
| **Max**____ | **kg**____ | **mo.**____ | **yr.**____ | **Tanner Stage**____ |

Reason(s) for partial waiver: Not Applicable

- ☐ 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: Not Applicable

mo._____ mo._____

yr._____ yr._____

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.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

**yr. 12 years to yr. 17 years**

**Comments:**

**Study ZOVA 3005 supported the safety of acyclovir 5% cream in children ages 12 and 17 years.**

*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}*

**Sean J. Belouin, R.Ph**
**Regulatory Project Manager**

**cc: NDA**
**HFD-950/ Terrie Crescenzi**
**HFD-960/ Grace Carmouze**
**(revised 9-24-02)**

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

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

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/s/

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Jeffrey Murray
12/24/02 12:08:54 PM

NDA 21-122

ZOVIRAX® CS (acyclovir) Cream, 5%

DEBARMENT CERTIFICATION

Glaxo Wellcome 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.

17 MAY 99

Charles E. Mueller
Head, Clinical Compliance
World Wide Compliance

Date

# NDA 21-478

# Zovirax® (acyclovir) Cream 5%

Treatment of Herpes Labialis

**Division of Antiviral**
**Drug Products**
**HFD-530**

**Review Team:**
Director-Debra Birnkrant, M.D.
Deputy Division Director-Jeff Murray, M.D., M.P.H.
Medical Team Leader-Katherine Laessig, M.D.
Medical Reviewer-Teresa Wu, M.D.
Chemistry Team Leader-Stephen Miller, Ph.D.
Chemistry Reviewer-Zi Quang Gu, Ph.D.
Pharmacology Team Leader-James Farrelly, Ph.D.
Pharmacology Reviewer-Anita Bigger, Ph.D.
Clinical Pharmacology Team Leader-Kellie Reynolds, PharmD.
Clinical Pharmacology Reviewer-Jooran Kim, PharmD.
Microbiology Team Leader-Julian O'Rear, Ph.D.
Microbiology Reviewr-Nilambar Biswal, Ph.D.
Statistical Team Leader-Greg Soon, Ph.D.
Statistical Reviewer-Fraser Smith, Ph.D.
Chief, Regulatory Project Manager-Anthony DeCicco, R.Ph.
Regulatory Project Manager-Sean Belouin, R.Ph.

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | | |
|---|---|---|---|
| NDA 21-478 | Efficacy Supplement Type: N/A | Supplement Numbers: N/A | |
| Drug: Zovirax® (acyclovir) Cream 5% | | Applicant: GlaxoSmithKline | |
| RPM: Sean J. Belouin, R.Ph | | HFD-530 | Phone = 301-827-2335 |
| Application Type: (X) 505(b)(1) ( ) 505(b)(2) | | Reference Listed Drug (NDA #, Drug name): | |

| | |
|---|---|
| ❖ Application Classifications: | |
| • Review priority | (X) Standard ( ) Priority |
| • Chem class (NDAs only) | |
| • Other (e.g., orphan, OTC) | |
| ❖ User Fee Goal Dates | January 31, 2003 |
| ❖ Special programs (indicate all that apply) | (X) None<br>Subpart H<br>() 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review |
| ❖ User Fee Information | |
| • User Fee | (X) Paid |
| • User Fee waiver | ( ) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other |
| • User Fee exception | ( ) Orphan designation<br>( ) No-fee 505(b)(2)<br>( ) 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) | N/A |
| • OC clearance for approval | N/A |
| ❖ 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)<br>( ) I ( ) II ( ) III ( ) IV<br><br>21 CFR 314.50(i)(1)<br>( ) (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 Summary (approvals only) | Completed |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | Rev. of Action Package-12/23/02 |

| General Information | |
|---|---|
| ❖ Actions | |
| • Proposed action | (X) AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | N/A |
| • Status of advertising (approvals only) | (X) Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | (X) Yes ( ) Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | ( ) None<br>(X) Press Release<br>( ) Talk Paper<br>( ) 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) | N/A |
| • Most recent applicant-proposed labeling | **Included** |
| • Original applicant-proposed labeling | **Included** |
| • Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | N/A |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | N/A |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | N/A |
| • Applicant proposed | **Included** |
| • Reviews | **Included in chemistry review** |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | **No new requests for applicant** |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | N/A |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | **Included in Action Package** |
| ❖ Memoranda and Telecons | **Included in Action Package** |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | N/A |
| • Pre-NDA meeting (indicate date) | **Included** |
| • Pre-Approval Safety Conference (indicate date; approvals only) | N/A |
| • Other | N/A |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | N/A |
| • 48-hour alert | N/A |
| ❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) | N/A |

| Clinical and Summary Information | |
|---|---|
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(12/24/02)* | **Medical Team Leader Review Included** |
| ❖ Clinical review(s) *(01/03/03)* | **Included** |
| ❖ Microbiology (efficacy) review(s) *(11/27/02)* | **Included** |
| ❖ Safety Update review(s) *(01/03/03)* | **Included in clinical review** |
| ❖ Pediatric Page(12/24/02) | **Included** |
| ❖ Statistical review(s) *(01/03/03)* | **Included in clinical review** |
| ❖ Biopharmaceutical review(s) *(12/17/02)* | **Included** |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)* | **N/A** |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | **N/A** |
| • Bioequivalence studies | **N/A** |
| **CMC Information** | |
| ❖ CMC review(s) *(01/23/03)* | **Included** |
| ❖ Environmental Assessment | |
| • Categorical Exclusion *(01/23/03)* | **Included** |
| • Review & FONSI *(indicate date of review)* | **N/A** |
| • Review & Environmental Impact Statement *(01/23/03)* | **Included** |
| ❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)* | **N/A** |
| ❖ Facilities inspection (provide EER report) | Date completed: **25 July 2002**<br>**(X)** Acceptable<br>( ) Withhold recommendation |
| ❖ Methods validation | ( ) Completed:<br>**(X)** Requested<br>( ) Not yet requested |
| **Nonclinical Pharm/Tox Information** | |
| ❖ Pharm tox review(s), including referenced IND reviews *(12/13/02)* | **Included** |
| ❖ Nonclinical inspection review summary | **N/A** |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | **N/A** |
| ❖ CAC ECAC report | **N/A** |

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/s/

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Sean Belouin
1/22/03 02:06:33 PM

## DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

| | |
|---|---|
| **Application #(s):** | NDA 21-478 |
| **Document Type:** | NDA Letters |
| **Document Group:** | NDA Approval Letters |
| **Document Name:** | Approval letter based on enclosed/submitted labeling text |
| **Shortcut ID Code:** | NDA-I1 |
| **COMIS Decision Code** | AP |
| **Drafted by:** | HFD-530/RPM/Belouin-12/23/2002 |
| **Revised by:** | |
| **Initialed by:** | HFD-530/DivDir/Birnkrant- LSI<br>HFD-530/DepDivDir/Murray- LSI<br>HFD-530/CPMS/DeCicco- LSI<br>HFD-530/MOTL/Laessig- LSI<br>HFD-530/MO/Wu- LSI<br>HFD-530/StatsTL/Sc... LSI<br>HFD-530/Stats/Smith- LSI<br>HFD-530/ChemTL/Miller- LSI<br>HFD-530/Chem/Gu- LSI<br>HFD-530/PharmacologyTL/Farrelly<br>HFD-530/Pharmacology/Bigger- LSI<br>HFD-530/BiopharmTL/Reynolds- LSI<br>HFD-530/Biopharm/Reynolds-<br>HFD-530/MicroTL/O'Rear- LSI<br>HFD-530/Micro/Biswal- LSI |
| **Finalized:** | HFD-530/RPM/Belouin- LSI |
| **Filename:** | V:\DAVDP\CSO\BELOUIN\IndigoNda's\NDA\21-478 Zovirax Cream\Letters\ZoviraxApprovalLetter.doc |
| **DFS Key Words:** | |
| **Notes:** | |

Version: 10/18/2002

## END OF DOCUMENT INFORMATION PAGE

**The letter begins on the next page.**

GlaxoWellcome

July 27, 1999

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15259-0001

**Re: Initial Application Fee**
**NDA 21-122; ZOVIRAX® (acyclovir) CS Cream 5%**
**User Fee ID No. 3768**

Please find enclosed Glaxo Wellcome check number 1571394 in the amount of $272,282.00 This initial payment is 100% of the application fee for the New Drug Application that is being filed with the Center for Drug Evaluation and Research, FDA.

Please find below the requested information regarding this application:

| | | |
|---|---|---|
| Type of Application: | New Drug Application with Clinical Data | X |
| | New Drug Application without Clinical Data | |
| | Supplemental New Drug Application with Clinical Data | |

Should you have any questions, please contact E. Allen Jones at (919) 483-9122.

Sincerely,

S. Wayne Talton for

Thomas A. Gerding
Director, Regulatory Affairs

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

# USER FEE COVER SHEET

*See Instructions on Reverse Side Before Completing This Form.*

1. APPLICANT'S NAME AND ADDRESS

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

2. TELEPHONE NUMBER *(Include Area Code)*
(919) 483-2100

3. PRODUCT NAME
ZOVIRAX® (acyclovir) CS Cream 5%

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? Yes
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).

5. USER FEE I.D. NUMBER
3768

6. LICENSE NUMBER / NDA NUMBER
NO21122

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)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

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

***A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.***

**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:**

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

**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.**

**Please DO NOT RETURN this form to this address.**

| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE | TITLE | DATE |
|---|---|---|
| S. Wayne Talton for<br>Thomas A. Gerding | Director, Regulatory Affairs | July 27, 1999 |

FORM FDA 3397 (5/98)

FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
PITTSBURGH PA 15259-0001

**GlaxoWellcome**
P.O. BOX 13358
RESEARCH TRIANGLE PARK, N.C. 27709

| DATE | CHECK NO. |
|---|---|
| 07/23/99 | 1571394 |
| RTPT | 010340 P: |

| DATE | INVOICE/CREDIT MEMO | TYPE | DESCRIPTION | GROSS | DISCOUNT | NET |
|---|---|---|---|---|---|---|
| 071699 | GLAXO INTERNAL USE ONLY: GUNNELL, WINTER<br>CR27228200<br>E. ALLEN JONES 5.5546 | | | 27228200 | STH D2644<br>00 | 483-91<br>272282 |
| | | | TOTAL | 27228200 | 000 | 2722820 |

THIS MULTI-TONE AREA OF THE DOCUMENT CHANGES COLOR GRADUALLY AND EVENLY FROM DARK TO LIGHT WITH DARKER AREAS BOTH TOP AND

Glaxo Wellcome Inc. a GlaxoSmithKline Company, N.C.

**GlaxoWellcome**
P.O. BOX 13358
RESEARCH TRIANGLE PARK, N.C. 27709

56-38
931

CHECK DATE 07/23/1999

CHECK NUMBER 1571394

CHECK VOID AFTER 120 DAYS

PAY ONLY P*272282*00 CTS CTS

****$272,282.00

TWO HUNDRED SEVENTY-TWO THOUSAND TWO HUNDRED EIGHTY-TWO DOLLARS AND 00 CENTS **********

Pay to the order of FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
PITTSBURGH PA 15259-0001

Authorized

⑈1571394⑈ ⑆053107633⑆010459 002194⑈

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12-09-02

FROM: Katherine A. Laessig, M.D.
Division of Antiviral Drug Products, HFD-530

TO: Division File

SUBJECT: Group Leader Memo for NDA 21-478, Zovirax (acyclovir) cream 5%

## 1.0 Background

On July 30, 1999, the sponsor submitted NDA 21-122 for Zovirax (acyclovir) cream 5% for the treatment of herpes labialis. It was accepted for filing and assigned a Standard review. The sponsor chose to withdraw the NDA on April 28, 2000, because of the upcoming merger with SmithKline Beecham. In October 2001, the sponsor entered into an agreement with Biovail Pharmaceuticals such that the sponsor agreed to resubmit and be responsible for the NDA, but after approval, Biovail will be the sole commercial distributor of the product in the U.S. and Puerto Rico. The NDA was resubmitted on April 1, 2002.

Acyclovir is a synthetic nucleoside analog with activity against herpes viruses. Acyclovir is phosphorylated to acyclovir monophosphate, a nucleotide analog, by the enzyme thymidine kinase. Acyclovir monophosphate is further converted to the di- and triphosphate forms. Acyclovir triphosphate inhibits viral replication by competitively inhibiting and inactivating the viral DNA polymerase, and via incorporation into and termination of the growing viral DNA chain. Currently approved formulations of acyclovir include 200 mg capsules, 400 and 800 mg tablets, 200 mg/5 ml suspension, acyclovir sodium for injection, and 5% ointment.

## 2.0 Summary of Study Results

This application contains the results of two efficacy trials for the treatment of recurrent herpes labialis, as well as numerous supportive trials. The two pivotal trials, ZOVA 3003 and ZOVA 3004, were replicate, multicenter, randomized, double-blind, vehicle controlled studies that compared Zovirax 5% cream and vehicle cream when used for the treatment of cold sores. Subjects initiated treatment within 1 hour of onset of prodromal symptoms, or in the absence of a

prodrome, when the first clinical signs of herpes labialis occurred. The primary endpoint was the duration of the episode as measured from the initiation of treatment to the loss of hard crust. Zovirax was applied topically 5 times daily for 4 days.

The efficacy results for both trials were similar. In ZOVA 3003, treatment with Zovirax 5% cream resulted in a 0.4-day decrease in duration of the herpes labialis episode, compared to the vehicle control. In ZOVA 3004, the treatment difference was slightly greater at 0.5 days. Both differences were statistically significant, with p values of 0.013 and 0.018, respectively.

There were no deaths or SAEs in ZOVA 3003. There were no deaths and one SAE (hospitalization for chest pain in a patient with h/o CAD and HTN) in ZOVA 3004. The most frequently reported adverse events in ZOVA 3003 were headache and cracked lips. Headache was reported in <1% of subjects in the Zovirax group, and in 3% of subjects in the control group. All other AEs occurred in <1% of subjects. Headache and flakiness of skin were the most commonly reported AEs in ZOVA 3004. Headache was reported in 1% of subjects in the Zovirax group, compared to 2% in the control group. Flakiness of skin was reported in <1% of subjects in the Zovirax group, and in 2% of the control group. All other adverse events were reported in 1% or fewer of study subjects.

For a discussion of the supportive studies presented in this application, please see the medical officers' reviews of Drs. Teresa Wu and Joseph Toerner.

3.0 **Recommendation**

The results of the clinical trials contained in this application support the safety and efficacy of Zovirax 5% cream for the treatment of recurrent herpes labialis. I concur with the findings of the medical officers' review of Drs. Teresa Wu and Joseph Toerner, and recommend that this application should be approved.

Katherine Laessig, M.D.

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

/s/

Kathrine Laessig
12/20/02 02:40:46 PM
MEDICAL OFFICER

Jeffrey Murray
12/24/02 10:46:49 AM
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14 pages redacted from this section of the approval package consisted of draft labeling