ANDA 74-930

MAY 13 1998

Fujisawa USA, Inc.
Attention: Laurence R. Myerson, Ph.D.
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

Dear Sir:

This is in reference to your abbreviated new drug application dated July 29, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Sodium Injection, 50 mg (base)/mL, in 10 mL (500 mg) and 20 mL (1 g) vials.

Reference is also made to your amendments dated May 9, July 18, September 5, October 2, October 31, and December 22, 1997; January 13, January 28, and correspondence dated March 2, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Acyclovir Sodium Injection 50 mg (base)/mL can be expected to have the same therapeutic effect as that of the reference listed drug product upon which the Agency relied as the basis of safety and effectiveness.

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ [redacted] 5/13/98

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

Peritoneal Dialysis:
No supplemental dose appears to be necessary after adjustment of the dosing interval.[40,41]

Administration:
The calculated dose should be further diluted in an appropriate intravenous solution at a volume selected for administration during each 1 hour infusion. Infusion concentrations of approximately 7 mg/mL or lower are recommended. In clinical studies, the average 70 kg adult received between 60 and 150 mL of fluid per dose. Higher concentrations (*e.g.*, 10 mg/mL) may produce phlebitis or inflammation at the injection site upon inadvertent extravasation. Standard, commercially available electrolyte and glucose solutions are suitable for intravenous administration; biologic or colloidal fluids (*e.g.*, blood products, protein solutions, etc.) are not recommended. Once diluted with infusion solution, each dose should be used within 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED:
Acyclovir Sodium Injection is available as:

Product No.	NDC No.	
302510	0469-3025-10	Acyclovir Sodium Injection equivalent to acyclovir, 50 mg/mL in a 10 mL plastic vial, in packages of 10.
302520	0469-3025-20	Acyclovir Sodium Injection equivalent to acyclovir, 50 mg/mL in a 20 mL plastic vial, in packages of 10.

Store at 15°-25°C (59°-77°F).

Discard unused portion.

CAUTION: Federal law prohibits dispensing without prescription.

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Fujisawa USA, inc.

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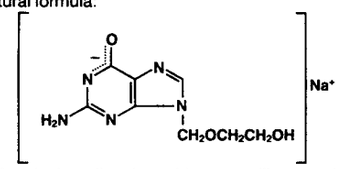
ACYCLOVIR SODIUM
INJECTION

FOR INTRAVENOUS INFUSION ONLY

DESCRIPTION:
Acyclovir Sodium Injection is an anti-viral drug, active against herpesviruses. It is a sterile, aqueous solution for intravenous infusion, containing 50 mg acyclovir per mL in Water for Injection, USP. The concentration is equivalent to 54.9 mg of acyclovir sodium per mL in Water for Injection, USP. The sodium content is approximately 5.1 mg/mL. The pH range of the solution is 10.85 to 11.50. Further dilution of Acyclovir Sodium Injection in an appropriate intravenous solution must be performed before infusion (see **DOSAGE AND ADMINISTRATION, *Administration***).

The chemical name of acyclovir sodium is 9-[(2-hydroxyethoxy)methyl] guanine sodium ($C_8H_{10}N_5O_3$·Na), and has the following structural formula:



Acyclovir sodium is a white, crystalline powder with a molecular weight of 247 daltons, and a solubility in water exceeding 100 mg/mL. At physiologic pH, acyclovir exists as the unionized form with a molecular weight of 225.21 and a maximum solubility of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY:

Mechanism of Antiviral Effects:
Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpesviruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV[2] converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with Herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme.

Acyclovir is not efficiently activated in cytomegalovirus infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir *in vitro*.

Microbiology:
The quantitative relationship between the *in vitro* susceptibility of herpes simplex virus to acyclovir and the clinical response to therapy has not been established in man, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction

intern Med. 1982;96:265-269.
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testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction in Vero cells) to 5.9-13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively).[1]

Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤ 0.9 mcg/mL acyclovir and 50% of all isolates were sensitive to ≤ 0.2 mcg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤ 2.2 mcg/mL and 50% of all isolates were sensitive to ≤ 0.7 mcg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

Most of the less sensitive clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17-1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85-3.98 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3-17.6 mcg/mL (plaque reduction, HEF cells) to 1.82-56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics:

The pharmacokinetics of acyclovir has been evaluated in 95 patients (9 studies). Results were obtained in adult patients with normal renal function during Phase 1/2 studies after single doses ranging from 0.5 to 15 mg/kg and after multiple doses ranging from 2.5 to 15 mg/kg every 8 hours. Pharmacokinetics was also determined in pediatric patients with normal renal function ranging in age from 1 to 17 years at doses of 250 mg/m^2 or 500 mg/m^2 every 8 hours. In these studies, dose-independent pharmacokinetics is observed in the range of 0.5 to 15 mg/kg. Proportionality between dose and plasma levels is seen after single doses or at steady state after multiple dosing.[23] When acyclovir was administered to adults at 5 mg/kg (approximately 250 mg/m^2) by 1-hr infusions every 8 hours, mean steady-state peak and trough concentrations of 9.8 mcg/mL (5.5 to 13.8 mcg/mL) and 0.7 mcg/mL (0.2 to 1.0 mcg/mL), respectively, were achieved. Similar concentrations are achieved in children over 1 year of age when doses of 250 mg/m^2 are given by 1-hr infusions every 8 hours. At a dose of 10 mg/kg given by 1-hr infusion every 8 hours, mean steady-state peak and trough concentrations were 22.9 mcg/mL (14.1 to 44.1 mcg/mL) and 1.9 mcg/mL (0.5 to 2.9 mcg/mL). Similar concentrations were achieved in children dosed at 500 mg/m^2 given by 1-hr infusion every 8 hours. Concentrations achieved in the cerebrospinal fluid are approximately 50% of plasma values. Plasma protein binding is relatively low (9% to 33%) and drug interactions involving binding site displacement are not anticipated.[23]

Renal excretion of unchanged drug by glomerular filtration and tubular secretion is the major route of acyclovir elimination accounting for 62% to 91% of the dose as determined by ^{14}C-labelled drug. The only major urinary metabolite detected is 9-carboxymethoxymethylguanine. This may account for up to 14.1% of the dose in patients with normal renal function. An insignificant amount of drug is recovered in feces and expired CO_2 and there is no evidence to suggest tissue retention.[23] However, postmortem examinations have shown that acyclovir is widely distributed in tissues and body fluids including brain, kidney, lung, liver, muscle, spleen, uterus, vaginal mucosa, vaginal secretions, cerebrospinal fluid and herpetic vesicular fluid.

The half-life and total body clearance of acyclovir is dependent on renal function as shown below.[23]

Creatinine Clearance (mL/min/1.73m^2)	Half-Life (hr)	Total Body Clearance (mL/min/1.73m^2)
>80	2.5	327
50-80	3.0	248
15-50	3.5	190
0 (Anuric)	19.5	29

Acyclovir was administered at a dose of 2.5 mg/kg to 6 adult patients with severe renal failure. The

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50-80	3.0	248
15-50	3.5	190
0 (Anuric)	19.5	29

Acyclovir was administered at a dose of 2.5 mg/kg to 6 adult patients with severe renal failure. The peak and trough plasma levels during the 47 hours preceding hemodialysis were 8.5 mcg/mL and 0.7 mcg/mL, respectively.[24, 25]

Consult **DOSAGE AND ADMINISTRATION** section for recommended adjustments in dosing based upon creatinine clearance.

The half-life and total body clearance of acyclovir in pediatric patients over 1 year of age is similar to those in adults with normal renal function (see **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND USAGE:
Acyclovir Sodium Injection is indicated for the treatment of initial and recurrent mucosal and cutaneous Herpes simplex (HSV-1 and HSV-2) and varicella-zoster (shingles) infections in immunocompromised patients. It is also indicated for herpes simplex encephalitis in patients over 6 months of age and for severe initial clinical episodes of herpes genitalis in patients who are not immunocompromised.

Herpes Simplex Infections in Immunocompromised Patients
A multicenter trial of acyclovir at a dose of 250 mg/m^2 every 8 hours (750 mg/m^2/day) for 7 days was conducted in 98 immunocompromised patients (73 adults and 25 children) with orofacial, esophageal, genital and other localized infections (52 treated with acyclovir and 46 with placebo). Acyclovir significantly decreased virus excretion, reduced pain, and promoted scabbing and rapid healing of lesions.[14,26,27,28]

Initial Episodes of Herpes Genitalis
In placebo-controlled trials, 58 patients with initial genital herpes were treated with intravenous acyclovir 5 mg/kg or placebo (27 patients treated with acyclovir and 31 treated with placebo) every

eight hours for 5 days. Acyclovir decreased the duration of viral excretion, new lesion formation, and duration of vesicles and promoted healing of lesions.[28,29,30]

Herpes Simplex Encephalitis

Sixty-two patients ages 6 months to 79 years with brain biopsy-proven herpes simplex encephalitis were randomized to receive either acyclovir (30 mg/kg/day) or adenine arabinoside (15 mg/kg/day) for 10 days (28 were treated with acyclovir and 34 with adenine arabinoside).[31] Overall mortality for acyclovir recipients at 6 months was 18% compared to 59% for adenine arabinoside recipients (P = 0.003). The proportion of acyclovir recipients functioning normally or with only mild sequelae (*e.g.*, decreased attention span) was 39% compared to 9% of adenine arabinoside recipients (P = 0.01). The remaining patients in both groups had moderate (*e.g.*, hemiparesis, speech impediment or seizure) or severe (continuous supportive care required) neurologic sequelae.

After 12 months of follow-up, two additional acyclovir recipients had died, resulting in an overall mortality of 25% compared to 59% for adenine arabinoside recipients (P = 0.02). Morbidity assessments at that time indicated that 32% of acyclovir recipients were functioning normally, or with only mild sequelae compared to 12% adenine arabinoside recipients (P = 0.06). Moderate to severe impairment was noted in all remaining patients in both groups who were available for evaluation. Patients less than 30 years of age and those who had the least severe neurologic involvement at time of entry into study had the best outcome with acyclovir treatment. An additional controlled study performed in Europe[32] demonstrated similar findings. The superiority of acyclovir over adenine arabinoside for neonatal herpes encephalitis has not been demonstrated.

Varicella-Zoster Infections in Immunocompromised Patients

A multicenter trial of intravenous acyclovir at a dose of 500 mg/m^2 every 8 hours for 7 days was conducted in immunocompromised patients with zoster infection (shingles). Ninety-four (94) patients were evaluated (52 patients were treated with acyclovir and 42 with placebo). Acyclovir halted progression of infection as determined by significant reductions in cutaneous dissemination, visceral dissemination, or the proportion of patients deemed treatment failures.[28,33]

A comparative trial of acyclovir and vidarabine was conducted in 22 severely immunocompromised patients with zoster infections. Acyclovir was shown to be superior to vidarabine as demonstrated by significant differences in the time of new lesion formation, the time to pain reduction, the time to lesion crusting, the time to complete healing, the incidence of fever and the duration of positive viral cultures. In addition, cutaneous dissemination occurred in none of the 10 acyclovir recipients compared to 5 of the 10 vidarabine recipients who presented with localized dermatomal disease.[34]

Diagnosis

Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. In initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. Whereas cutaneous lesions associated with Herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may assist in the diagnosis.[35]

The Tzanck smear does not distinguish varicella-zoster from herpes simplex infections. Culture of varicella-zoster is not widely available.

Herpes encephalitis should be confirmed by brain biopsy to obtain tissue for histologic examination and viral culture and to exclude other causes of neurologic disease. A presumptive diagnosis of herpes encephalitis may be made on the basis of focal changes in the temporal lobe visualized with various diagnostic methods including magnetic resonance imaging, computerized tomography, radionuclide scans or electroencephalography. Culture of the cerebrospinal fluid for herpes simplex virus is unreliable.

CONTRAINDICATIONS:

Acyclovir Sodium Injection is contraindicated for patients who develop hypersensitivity to the drug.

WARNINGS:

Acyclovir Sodium Injection is intended for intravenous infusion only, and should not be administered topically, intramuscularly, orally, subcutaneously, or in the eye. Intravenous infusions must be given over a period of at least 1 (one) hour to reduce the risk of renal tubular damage (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS:

were inconclusive at concentrations at least 150 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 120 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 the same as human levels. At 50 mg/kg/day, s.c. in the rat (1 to 2 times human levels), 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 (1 to 3 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (4 to 9 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day, s.c. (1 to 2 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 were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (4 to 9 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 one-month study and were 2 to 4 times human levels in the six-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 4 to 8 times human levels, while at 200 mg/kg/day they were 13 to 25 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (2 to 3 times human levels) and in dogs given 60 mg/kg/day orally for one year (the same as human levels).

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 the same as, 4 and 9, and 1 and 2 times, respectively, human levels. In a non-standard test in rats there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.[37] In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 5 and 10 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.[38,39] 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.

ADVERSE REACTIONS:

The adverse reactions listed below have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received acyclovir at approximately 5 mg/kg (250 mg/m^2) three times daily, and approximately 300 patients who received approximately 10 mg/kg (500 mg/m^2) three times daily.

The most frequent adverse reactions reported during acyclovir administration were inflammation or phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum creatinine or BUN in 5% to 10% (the higher incidence occurred usually following rapid [less than 10 minutes] intravenous infusion). Nausea and/or vomiting occurred in approximately 7% of the patients (the majority occurring in non-hospitalized patients who received 10 mg/kg). Itching, rash or hives occurred in approximately

varicella-zoster from herpes simplex infections. Culture of varicella-zoster is not widely available.

Herpes encephalitis should be confirmed by brain biopsy to obtain tissue for histologic examination and viral culture and to exclude other causes of neurologic disease. A presumptive diagnosis of herpes encephalitis may be made on the basis of focal changes in the temporal lobe visualized with various diagnostic methods including magnetic resonance imaging, computerized tomography, radionuclide scans or electroencephalography. Culture of the cerebrospinal fluid for herpes simplex virus is unreliable.

CONTRAINDICATIONS:
Acyclovir Sodium Injection is contraindicated for patients who develop hypersensitivity to the drug.

WARNINGS:
Acyclovir Sodium Injection is intended for intravenous infusion only, and should not be administered topically, intramuscularly, orally, subcutaneously, or in the eye. Intravenous infusions must be given over a period of at least 1 (one) hour to reduce the risk of renal tubular damage (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS:

General:
The recommended dosage, frequency and length of treatment should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

Although the aqueous solubility of acyclovir (for infusion) is > 100 mg/mL, precipitation of acyclovir crystals in renal tubules can occur if the maximum solubility of free acyclovir (2.5 mg/mL at 37°C in water) is exceeded or if the drug is administered by bolus injection. This complication causes a rise in serum creatinine and blood urea nitrogen (BUN), and a decrease in renal creatinine clearance. Ensuing renal tubular damage can produce acute renal failure.

Abnormal renal function (decreased creatinine clearance) can occur as a result of acyclovir administration and depends on the state of the patient's hydration, other treatments, and the rate of drug administration. Bolus administration of the drug leads to a 10% incidence of renal dysfunction, while in controlled studies, infusion of 5 mg/kg (250 mg/m^2) and 10 mg/kg (500 mg/m^2) over an hour was associated with a lower frequency - 3.8%. Concomitant use of other nephrotoxic drugs, pre-existing renal disease, and dehydration make further renal impairment with acyclovir more likely. In most instances, alterations of renal function were transient and resolved spontaneously or with improvement of water and electrolyte balance, drug dosage adjustment or discontinuation of drug administration. However, in some instances, these changes may progress to acute renal failure.

Administration of acyclovir by intravenous infusion must be accompanied by adequate hydration. Since maximum urine concentration occurs within the first 2 hours following infusion, particular attention should be given to establishing sufficient urine flow during that period in order to prevent precipitation in renal tubules. Recommended urine output is ≥ 500 mL per gram of drug infused. In patients with encephalitis, the recommended hydration should be balanced by the risk of cerebral edema.

When dosage adjustments are required they should be based on estimated creatinine clearance (see **DOSAGE AND ADMINISTRATION**).

Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma. Acyclovir should be used with caution in those patients who have underlying neurologic abnormalities and those with serious renal, hepatic, or electrolyte abnormalities or significant hypoxia. It should also be used with caution in patients who have manifested prior neurologic reactions to cytotoxic drugs or those receiving concomitant intrathecal methotrexate or interferon.

Exposure to HSV isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. These viruses usually are deficient in thymidine kinase (required for acyclovir activation) and are less pathogenic in animals. Similar isolates have been observed in severely immunocompromised patients during the course of controlled and uncontrolled studies of intravenously administered acyclovir. These occurred in patients with severe combined immunodeficiencies or following bone marrow transplantation. The presence of these viruses was not associated with a worsening of clinical illness and, in some instances, the virus disappeared spontaneously. The possibility of the appearance of less sensitive viruses must be recognized when treating such patients.[11-19] The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has not been established.

Drug Interactions:
Co-administration of probenecid with acyclovir has been shown to increase the mean half-life

Acyclovir concentrations have been [illegible] in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels.[38,39] 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.

ADVERSE REACTIONS:
The adverse reactions listed below have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received acyclovir at approximately 5 mg/kg (250 mg/m^2) three times daily, and approximately 300 patients who received approximately 10 mg/kg (500 mg/m^2) three times daily.

The most frequent adverse reactions reported during acyclovir administration were inflammation or phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum creatinine or BUN in 5% to 10% (the higher incidence occurred usually following rapid [less than 10 minutes] intravenous infusion). Nausea and/or vomiting occurred in approximately 7% of the patients (the majority occurring in non-hospitalized patients who received 10 mg/kg). Itching, rash or hives occurred in approximately 2% of patients. Elevation of transaminases occurred in 1% to 2% of patients.

Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma (see **PRECAUTIONS**).

Adverse reactions which occurred at a frequency of less than 1% and which were probably or possibly related to intravenous acyclovir administration were: anemia, anuria, hematuria, hypotension, edema, anorexia, lightheadedness, thirst, headache, diaphoresis, fever, neutropenia, thrombocytopenia, abnormal urinalysis (characterized by an increase in formed elements in urine sediment) and pain on urination.

Other reactions have been reported with a frequency of less than 1% in patients receiving acyclovir, but a causal relationship between acyclovir and the reaction could not be determined. These include pulmonary edema with cardiac tamponade, abdominal pain, chest pain, thrombocytosis, leukocytosis, neutrophilia, ischemia of digits, hypokalemia, purpura fulminans, pressure on urination, hemoglobinemia and rigors.

Observed During Clinical Practice:
Based on clinical practice experience in patients treated with intravenous 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, pain, and rarely, anaphylaxis
Digestive: elevated liver function tests, nausea
Hemic and Lymphatic: leukopenia
Nervous: agitation, coma, confusion, convulsions, delirium, hallucinations, obtundation, psychosis
Skin: rash
Urogenital: elevated blood urea nitrogen, elevated creatinine, renal failure

OVERDOSAGE:
Overdosage has been reported following administration of bolus injections, or inappropriately high doses, and in patients whose fluid and electrolyte balance was not properly monitored. This has resulted in elevations in BUN, serum creatinine and subsequent renal failure. Lethargy, convulsions and coma have been reported rarely.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded (see **PRECAUTIONS**). Renal lesions 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; 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. In the event of overdosage, sufficient urine flow must be maintained to prevent precipitation of drug in renal tubules. Recommended urine output is ≥ 500 mL per gram of drug infused. A six-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:

CAUTION - RAPID OR BOLUS INTRAVENOUS AND INTRAMUSCULAR OR SUBCUTANEOUS INJECTION MUST BE AVOIDED. Therapy should be initiated as early as possible following onset of signs and symptoms. For

with serious renal, hepatic, or electrolyte abnormalities or significant hypoxia. It should also be used with caution in patients who have manifested prior neurologic reactions to cytotoxic drugs or those receiving concomitant intrathecal methotrexate or interferon.

Exposure to HSV isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. These viruses usually are deficient in thymidine kinase (required for acyclovir activation) and are less pathogenic in animals. Similar isolates have been observed in severely immunocompromised patients during the course of controlled and uncontrolled studies of intravenously administered acyclovir. These occurred in patients with severe combined immunodeficiencies or following bone marrow transplantation. The presence of these viruses was not associated with a worsening of clinical illness and, in some instances, the virus disappeared spontaneously. The possibility of the appearance of less sensitive viruses must be recognized when treating such patients.[11-19] The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has not been established.

Drug Interactions:

Co-administration of probenecid with acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[36] The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

The data presented below include references to peak steady state plasma acyclovir concentrations observed in humans treated with 30 mg/kg/day (10 mg/kg/every 8 hr, dosing appropriate for treatment of herpes zoster or herpes encephalitis), or 15 mg/kg/day (5 mg/kg/every 8 hr, dosing appropriate for treatment of primary genital herpes or herpes simplex infections in immunocompromised patients). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see **CLINICAL PHARMACOLOGY: *Pharmacokinetics***).

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 in both the mouse and rat bioassay were lower than concentrations in humans.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (3 to 5 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (3 to 6 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 (5 to 10 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (31 to 61 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (3 to 6 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 13 to 25 times the acyclovir plasma levels achieved in man. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 20 to 40 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

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded (see **PRECAUTIONS**). Renal lesions 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; 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. In the event of overdosage, sufficient urine flow must be maintained to prevent precipitation of drug in renal tubules. Recommended urine output is ≥ 500 mL per gram of drug infused. A six-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:

CAUTION - RAPID OR BOLUS INTRAVENOUS AND INTRAMUSCULAR OR SUBCUTANEOUS INJECTION MUST BE AVOIDED. Therapy should be initiated as early as possible following onset of signs and symptoms. For diagnosis - see INDICATIONS AND USAGE.

Dosage:

HERPES SIMPLEX INFECTIONS

MUCOSAL AND CUTANEOUS HERPES SIMPLEX (HSV-1 and HSV-2) INFECTIONS IN IMMUNOCOMPROMISED PATIENTS - 5 mg/kg infused at a constant rate over 1 hour, every 8 hours (15 mg/kg/day) for 7 days in adult patients with normal renal function. In children under 12 years of age, more accurate dosing can be attained by infusing 250 mg/m^2 at a constant rate over 1 hour, every 8 hours (750 mg/m^2/day) for 7 days.

SEVERE INITIAL CLINICAL EPISODES OF HERPES GENITALIS - The same dose given above - administered for 5 days.

HERPES SIMPLEX ENCEPHALITIS - 10 mg/kg infused at a constant rate over at least 1 hour, every 8 hours for 10 days. In children between 6 months and 12 years of age, more accurate dosing is achieved by infusing 500 mg/m^2, at a constant rate over at least one hour, every 8 hours for 10 days.

VARICELLA ZOSTER INFECTIONS

ZOSTER IN IMMUNOCOMPROMISED PATIENTS - 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days in adult patients with normal renal function. In children under 12 years of age, equivalent plasma concentrations are attained by infusing 500 mg/m^2 at a constant rate over at least 1 hour, every 8 hours for 7 days. Obese patients should be dosed at 10 mg/kg (Ideal Body Weight). A maximum dose equivalent to 500 mg/m^2 every 8 hours should not be exceeded for any patient.

PATIENTS WITH ACUTE OR CHRONIC RENAL IMPAIRMENT:

Refer to **DOSAGE AND ADMINISTRATION** section for recommended doses, and adjust the dosing interval as indicated in the table below.

Creatinine Clearance (mL/min/1.73m^2)	Percent of Recommended Dose	Dosing Interval (hours)
>50	100%	8
25-50	100%	12
10-25	100%	24
0-10	50%	24

Hemodialysis:

For patients who require dialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a six-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[24,25]

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-930

3. NAME AND ADDRESS OF APPLICANT
Fujisawa USA, Inc.
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies that U.S. Patent No. 4,199,574, expiring on April 22, 1997, will not be infringed upon by the manufacture, use or sale by Fujisawa USA, Inc. of Acyclovir Sodium Injection for which this application is submitted. There is no marketing exclusivity in effect for the listed drug.

Innovator: Burroughs Wellcome - Zovirax® Sterile Powder

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir Sodium Injection

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

9. AMENDMENTS AND OTHER DATES:
Firm:
7/29/96 - Original.
9/20/96 - Response to refuse to file letter.
10/30/96 - O/NC, Suitability Petition, response to phone memo.
4/22/97 -O/NC, intent to file amendment.
5/9/97 - Response to 1st def. letter (chem., micro., & labeling). Subject of this review.
7/8/97 - O/NC, intent to file amendment.
7/18/97 - Response to 2nd def. facsimile (micro. & labeling). Subject of this review.
9/5/97 - Response to phone memo regarding MV. Subject of this review.
10/2/97 - Response to memo regarding MV. Subject of this review.
10/31/97 - Response to phone memo. Subject of this review.
12/22/97 - Response to 2nd def. facsimile (chem.). Subject of this review.
1/13/98 - Response to phone memo, [redacted]. Subject of this review.
1/28/98 - Response o phone memo, (b)(4)(CC) Subject of this review.

FDA:
9/13/96 - Refuse to file letter.
11/4/96 - Memo, regarding completeness of Bio. waiver.
11/21/96 - Acknowledgment.
12/6/96 - 1st Micro. Review, unacceptable.
1/28/97 - Bio. review, waiver granted.
2/4/97 - Bio. letter, no further questions.
4/18/97 - 1st def. letter,(chem., micro., & labeling).
6/5/97 - 2nd Micro. Review, unacceptable.
7/2/97 - 2nd def. facsimile, (micro. & labeling).
8/4/97 - 3rd Micro. review, acceptable.
8/20/97 - Methods validation from Northeast Regional Laboratory, address problems before approval for regulatory purposes.
8/28/97 - Phone memo, sent laboratory's comments to firm.
9/23/97 - Memo, problems with MV.
10/7/97 - MV satisfactory.
10/23/97 - Phone memo, (b)(4)(CC)
12/10/97 - 2nd def. facsimile (chem.).
1/12/98 - Phone memo, (b)(4)(CC)
1/27/98 - Phone memo,

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
(b)(4)(CC)

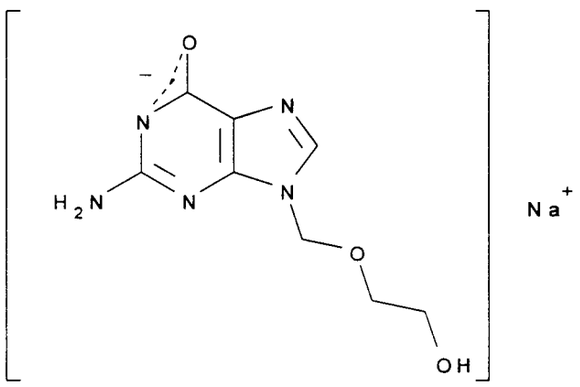
13. DOSAGE FORM
Liquid

14. POTENCY
50 mg/mL
(10 mL & 20 mL vials)

15. CHEMICAL NAME AND STRUCTURE

Acyclovir Sodium

$C_8H_{10}N_5NaO_3$; M.W. = 247.19



9-[(2-Hydroxyethoxy)methyl]guanine monosodium salt.
CAS [69657-51-8]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Bio., Micro., EER, labeling, MV, and DMFs acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER: Norman Gregory

DATE COMPLETED:
1/16/98 (chem.)
8/4/97 (micro.)
8/26/97 (labeling)
10/7/97 (MV)

ANDA APPROVAL SUMMARY

ANDA: 74-930 DRUG PRODUCT: Acyclovir Sodium STRENGTH: 50 mg/mL

FIRM: Fujisawa USA, Inc. DOSAGE FORM: Injection

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable for all on 2/13/97.

BIO STUDY: The waiver of *in-vivo* bioequivalence study for 50 mg/mL (500 mg/vial and 1000 mg/vial) requested under 21 CFR §320.22(b)(1) was granted on 1/28/97.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Active Ingredient: Satisfactory for regulatory purposes on 10/7/97 from N.E. Regional Lab.

Finish Dosage Form: Same as above.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Protocol: Satisfactory.

Exp.Date: 18 months - 40°C ± 2°C/75% R.H. ± 5% R.H., 3 months, 1 lot each strength; and R.T. (25°C ± 2.5°C/60% R.H. ± 5% R.H.), 18 months, 1 lot each strength. Lot #R035-14A, Lot #R035-15A, and Lot #R035-16A (10 mL vial), and Lot #R035-14B, Lot #R035-15B, and Lot #R035-16B (20 mL vial).

Container/Closure systems are the same.

LABELING: Container: Satisfactory in FPL.
Carton: Satisfactory in FPL.
Insert: Satisfactory in FPL.

STERILIZATION VALIDATION (IF APPLICABLE):

(b)(4)(TS) Micro. acceptable on 8/4/97.

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

(b)(4)(CC) Lot #R035-14A, Lot #R035-15A, and Lot #R035-16A (10 mL vial), and Lot #R035-14B, Lot #R035-15B, and Lot #R035-16B (20 mL vial), source of NDS acceptable (b)(4)(CC).

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

(b)(4)(CC) Lot #R035-14A, Lot #R035-15A, and Lot #R035-16A (10 mL vial), and Lot #R035-14B, Lot #R035-15B, and Lot #R035-16B (20 mL vial).

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

(b)(4)(CC) process the same.

CHEMIST: Norman Gregory /S/ 2/9/98 DATE: 1/16/98

SUPERVISOR: U. Venkataram, Ph.D. DATE: 1/22/98

/S/ 2/9/98

OFFICE OF GENERIC DRUGS, HFD-640
Microbiologist's Review #3
August 4, 1997

A. 1. **ANDA** 74-930

APPLICANT Fujisawa USA, Inc.

2. PRODUCT NAME: **Acyclovir Sodium Injection, 50 mg/mL**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
10 mL and 20 mL Single-dose Vials (Liquid), Intravenous

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Anti-viral

B. 1. DATE OF INITIAL SUBMISSION: September 20, 1996
(Received, September 23, 1996)

2. DATE OF AMENDMENT: July 18, 1997
Subject of this Review (Received, July 22, 1997)

3. RELATED DOCUMENTS: DMF (V) [redacted]
Amendment, April 14, 1997

4. ASSIGNED FOR REVIEW: 7/31/97

C. REMARKS: The amendment provides for the response to the microbiology deficiencies in the facsimile dated July 2, 1997.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant".

/S/ [redacted] 8/5/97
Andrea S. High, Ph. D.

/S/ [redacted] 8/8/97

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\74-930a2
Initialed by F. Fang or F. Holcombe, Jr.

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

ANDA Number: 74-930 Date of Submission: July 29, 1996

Applicant's Name: Fujisawa USA, Inc.

Established Name: Acyclovir Injection, 50 mg/mL (10 mL and 20 mL Vials)

Labeling Deficiencies:

1. GENERAL COMMENT:

   The July-August 1996 Pharmacopeial Forum (Vol. 22, Number 4) proposes the established name "Acyclovir for Injection" rather than "Acyclovir Sodium for Injection". Please revise your labels and labeling for your product to read "Acyclovir Injection" rather than "Acyclovir Sodium Injection" accordingly. The "equivalent to" statement in the expression of strength may now be deleted.

2. CONTAINER (10 mL and 20 mL)

   a. We encourage the use of boxing, contrasting colors, or other means to differentiate the strengths of your products.

   b. Revise the expression of strength to reflect the total strength present in each vial, e.g., "500 mg/10 mL".

   c. The "Each mL contains" statement appearing on your container label may be deleted [see 21 CFR 201.100(a)(5)(iii)].

   d. Please include the following statement, "Discard Unused Portion".

3. CARTON (10 X 10 mL and 10 X 20 mL Tray Labels)

   See GENERAL COMMENT and comments for CONTAINER above.

4. INSERT

a. GENERAL

i. See GENERAL COMMENT above.

ii. Revise to read "mcg" rather than "μg" throughout your package insert labeling.

b. DESCRIPTION

i. Make the following revision in the second sentence, "...solution for intravenous infusion,...".

ii. Make the following revision in the first sentence, "...against herpesviruses.", ("herpesviruses", one word).

iii. Include the mg amount of sodium per mL.

iv. We encourage the inclusion of a pH range rather than, "...approximately 11".

v. Make the following revision in the fifth sentence, "...see **DOSAGE AND ADMINISTRATION, Administration)**".

vi. Delete the hyphen between "guanine" and "sodium" in the first sentence of the second paragraph.

c. CLINICAL PHARMACOLOGY (Pharmacokinetics)

Revise to read, "acyclovir" rather than "acyclovir sodium" in the sixth sentence of the first paragraph and the first sentence following the table.

d. INDICATIONS AND USAGE

i. Revise to read "acyclovir" rather than "acyclovir sodium" throughout this section.

ii. Herpes Simplex Encephalitis

Revise to read "adenine arabinoside" rather than "Vira-A" and "adenine arabinoside recipients" rather than "Vira-A treated patients" throughout this subsection.

iii. Varicella-Zoster Infections in Immunocompromised Patients

Revise to read, "A multicenter trial of intravenous acyclovir...".

e. PRECAUTIONS

Revise to read "acyclovir" rather than "acyclovir sodium" throughout this section.

f. ADVERSE REACTIONS

i. Revise to read "acyclovir" rather than "acyclovir sodium" throughout this section.

ii. Observed During Clinical Practice

Make the following revision in the first sentence, "...treated with intravenous acyclovir...".

g. DOSAGE AND ADMINISTRATION

i. Administration

We acknowledge your comment that this subsection was revised to include specific IV infusion solutions. We are unaware, however, of any differences in your product which would support the departure in labeling from the general statement made in the labeling of the reference listed drug. Either explain how your product differs in the possible solutions for dilution or make the following revision in the fifth and sixth sentences, "Standard, commercially available electrolyte and glucose solutions are suitable for intravenous administration; biologic or colloidal...".

ii. Add the following as the last paragraph in this section:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

h. HOW SUPPLIED

Add the following text as the at the beginning of this section:

Acyclovir injection is available as:

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

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

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

/S/ [redacted] for/

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

076-268

M E M O R A N D U M

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

DATE : November 4, 1996

TO : Acting Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 11/4/96

SUBJECT: Examination of the waiver of *in vivo* bioequivalence submitted with ANDA 74-930, Fujisawa USA for Acyclovir Sodium Injection, 50 mg/mL, 10 mL and 20 mL vials, to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4)(B)(iv).

Fujisawa USA has submitted an ANDA 74-930 for Acyclovir Sodium Injection, 50 mg/mL, 10 mL and 20 mL vials. The ANDA contains a certification pursuant to 21 USC 355(j)(2)(A)(vii)(iv) stating that patent #4199574 expiring April 22, 1997, will not be infringed by the manufacture or sale of the proposed product. In order to accept an ANDA for filing that contains such a patent certification, the Agency must formally make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the waiver submitted by Fujisawa on July 29, 1996, for its product, Acyclovir Sodium Injection, satisfies the statutory requirements of "completeness" so that the ANDA may be filed and that a period of six months of market exclusivity can be granted to the applicant who submitted the first substantially complete ANDA under 21 USC 355(j)(4)(B)(iv).

A "complete" bioavailability or bioequivalence waiver is defined as one that conforms with an appropriate FDA regulations and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

The issue raised in the current situation revolves around whether the waiver can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason:

/S/ [redacted]

Acting Director, Division of Bioequivalence

11/5/96

Date

1.1

9-20-96

ANDA 74-930

Fujisawa USA, Inc.
Attention: Jerry D. Johnson, Ph.D.
3 Parkway North, 3rd Floor
Deerfield IL 60015-2548

FEB - 4 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Sodium Injection, 50 mg/mL, 10 mL and 20 mL vials.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/ [redacted]

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 28 1997

Acyclovir Sodium Injection
50 mg/mL - 10 mL and 20 mL Vials
ANDA # 74-930
Reviewer: Moheb H. Makary
WP 74930W.796

Fujisawa USA, Inc.
Deerfield, Illinois
Submission Date:
July 29, 1996

Review of Waiver Requests

I. Objective

The firm is requesting waivers of in vivo study requirements based on 21 CFR 320.22 (b)(1), for its Acyclovir Sodium Injection, 50 mg/mL - 10 mL and 20 mL Vials (total drug content 500 mg and 1 gram, respectively). It is a sterile, aqueous solution. The innovator products are Zovirax^{R} Sterile Powder (Sterile Acyclovir Sodium, lyophilized powder for reconstitution) For Injection, 500 mg and 1 g vials, manufactured by Glaxo Wellcome. The firm submitted a suitability petition requesting a change in dosage form from that of the listed drug product (i.e., from a lyophilized powder for reconstitution to a ready-to-use solution). The Agency approved the petition on June 9, 1994. The firm included a copy of the FDA approval letter in the submission.

Acyclovir Sodium Sterile Powder is indicated for the treatment of initial and recurrent mucosal and cutaneous Herpes simplex and Varicella-zoster infections in immunocompromised patients.

II. Formulations: **(Not to be released under FOI)**

Ingredients	Test		Reference	
	Acyclovir Sodium For Injection		Zovirax® Sterile Powder For Injection	
	500 mg	1000 mg	500 mg	1000 mg
Acyclovir Sodium	(b)(4)(TS)			
Water for Injectic				
USP				
Nitrogen, NF				

[1] Equivalent to 50 mg Acyclovir.

	Test Product Configurations	
Primary Packaging	Acyclovir Sodium Injection	
	50 mg/mL	50 mg/mL
Fill Volume (mL)/Vial Size (mL)	10/10	20/20

III. Comments:

1. As shown above, the proposed test products, Acyclovir Sodium Injection, 50 mg/mL - 10 mL and 20 mL Vials (500 mg/Vial and 1 g/Vial) contain the same active ingredient in the same quantities per unit vial as the reference products, Zovirax® Sterile Powder for Injection, 500 mg/Vial and 1 g/Vial.

2. The reference products, Zovirax® Sterile Powder for Injection, 500 mg/Vial and 1 g/Vial are marketed as a lyophilized powder. The proposed test products, Acyclovir Sodium Injection, 50 mg/mL - 10 mL and 20 mL Vials (500 mg/Vial and 1 g/Vial) are sterile, aqueous solution. The ready-to-use solution was the subject of an approved petition, Docket # 93P-0469/CP1, dated June 9, 1994. Waivers of in vivo bioequivalence study requirements may be granted based on 21 CFR 320.22 (b)(1).

IV. Recommendation:

The Division of Bioequivalence agrees that the information submitted by Fujisawa USA, Inc., demonstrates that Acyclovir Sodium Injection 50 mg/mL - 10 mL (500 mg/Vial and 1 gram/Vial), fall under Section 320.22 (b)(1) of Bioavailability/Bioequivalence Regulations. Waivers of in vivo bioequivalence study for the test products are granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulations manufactured by Fujisawa USA, Inc., to be bioequivalent to Zovirax® Sterile Powder for Injection 500 mg/Vial and 1 gram/Vial manufactured by Glaxo Wellcome.

The firm should be informed of the above recommendation.

/S/

Moheb H Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /S/ [redacted]
FT INITIALLED RMHATRE [redacted] Date: 1/13/97

Concur: /S/ [redacted] 1/28/97

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/1-13-97/wp 74930W.796
cc: ANDA # 74-930, original, HFD-658 (Makary), Drug File.

ANDA 74-930

Fujisawa USA, Inc.
Attention: Jerry D. Johnson, Ph.D.
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

NOV 21 1996

Dear Sir:

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

Reference is also made to our "Refuse to File" letter dated September 13, 1996, and your amendment dated September 20, 1996.

NAME OF DRUG: Acyclovir Sodium Injection, 50 mg/mL in 10 mL and 20 mL vials

DATE OF APPLICATION: July 29, 1996

DATE OF RECEIPT: July 30, 1996

DATE ACCEPTABLE FOR FILING: September 23, 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,

/S/ 11/21/96

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

ARCHIVAL

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 31

/S/ [redacted]

Fujisawa

September 20, 1996

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

AMENDMENT.

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL-10 mL and 20 mL Vials

AMENDMENT TO UNAPPROVED ANDA

Dear Mr. Sporn:

Fujisawa USA, Inc. submits this amendment in response to comments in a letter dated September 13, 1996, from the Office of Generic Drugs, Division of Labeling and Program Support. (See Attached)

This amendment contains additional information that should make the ANDA for Acyclovir Sodium Injection sufficiently complete to merit a critical technical review. The ANDA Suitability Petition that was referenced in the application as the basis of submission is revised to reflect the approved petition for (b)(4)(CC) [redacted] (Attachment A).

The Patent Certification and Exclusivity Statement is revised to indicate that "Fujisawa USA, Inc. will comply with the requirements under 21 CFR 314.95 (a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug and with the requirements under 21 CFR 314.95 (c) with respect to the content of the notice". In addition, a statement as to whether the listed drug is entitled to a period of marketing exclusivity is also provided (Attachment B).

In compliance with 21 CFR 314.96(b), a true and complete copy of this amendment has been sent to Mr. E. Pitt Smith, District Director, Buffalo District, Food and Drug Administration, 599 Delaware Ave., Buffalo, New York 14202. We certify that the field copy is a true and complete copy of the amendment.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at **(847) 317-8200** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

/S/ [redacted]

Lincy Michael
Senior Regulatory Scientist

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RECEIVED
SEP 23 1996
GENERIC DRUGS

ANDA 74-930

Fujisawa USA, Inc.
Attention: Jerry D Johnson, Ph.D.
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

SEP 13 1996

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated July 29, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Sodium Injection 50 mg/mL in 10 mL and 20 mL vials.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

The ANDA Suitability Petition you reference as the basis of submission for your application is incorrect. Please revise your basis of submission.

Your patent statement indicates that the U.S. Patent No. 4,199,574 "will not be infringed upon by the manufacture, use or sale by Fujisawa USA, Inc. of Acyclovir Sodium Injection for which this application is submitted." You must accompany this certification by a statement that the applicant, Fujisawa USA, Inc., will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the content of the notice. Please provided an amended patent certification.

In addition, you have failed to provide a statement as to whether, according to the information published in the list, the reference listed drug is entitled to a period of marketing exclusivity [refer to 21 CFR 314.94(3)(ii)]. Please provide this statement.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Harvey Greenberg
Project Manager
(301) 594-0315

Sincerely yours,

/S/ [redacted] 9/13/96

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

ANDA 74-930
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief /S/ [redacted] 9/12/96 date
HFD-615/HGreenberg, CSO [redacted] 9/12/96 date
HFD-647/JSimmons, Chem Branch date
X:\NEW\FIRMSAM\FUJISAWA\LTRS&REV\74930.RTF
F/T bcw/9-12-96
ANDA Refuse to File!

9/6/96 [redacted]

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-[redacted]

[redacted]

Fujisawa

July 29, 1996

RECEIVED

JUL 30 1996

GENERIC DRUGS

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: Acyclovir Sodium Injection
50 mg/mL - 10 mL and 20 mL Vials
Manufacturing Site: Grand Island, NY
Number of Volumes: 4 Volumes

Dear Mr. Sporn:

This application is being submitted, in duplicate, as an Abbreviated New Drug Application in accordance with Title I, Sec. 101. Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) to seek marketing clearance for Acyclovir Sodium Injection. Enclosed, for your convenience, are three copies of the analytical methods and validation section for the drug substance and finished dosage form.

Fujisawa USA, Inc. will manufacture this product at 3159 Staley Road, Grand Island, NY 14072. This application contains all the information required describing the manufacturing and control of Acyclovir Sodium Injection 50 mg/mL (10 mL and 20 mL vials) using [redacted] gray stopper. Applicable general procedural approaches/data may be cross-referenced to Fujisawa USA, Inc., Type V DMF #[redacted] In addition, this application contains a request for the waiver of in vivo bioequivalence studies.

This application has been formatted according to the information in **Office of Generic Drugs Policy and Procedure Guide #30-91, April 10, 1991.**

An archival and review copy of this submission are provided for your review. Furthermore, in compliance with 21 CFR 314.94(d)(5), a true and complete copy of this abbreviated application is being provided to Mr. E. Pitt Smith, District Director, Buffalo District Director, Food and Drug Administration, 599 Delaware Ave., Buffalo, New York 140202. We certify that the field copy is a true copy of the Abbreviated New Drug Application herewith submitted.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at **(847) 317-8200** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

Lincy Michael

Lincy Michael
Regulatory Scientist

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1/29/98

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

January 28, 1998

ORIGINAL

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
Metro Park North II - HFD-600
7500 Standish Place, Rm. 150
Rockville, Maryland 20855-2773

NEW CORRESP
NC To FA Fax

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL -10 mL and 20 mL Vials
Manufacturing Site:Grand Island,NY

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application submitted July 29, 1996. Reference is also made to the telephone conversation between Ubrani Venkataram and Tim Ames (FDA) and Lincy Michael (Fujisawa USA, Inc.) on 1/27/98. We are responding to the items discussed during the telephone conversation.

As proposed by the FDA, the finished product release specifications and stability specifications for Acyclovir Sodium Injection are revised to include limits for Guanine (Attachment 1). The post approval stability commitments are also revised to incorporate test schedule for Guanine (Attachment 1). The test method for the quantitation of impurities in acyclovir sodium raw material and acyclovir sodium injection has been revised to include calculations for Guanine in the finished product (Attachment 2).

In compliance with 21 CFR §314.96(b), a true and complete copy of this amendment is being submitted to the Acting District Director, Buffalo District, Food and Drug Administration, 599 Delaware Ave., Buffalo NY 14202.

Should you have any questions concerning this application, please contact the undersigned at **(847) 317-8200** or Laurence R. Meyerson, Ph.D. at **(847) 317-8642**.

Sincerely,

/S/ [redacted]

Lincy Michael
Senior Regulatory Scientist

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Telephone Conversation Memorandum

ANDA: 74-930

DRUG: Acyclovir Sodium Injection, 50 mg/mL

FIRM: Fujisawa USA

PERSONS INVOLVED: Lincey Michael, Fujisawa
Tim Ames, FDA

PHONE NUMBER: 847-317-8200

DATE: 1/27/98

Called firm to request the addition of an impurity specification for guanine (b)(4)(CC) be added to the finish product release specs as well as the stability protocol for this product. I informed Lmichaels that since this was a (b)(4)(CC) well as a (b)(4)(CC) it was appropriate to be requesting these additional specs and that all other approved ANDAs have similar specifications. Lmichaels indicated she'd discuss these issues with her analytical dept. and then make the appropriate response.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD

/S/

cc: ANDA 74-930
Division file (1)
HFD-617/TAmes/PHONE.166
File: X:\new\firmsam\fujisawa\telecons\phone.166

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

ARCHIVAL

January 13, 1998

1/16/98
NEW CORRESP
To Fax

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
Metro Park North II - HFD-600
7500 Standish Place, Rm. 150
Rockville, Maryland 20855-2773

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL -10 mL and 20 mL Vials
Manufacturing Site: Grand Island, NY

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application submitted July 29, 1996. Reference is also made to the telephone conversation between Ubrani Venkataram, Norman Gregory and Tim Ames (FDA) and Lincy Michael (Fujisawa USA, Inc.) on 1/12/98. We are responding to the items discussed during the telephone conversation.

As proposed by the FDA, Fujisawa USA will pursue with an 18 months expiration dating for Acyclovir Sodium Injection. The post approval stability commitments are revised to incorporate the 18 month expiration date (Attachment 1). The finished product stability specifications are also revised to reflect the limits proposed by the FDA for the impurity peaks (Attachment 2).

In compliance with 21 CFR §314.96(b), a true and complete copy of this amendment is being provided to the Acting District Director, Buffalo District, Food and Drug Administration, 599 Delaware Ave., Buffalo NY 14202.

RECEIVED
JAN 14 1998
GENERIC DRUGS

Should you have any questions or require additional information concerning this application, please contact the undersigned at **(847) 317-8200** or Laurence R. Meyerson, Ph.D. at **(847) 317-8642**.

Sincerely,

/S/ [redacted]

Lincy Michael
Senior Regulatory Scientist

L:\WP60\COMPLETE\1998\01.108

Telephone Conversation Memorandum

ANDA: 74-930

DRUG: Acyclovir Sodium Injection, 50 mg/mL

FIRM: Fujisawa USA, Inc.

PERSONS INVOLVED: Lincy Michael, Fujisawa
Tim Ames, Norman Gregory, and Ubrani Venkataram, FDA

PHONE NUMBER: 847-317-8200

DATE: 1/12/98

Called firm to request establisment of stability specifications be set for the (b)(4)(CC) NGregory informed LMichaels that the finished product specs cited in the last amendment appeared to be acceptable but the firm needs to establish stability specification and recommended the following specs: (b)(4)(CC)

LMichael indicated the specs in the 12/22/97 submission were really in-process specs. UVenkataram indicated these were considered finished product release specs should be indicated as such. UVenkataram and NGregory indicated the firm needed to adopt the recommend stability specs (b)(4)(CC) (b)(4)(CC) and either adopt an 18 month expiry period, which would allow for the approval process to proceed, or provide CRT stability data for 24 months, to establish a 24 month expiry period. It also indicated that if the firm opted for an 18 month expiry period in order to obtain a 24 month expiry post approval, would require 3 lots of real time CRT data.

LMichael indicated she would discuss the proposals with her management and let us know how they would proceed and she would fax in her specification changes

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD
/S/

cc: ANDA 74-930
Division file (1)
HFD-617/TAmes/PHONE.164
File: X:\new\firmsam\fujisawa\telecons\phone.164

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

December 22, 1997

ARCHIVAL

NEW CORRESP

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration, HFD-600
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, Maryland 20855-2773

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL - 10 mL and 20 mL Vials
Manufacturing Site: Grand Island, NY

FACSIMILE AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application submitted July 29, 1996. As per the discussion in our teleconference of December 18, 1997 we are responding to the observations noted in the FDA facsimile dated December 10, 1997 and hereby submit this amendment. For ease of review, we have organized the FDA observations with the corresponding Fujisawa USA, Inc. responses in the order as delineated in the letter.

In compliance with 21 CFR §314.96(b), a true and complete copy of this amendment is being provided to the Acting District Director, Buffalo District, Food and Drug Administration, 599 Delaware Ave., Buffalo NY 14202.

Your prompt completion of the review of our ANDA application #74-930 for Acyclovir Sodium Injection is greatly appreciated.

Should you have any questions or require additional information concerning this application, please contact the undersigned at **(847) 317-8200** or Laurence R. Meyerson, Ph.D. at **(847) 317-8642.**

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist

RECEIVED
DEC 23 1997
GENERIC DRUGS

ARCHIVAL

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

October 31, 1997

NAI
11/6/97 NRC

NC

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
Metro Park North II - HFD-600
7500 Standish Place, Rm. 150
Rockville, Maryland 20855-2773

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL - 10 mL and 20 mL Vials
Manufacturing Site: Grand Island, NY

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application submitted July 29, 1996. Reference is also made to the telephone conversation between Ubrani Venkataram and Tim Ames (FDA) and Lincy Michael (Fujisawa USA, Inc.) on 10/23/97. We are responding to the items discussed during the telephone conversation.

In compliance with 21 CFR §314.96(b), a true and complete copy of this amendment is being provided to the Acting District Director, Buffalo District, Food and Drug Administration, 599 Delaware Ave., Buffalo NY 14202.

Should you have any questions or require additional information concerning this application, please contact the undersigned at **(847) 317-8200** or Laurence R. Meyerson, Ph.D. at **(847) 317-8642**.

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist

RECEIVED
NOV 3 1997
GENERIC DRUGS

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...USA, Inc.
...Three Parkway North
...15-2548
...217-8800 • Telefax (847) 317-7286

Fujisawa

...97

...Sporn, Director
...neric Drugs
...rug Evaluation and Research
...Drug Administration
...North II - HFD-600
...lish Place, Rm. 150
...Maryland 20855-2773

1/1/97

NEW CORRESP

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL - 10 mL and 20 mL Vials
Manufacturing Site: Grand Island, NY

TELEPHONE AMENDMENT

...Sporn:

...ce is made to our Abbreviated New Drug Application submitted July 29, 1996. Reference ...ade to the telephone conversation between Norman Gregory (FDA) and Lincy Michael ...a USA, Inc.) on 10/2/97. As discussed during the telephone conversation, we are ...ng revised copies [redacted]

...pliance with 21 CFR §314.96(b), a true and complete copy of this amendment is being ...d to the Acting District Director, Buffalo District, Food and Drug Administration, 599 ...re Ave., Buffalo NY 14202.

...you have any questions or require additional information concerning this application, ...contact the undersigned at **(847) 317-8200** or Laurence R. Meyerson, Ph.D. at **(847) 317-...**

...ncerely,

Lincy Michael
Senior Regulatory Scientist

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ARCHIVAL

Fujisawa

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-7286

AMENDMENT

N/AM

September 5, 1997

Mr. [illegible] Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration, HFD-600
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, Maryland 20855-2773

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL - 10 mL and 20 mL Vials
Manufacturing Site: Grand Island, NY

TELEPHONE AMENDMENT

BEST AVAILABLE COPY

Dear [illegible] Sporn:

[illegible] is made to our Abbreviated New Drug Application submitted July 29, 1996. [illegible] is also made to the attached facsimile dated August 28, 1997. We are responding [illegible]tions noted in the facsimile and hereby submit this telephone amendment. For [illegible]e have organized the FDA observations with the corresponding Fujisawa [illegible] in the order as delineated in the letter.

[illegible]R §314.96(b), a true and complete copy of this amendment is being pro[illegible] [illegible]t Director, Buffalo District, Food and Drug Administration, 599 De[illegible] [illegible] 14202.

Should you have [illegible]ns o[illegible]ire additional information concerning this application, please contact the u[illegible]ed at [illegible]17-8200 or Laurence R. Meyerson, Ph.D. at (847) 317-8642.

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist

RECEIVED
SEP 0 3 1997
GENERIC DRUGS

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FUJISAWA USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

July 18, 1997

NDA ORIG AMENDMENT

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration, HFD-600
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, Maryland 20855-2773

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL - 10 mL and 20 mL Vials
Manufacturing Site: Grand Island, NY

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application submitted July 29, 1996. Reference is also made to the attached facsimile dated July 2, 1997. We are responding to the observations noted in the facsimile and hereby submit this telephone amendment. For ease of review, we have organized the FDA observations with the corresponding Fujisawa USA, Inc. responses in the order as delineated in the letter.

In compliance with 21 CFR §314.96(b), a true and complete copy of this amendment is being provided to the Acting District Director, Buffalo District, Food and Drug Administration, 599 Delaware Ave., Buffalo NY 14202.

Should you have any questions or require additional information concerning this application, please contact the undersigned at **(847) 317-8200** or Laurence R. Meyerson, Ph.D. at **(847) 317-8642.**

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist

ARCHIVAL

sawa USA, Inc.
ay North Center, Three Parkway North
field, Illinois 60015-2548
(847) 317-8800 • Telefax (847) 317-7286

Fujisawa

NAI "Will respond" 7/14/97

NEW CORRES
NC

July 8, 1997

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150, HFD-600
Rockville, MD 20855-2773

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL
Manufacturing Site: Grand Island, NY

INTENT TO FILE AN AMENDMENT

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application that was submitted on 7/29/96 for the above mentioned drug product. Reference is also made to the facsimile dated July 2, 1997. In accordance with 21 CFR 314.120(a)(1), Fujisawa USA, Inc. is informing you of our **intent to file a telephone amendment** in response to this facsimile in the near future.

Should you require clarification or have any questions, please contact the undersigned at **(847) 317-8200** or Laurence R. Meyerson, Ph.D. at **(847) 317-8642**.

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist

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GENERIC DRUGS

ARCHIVAL

Fujisawa

Inc.
Three Parkway North
60015-2548
Telefax (847) 317-7286

NAI
"Will Respond"
4/29/97 NEW CORRESP
LC

Sporn, Director
Generic Drugs
Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150, HFD-600
Rockville, MD 20855-2773

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL
Manufacturing Site: Grand Island, NY

INTENT TO FILE AN AMENDMENT

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application that was submitted on 7/29/96 for the above mentioned drug product. Reference is also made to the not approvable letter dated April 18, 1997. In accordance with 21 CFR 314.120(a)(1), Fujisawa USA, Inc. is informing you of our **intent to file a minor amendment** in response to this not approvable letter in the near future.

Should you require clarification or have any questions, please contact the undersigned at **(847) 317-8200** or Laurence R. Meyerson, Ph.D. at **(847) 317-8642**.

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist

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RECEIVED
APR 2 8 1997
GENERIC DRUGS

ARCHIVAL

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

October 30, 1996

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 74-930
Acyclovir Sodium Injection
50 mg/mL-10 mL and 20 mL Vials

AMENDMENT TO UNAPPROVED ANDA

Dear Mr. Sporn:

Fujisawa USA, Inc. submits this amendment in response to a request from the Office of Generic Drugs (telephone communication from Harvey Greenberg on October 25, 1996).

This amendment contains a copy of the ANDA Suitability Petition that was approved for (b)(4)(CC) (b)(4)(CC) (Attachment A).

In compliance with 21 CFR 314.96(b), a true and complete copy of this amendment has been sent to Mr. E. Pitt Smith, District Director, Buffalo District, Food and Drug Administration, 599 Delaware Ave., Buffalo, New York 14202. We certify that the field copy is a true and complete copy of the amendment.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at **(847) 317-8200** or Laurence R. Meyerson, Ph.D. at **(847) 317-8642**.

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist