CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74976

CORRESPONDENCE

GENPHARM

Telephone Amendment

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

NEW CORRESP

RE: ANDA No. 74-976
ACYCLOVIR TABLETS
400 & 800 mg

Dear Sirs/Madam:

Please find enclosed a Telephone Amendment to ANDA# 74-976.

For the reviewer's convenience, we have:

a) formatted our amendment such that each comment made by the reviewer has been restated in *italic* print;
b) provided our response following the comment.

We have enclosed one (1) archival, one (1) review copy and one (1) field copy of the application in accordance with 21 CFR § 314.55. In each copy, a signed form FDA 356h by our US agent is submitted. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephone communications to Genpharm at 1-800-661-7134 or you may contact our U.S. agent, Dr. Anita M. Goodman of Lipha Pharmaceuticals, Inc. New York, New York, at (212) 223-1282.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

Richard K. Pike
Director, Regulatory Affairs

GENPHARM INC. 65 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

GENPHARM

ORIG AMENDMENT.

N/AF

January 7, 1998

Office of Generic Drugs, CDER, FDA

Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

AMENDMENT

RE: ANDA No. 74-976
ACYCLOVIR TABLETS
400 mg & 800 mg

Dear Sirs/Madam:

Please find enclosed our ***Labeling AMENDMENT*** to ANDA # 74-976 for Acyclovir Tablets 400 mg & 800 mg.

This amendment was prepared because this ANDA shares an insert with ANDA # 74-977 (Acyclovir Capsules 200 mg). On Dec., 9, 1997, we received a Facsimile Amendment to revise the insert for ANDA # 74-977. The insert provided in this amendment is identical to the insert provided in the response for ANDA # 74-977.

We have enclosed one (1) archival and one (1) review copy of the application in accordance with 21 CFR § 314.55.

We trust the information submitted is sufficient for this amendment to be evaluated.

A signed form FDA 356h by our US agent, Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, N.Y. is submitted. Although Dr. Anita Goodman is our US Agent, should you have any questions, please contact the undersigned at 1-800-661-7134.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

Richard K. Pike
Director, Regulatory Affairs

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JAN 09 1998

GENERIC DRUGS

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GENPHARM

December 12, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

FACSIMILE AMENDMENT

RE: ANDA No. 74-976
ACYCLOVIR TABLETS
400 mg & 800 mg

Dear Sirs/Madam:

Please find enclosed our ***FACSIMILE AMENDMENT*** to ANDA # 74-976 in response to the faxed letter dated Nov. 17, 1997 from Timothy Ames, Project Manager .

For the reviewers' convenience, we have:

a) attached a copy of the letter dated Nov. 17, 1997;
b) formatted our amendment such that each comment made by the reviewer has been restated in *italic* print;
c) provided our response following the comment.

We have enclosed one (1) archival and one (1) review copy of the application in accordance with 21 CFR § 314.55. We also hereby certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated.

Along with our responses, a signed form FDA 356h by our US agent, Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, N.Y. is submitted. Although Dr. Anita Goodman is our US Agent, should you have any questions, please contact the undersigned at 1-800-661-7134.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

R.K. Pike

Richard K. Pike
Director, Regulatory Affairs

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GENERIC DRUGS

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GENPHARM

AH noted ① To chemistry the ② labeling reviewer for review
J 10/10/97

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

MINOR AMENDMENT

OCT 01 1997

RE: ANDA No. 74-976
ACYCLOVIR TABLETS
400 mg & 800 mg

Dear Sirs/Madam:

Please find enclosed a ***MINOR AMENDMENT*** to ANDA # 74-976 in response to the faxed letter dated May 20, 1997 from Tim Ames, Project Manager which we received on May 22, 1997.

For the reviewers' convenience, we have:

a) attached a copy of the letter dated May 20, 1997;
b) formatted our amendment such that each comment made by the reviewer has been restated in *italic* print;
c) provided our response following the comment.

We have enclosed one (1) archival and one (1) review copy of the application in accordance with 21 CFR § 314.55. We also hereby certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated.

Along with our responses, a signed form FDA 356h by our US agent, Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, N.Y. is submitted. Although Dr. Anita Goodman is our US Agent, should you have any questions, please contact the undersigned at 1-800-661-7134.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

R. K. Pike.

Richard K. Pike
Director, Regulatory Affairs

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OCT 03 1997
GENERIC DRUGS

FACSIMILE AMENDMENT

NOV 17 1997

ANDA: 74-976

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT Sanpharm Inc PHONE 212-223-1282
ATTN: c/o Dr Qadir Goodman FAX 212-223-1398

FROM: Timothy W. Ames, PROJECT MANAGER (301-827-5849)

Dear ~~Sir/Madam~~: Dr. Goodman

This facsimile is in reference to your abbreviated new drug/antibiotic application dated 9/27/96, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Acyalovir Tablets, 400mg & 800mg

Reference is also made to your amendment(s) dated 10/1/97.

Attached are 4 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a seperate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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NOV 17 1997

38. Chemistry-Comments to be Provided to the Applicant

ANDA: 74-976 APPLICANT: Ganpharm Inc.

DRUG PRODUCT: Acyclovir Tablets, 400 mg & 800 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. Regarding Manufacturing and Processing:

2. Regarding Laboratory Controls (Finished Dosage Form):

Please revise and resubmit your finished product specifications and Certificate of Analysis (COA) for both strengths and change your Dissolution specification to NLT (Q) in 30 minutes (refer to the Division of Bioequivalence letter dated October 10, 1997).

3. Regarding Stability:

Please revise and resubmit your stability specifications and stability reports for both strengths and change your Dissolution specification to NLT (Q) in 30 minutes (refer to the Division of Bioequivalence letter dated October 10, 1997).

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

MAY 20 1997

ANDA/ 74-976

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-277[redacted]

TO: APPLICANT Genpharm Inc. PHONE 212-223-1282
ATTN: c/o Dr Anita M. Goodman FAX 212-223-1398

FROM: Tim Amos PROJECT MANAGER (301-594-)

Dear Sir/Madam: Dr Goodman

This facsimile is in reference to your abbreviated new drug/ antibiotic application dated 9/27/97, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Acyclovir Tablets, 400mg & 800mg

Reference is also made to your amendment(s) dated —.

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (11 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing. For further clarification or assistance please contact the Project Manager listed above.

SPECIAL INSTRUCTIONS: The issues transmitted in this Fax should be addressed concurrent with or following your response to the 4/30/97 letter from the Division of Bioequivalence

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.
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MAY 20 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-976 APPLICANT: Ganpharm Inc.

DRUG PRODUCT: Acyclovir Tablets, 400 mg & 800 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Regarding Composition:

2. Regarding Active Ingredient:

3. Regarding Manufacturing and Processing:

4. Regarding Container/Closure:

5. Regarding Laboratory Controls (Finished Dosage Form):

6. Regarding Stability:

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

Please be advised that the suitability of the proposed dissolution procedure and specification will be established upon completion of review by the Division of Bioequivalence. Also, methods validation is pending acceptable dissolution specifications.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA Number: 74-976

Date of Submission: September 27, 1996

Applicant's Name: Genpharm Inc.

Established Name: Acyclovir Tablets, 400 mg and 800 mg

Labeling Deficiencies:

1. **CONTAINER:**

   a. **General Comment**

      We encourage you to differentiate between the container labels of your 400 mg and 800 mg tablet dosage forms as well as your 200 mg capsule dosage form, [the subject of ANDA 74-977] by using boxing and/or contrasting colors.

   b. **400 mg and 800 mg (100s)**

      i. Immediately beneath the established name delete "(Acyclovir)".

      ii. Relocate the tablet strength to immediately follow the established name and delete "Each tablet contains ___".

   c. **800 mg (unit dose blister)**

      i. Revise "tablets" to read "tablet".

      ii. See comments b(i) and b(ii).

2. **CARTON:** 800 mg (unit-dose 100s)

   a. See comments 1(b)(i)and 1(b)(ii) under CONTAINER.

   b. Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be with a child resistant container. We suggest the following text:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.
(Note: The second sentence is optional.)

3. INSERT

a. General Comment

i. When abbreviating micrograms we encourage the use of "mcg" rather than "μg". Please revise your insert labeling accordingly.

ii. Please refer to the enclosed mocked-up copy of your draft insert labeling for further revisions.

b. DESCRIPTION

i. Revise the first sentence to read, "Acyclovir is an antiviral drug".

ii. Include the chemical formula:

$C_8H_{11}N_5O_3$

iii. To be in accord with USP 23, make the following revisions in the last paragraph:

...a white to off-white crystalline powder with a molecular weight of 225.21, and ...

c. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

i. Delete the first sentence of the third paragraph, "A single ... solution" and revise the last sentence to read, "In a reported single-dose bioavailability/bioequivalence study in 24 volunteers, ...

ii. Revise the fifth paragraph to read:

In another study the influence of food ...

d. INDICATIONS AND USAGE (Chickenpox)

In the first sentence of the first and second paragraphs print "with 24 hours" in bold print.

e. **PRECAUTIONS**

i. **Information for Patients (*Genital Herpes Infections*)**

Second paragraph, last sentence -

... number of chromosomes.[28]
["28" instead of "29"]

ii. **Pediatric Use**

... in pediatric patients less ...

f. **ADVERSE REACTIONS (Observed During Clinical Practice)**

Nervous

...paresthesia, seizure, somnolence...
[Add "seizure"].

g. **HOW SUPPLIED**

i. **Indicate that your tablets are "unscored".**

ii. **We encourage you to include the following statement at the end of this section, "CAUTION: Federal law prohibits dispensing without prescription".**

h. **REFERENCES**

Revise as follows:

i. 4. **Furman FA, ...**

ii. 7. **... In: Turner [add space] ...ed 3. [add period] ... Linvingstone; 1983: [add space] ...**

iii. 17. **... *Am J Med*.... [italic print]**

iv. 18. **... *N Engl J Med* ... [italic print]**

v. 27. **... *Lancet* ... [italic print]**

vi. 37. **... Rotbart HA, ...**

Please revise your container labels, carton and package insert labeling, as instructed above, and submit final printed (or printers proof) package insert labeling and final printed container labels and carton labeling. Please

note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only for tentative approval.

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

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

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

Enclosure: Mock-up copy of draft labeling

suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, orally administered Acyclovir should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility) should become in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus this regimen should be considered only for appropriate patients with annual re-evaluation.

Limited studies [31,32] have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

Herpes Zoster Infections:
In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to Acyclovir and 94 to placebo). Acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.[33]

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to Acyclovir and 43 to placebo), Acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing and cessation of pain, reduced the duration of new lesion formation and reduced prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia or hyperesthesia).[34]

Chickenpox:
In a double-blind, placebo-controlled efficacy study in 110 normal patients, ages 5 to 16 years, who presented within 24 hours of the onset of a typical chickenpox rash, Acyclovir was administered orally 4 times daily for 5 to 7 days at doses of 10, 15 or 20 mg/kg depending on the age group. Treatment with Acyclovir reduced the maximum number of lesions (336 vs. greater than 500: lesions beyond 500 were not counted). Treatment with Acyclovir also shortened the mean time to 50% healing (7.1 days vs. 8.7 days), reduced the number of vesicular lesions by the second day of treatment (49 vs. 113), and decreased the proportion of patients with fever (temperature greater than 100°F) by the second day (19% vs. 57%). Treatment with Acyclovir did affect the antibody response to varicella-zoster virus measured 1 month and 1 year following the treatment.[35]

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orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see Pharmacokinetics).

6. CLINICAL PHARMACOLOGY

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weaning mice. Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* in human lymphocytes a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels. Results in the other five mammalian cell loci follow at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day, s.c.), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites, and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels

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were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the 1-month study and were 24 to 48 times human levels in the 6-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for 1 month (21 to 41 times human levels) and in dogs given 60mg/kg/day orally for 1 year (6 to 12 times human levels).

abnormalities

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.) rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels in a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies and maternal toxicity.[43] In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of Acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels. [43,44] These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when Acyclovir is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS:

Herpes Simplex: ***Short-Term Administration:*** The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered Acyclovir were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse events, each of which occurred in 1 of 298 patient treatments with orally administered Acyclovir (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the

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prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with Acyclovir were: nausea (4.8%), diarrhea (2.4%), headache (1.9%) and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with Acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%) and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%) and paresthesia (0.8%). Adverse events reported by 329 patients during the third year included asthenia (1.2%), paresthesia (1.2%) and headache (0.9%).

Herpes Zoster: The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral Acyclovir 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%) and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%) and constipation (2.4%).

Chickenpox: The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral Acyclovir in 495 patients were: diarrhea (3.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%) and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%) and insomnia (0.4%).

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral Acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis
Nervous: confusion, dizziness, hallucinations, paresthesia, somnolence (These symptoms may be marked, particularly in older adults.)
Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea
Hemic and Lymphatic: leukopenia, lymphadenopathy
Musculoskeletal: myalgia
Skin: alopecia, pruritus, rash, ~~urticaria~~ → urticaria
Special Senses: visual abnormalities
Urogenital: elevated creatinine

OVERDOSAGE: Patients have ingested intentional overdoses of up to 100 capsules (20 g) of Acyclovir, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days;

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rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION:

Treatment of Initial Genital Herpes: 200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg (two 200 mg capsules or one 400 mg tablet) 2 times daily for up to 12 months, followed by re-evaluation. See INDICATIONS AND USUAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

Intermittent Therapy: 200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules, two 400 mg tablets or one 800 mg tablet) every 4 hours orally, 5 times daily for 7 to 10 days.

Treatment of Chickenpox: ***Children (2 years of age and older):*** 20 mg/kg per dose orally four times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.
Adults and Children over 40 kg: 800 mg four times daily for 5 days.
Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications:

GENPHARM

NEW

Telephone Amendment

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

SEP 08 1997

RE: **ANDA No. 74-976**
ACYCLOVIR TABLETS 400 mg & 800 mg
Comparative Dissolution Profiles

Dear Sirs:

As discussed in a telephone request with Ms. Lizzie Sanchez on September 4, 1997, to assist the reviewer, we have enclosed **all** the comparative dissolution profiles for the above mentioned ANDA. The comparative dissolution profiles will consist of the individual dissolution data, statistical summary, and a dissolution study cover page specifying the dissolution parameters used.

Please note, the first comparative dissolution testing was performed with Genpharm's in house method SP0048.A. (dissolution medium 0.1N HCl, which will be the medium specified in the upcoming Pharmacopeial Forum (see letter attached). FDA had later requested for comparative dissolution to be performed in water as per the Pharmacopeial Forum (volume 22, number 4, page 2493). Following the submission of the dissolution request, FDA later requested in an amendment letter dated Apr. 30, 1997 to perform comparative dissolution testing in the mediums: a) 0.05 M Phosphate buffer pH=6.8 and b) 0.05 M Acetate buffer pH=4.5.

Accompanied in this amendment is a form FDA 356h signed by our US agent, Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, N.Y. The pages of the dissolution data have been paginated on the bottom right hand corner of the page.

An archival copy and a review copy is provided.

RECEIVED

SEP 10 1997

GENERIC DRUGS

/...cont'd

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

Should you have any questions, please contact the undersigned at 1-800-661-7134.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

Richard K. Pike
Director, Regulatory Affairs

GENPHARM

NAI - "Bio Equivalence" 7/3/97

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

FACSIMILE AMENDMENT

NEW CORRESP BIOAVAILABILITY

RE: ANDA No. 74-976
ACYCLOVIR TABLETS
400 mg & 800 mg

JUN 02 1997

Dear Sirs/Madam:

Please find enclosed a ***FACSIMILE AMENDMENT*** to ANDA # 74-976 in response to the faxed letter dated Apr. 30, 1997 from Lizzie Sanchez, Project Manager which we received on May 2, 1997.

For the reviewers' convenience, we have:

a) attached a copy of the letter dated Apr. 30, 1997;
b) formatted our amendment such that each comment made by the reviewer has been restated in *italic* print;
c) provided our response following the comment.

We have enclosed one (1) archival and one (1) review copy of the application in accordance with 21 CFR § 314.55.

We trust the information submitted is sufficient for this amendment to be evaluated. Dr. Anita Goodman is our US Agent, however, should you have any questions, please contact the undersigned at 1-800-661-7134.

Along with our responses, a signed form FDA 356h by our US agent, Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, N.Y. is submitted.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

for Richard K. Pike
Director, Regulatory Affairs

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JUN 04 1997
GENERIC DRUGS

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ANDA 74-976

APR 30 1997

Lipha Pharmaceuticals, Inc.
U.S. Agent for Genpharm, Inc.
Attention: Anita M. Goodman
9 West 57th Street, Suite 3825
New York NY 10019-2701

Dear Madam:

Reference is made to the Abbreviated New Drug Application submitted on September 27, 1996 and amendments dated January 16, 22 and February 5, 1997, for Acyclovir Tablets, 400 mg and 800 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. Lot 102563 of Acyclovir was used for the bio-study. In volume 1.5 page 002374 information relating to the potency of bulk lot # 102394 is given. The sponsor must establish that bio-lot 102563 is the same as bulk lot 102394 for the dissolution data to be acceptable. If not, what is the potency for the bio-lot? Also, if they are different, a dissolution study must be done in 0.1N HCl using the bio-lot since the proposal is to establish 0.1N HCl as the dissolution media.

2. The following subjects in the fasting study exhibited an increase in the terminal phase of their plasma concentration time curves:

Treatment-Test		
Subject	Time	Conc

Treatment-Reference

Subject Time Conc

Please explain how it was determined that these subjects were in the log-linear phase since the terminal data was increasing.

3. The data for the subjects in deficiency # 2 should be deleted from the estimation of AUC(0-inf).

4. The submission of September 27, vol 1.5 page 002372, includes dissolution data for a study conducted in acid for the 400 mg tablet with no statistical summary. In the January 22 submission, dissolution data collected in acid was submitted on pages 4-5, which was difficult to interpret and appeared to be done on only 6 tablets. The summary for the dissolution supported this as 6 tablet data. In the February 5 submission, no data was submitted for dissolution in acid for the 400 mg tablet. Please submit completely documented comparative dissolution data, including conditions, for 12 tablets each of both test and reference acyclovir products in 0.1N HCl, which is proposed as the final dissolution medium.

5. Explain why the reported value in the long-term stability

6. Also submit additional dissolution data in the following media so that this information can be used in establishing a dissolution specification for their tablet. The media and conditions requested are:

I.	
Apparatus:	II
Medium:	0.05 M Phosphate Buffer pH=6.8
RPM:	50
No. of Units:	12
II.	
Apparatus:	II
Medium:	0.05 M Acetate Buffer pH=4.5
RPM:	50
No. of Units:	12

As described under 21 CFR 314.96, an action which will amend this application is required, should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

GENPHARM

February 5, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: **ACYCLOVIR TABLETS 400 mg & 800 mg ANDA** (ANDA No. 74-976)
Comparative Dissolution Profiles using PF volume 22, Number 4 dissolution method (p.2493)

Dear Sirs:

Please find enclosed comparative dissolution profiles with the individual dissolution data using the PF volume 22, Number 4 dissolution method as requested by Lizzie Sanchez in a telephone conversation on January 24, 1997 for the above mentioned ANDA.

This submission consist of 1 volume containing the dissolution data, accompanied by a form FDA 356h signed by our US agent, Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, N.Y. The dissolution data are provided in their respective tabbed Section of the ANDA for placement into the original ANDA.

Two copies of volume 1 are submitted, an archival copy (blue folder) and the review copy (orange folder).

Should you have any questions, please contact the undersigned at 1-800-661-7134.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

Richard K. Pike
Director, Regulatory Affairs

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FEB 07 1997
GENERIC DRUGS

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GENPHARM

January 22 , 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Dissolution Data for ACYCLOVIR TABLETS 400 mg & 800 mg ANDA (ANDA No. 74-976)

Dear Sirs:

Please find enclosed dissolution data as requested by Lizzie Sanchez in a telephone conversation on January 21, 1997 for the above mentioned ANDA.

This submission consist of 1 volume containing the dissolution data, accompanied by a form FDA 356h signed by our US agent, Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, N.Y. The dissolution data are provided in their respective section of the ANDA for placement into the original ANDA.

Two copies of volume 1 are submitted, an archival copy (blue folder) and the review copy (orange folder).

Should you have any questions, please contact the undersigned at 1-800-661-7134.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

Richard K. Pike
Director, Regulatory Affairs

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JAN 27 1997
GENERIC DRUGS

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RECORD OF TELEPHONE CONVERSATION

DATE: 2/9/98

PRODUCT NAME: Acyclovir Tablets, 400 mg & 800 mg
Acyclovir Capsules, 200 mg

ANDA/AADA NUMBER: 74-976 & 74-977

FIRM NAME: Genpharm Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Bruce Goddard
Lipha Pharmaceuticals, U.S. Agent
Dir. Reg. Affairs
(212) 223-1280

PARTICIPANT(S) TELEPHONE:
Mr. Norman R. Gregory, Review Chemist, Branch VI , OGD, CDER, FDA

MINUTES OF CONVERSATION:
I called the U.S. agent do they could convey the following concerns to the applicant:

These concerns will be conveyed to the applicant and their respone faxed followed by hard copy.

NAME OF OGD REPRESENTATIVE: Norman R. Gregory

SIGNATURE OF OGD REPRESENTATIVE:

DIVISION/BRANCH: Office of Generic Drugs
Division II, Branch VI.

MINUTES PREPARED BY:

Mr. Norman R. Gregory, Review Chemist, Branch VI , OGD, CDER, FDA

RECORD OF TELEPHONE CONVERSATION

DATE: 2/12/98

PRODUCT NAME: Acyclovir Tablets, 400 mg & 800 mg
Acyclovir Capsules, 200 mg

ANDA/AADA NUMBER: 74-776 &74-977

FIRM NAME: Genpharm Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Kim Chu, Regulatory Affaires Associate
(800) 661-7134

PARTICIPANT(S) TELEPHONE:
Mr. Norman R. Gregory, Review Chemist, Branch VI , OGD, CDER, FDA

MINUTES OF CONVERSATION:
Returned firms phone call to clarify questions from phone memo of 2/9/98 regarding the following:

This information will be submitted.

NAME OF OGD REPRESENTATIVE: Norman R. Gregory

SIGNATURE OF OGD REPRESENTATIVE:

DIVISION/BRANCH: Office of Generic Drugs
Division II, Branch VI.

MINUTES PREPARED BY:

Mr. Norman R. Gregory, Review Chemist, Branch VI , OGD, CDER, FDA

GENPHARM

11/20/96

September 27, 1996

Office of Generic Drugs
CDER, Food & Drug Administration
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE:

ANDA for Acyclovir Tablets 400 mg & 800 mg

Dear Director, Office of Generic Drugs:

Genpharm Inc. submits today an original abbreviated new drug application ("ANDA") seeking approval to market Acyclovir tablets 400 mg and 800 mg strengths that is bioequivalent to the listed drug, Zovirax® (Acyclovir) 400 mg & 800 mg Tablets, manufactured by Glaxo Welcome Inc. (USA), pursuant to NDA #N20089 001 and #N20089 002.

This ANDA consists of seven volumes. Genpharm is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section (VI). A separate copy of the Bioequivalence section is provided in the orange folder.

For more detailed information of the organisation of the ANDA, please refer to the introduction page, "Executive Summary - Organisation of the ANDA."

A letter from Genpharm Inc. appointing Dr. Anita Goodman as the Agent in the United States immediately follows the Executive Summary.

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of this ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generics Drugs) was sent to out local district office. This "field copy" was contained in a burgundy folder.

We request that all information in this file be treated as confidential within the meaning of 21 CFR section 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your office.

GENPHARM INC. 37 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S6 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

Should you have any questions regarding the information in this submission, please do not hesitate to call me at 1-800-661-7134.

Thank you for your prompt handling of this submission.

Sincerely,
Genpharm Inc.

Richard K. Pike
Director, Regulatory Affairs

ANDA 74-976

Lipha Pharmaceuticals Inc.
Attention: Anita M. Goodman, M.D.
U.S. Agent for: Genpharm Inc.
9 West 57th Street
Suite 3825
New York, NY 10019-2701

DEC 4 1996

Dear Madam:

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

NAME OF DRUG: Acyclovir Tablets 400 mg and 800 mg

DATE OF APPLICATION: September 27, 1996

DATE OF RECEIPT: October 10, 1996

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

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

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

12/4/96

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

cc: DUP/Jacket

GENPHARM

January 16, 1997

NEW CORRESP

Bio. Inc.
LAI 1/21/97
LRL

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room E150
Rockville, Maryland 20855-2773

Attention: Mr. Larry Galvin
cc: Ms. Lizzie Sanches

REF: ANDA 74-976
Acyclovir Tablets 800 mg & 400 mg

Re: Bioequivalence Data Diskettes

Further to a call from Mr. Larry Galvin we have included diskettes (total 2 diskettes) containing the Biostudy data for 800 mg Acyclovir Tablets. One diskette contains the data for the project no 1642, and the other diskette contains the data for the project no 1644.

Also attached are the hard copies of File Information.

Two copies of the information is being submitted - Review Copy (Orange Folder), and Archival Copy (Blue Folder). The diskettes are included only in the Orange Folder.

We trust the information provided is satisfactory for your review. Should you have any questions or require further clarification please do not hesitate to contact us.

Sincerely,
Genpharm Inc.

R. K. Pike

Richard K. Pike
Director, Regulatory Affairs

RECEIVED
JAN 17 1997
GENPHARM INC.