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Application Number 21-304

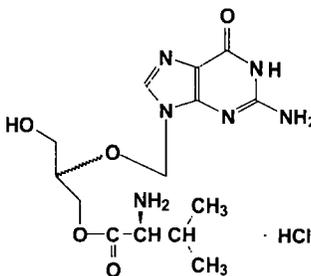
PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

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DIVISION NAME: Division of Antiviral Drug Products
HFD#: 530
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SPONSOR (OR AGENT): Syntex (U.S.A.) LLC
3401 Hillview Avenue
Palo Alto, CA 94304

MANUFACTURER OF DRUG SUBSTANCE: F. Hoffmann-La Roche Ltd.
Grenzacherstrasse 124
CH-4070 Basel, Switzerland

DRUG:
Code Name: Ro 107-9070-194
Generic Name: Valganciclovir HCl
Trade Name: VALCYTE™
Chemical Name: L-Valine, ester with 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine, monohydrochloride
CAS Registry Number: 175865-59-5
Molecular Formula: Molecular Weight: C₁₄H₂₂N₆O₅ HCl: 390.83
Structure:



RELEVANT INDS IND 48,106
DRUG CLASS: Nucleoside analog
INDICATION: Treatment of CMV retinitis in patients with AIDS
CLINICAL FORMULATION: The drug product, VALCYTE™ is contained in a tablet containing 450 mg as the free base. Inactive ingredients are microcrystalline

cellulose, povidone K-30, crospovidone and stearic acid

ROUTE OF ADMINISTRATION: Oral

INTRODUCTION:

Valganciclovir is a valine ester of ganciclovir that is rapidly hydrolyzed to parent drug after oral administration and can be considered a prodrug of ganciclovir. Shortly after administration of valganciclovir, most of the systemic exposure to an active moiety is due to ganciclovir. It is indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. The prodrug delivers an absolute bioavailability of approximately 60% that is an approximate ten-fold improvement over the currently approved oral ganciclovir formulation. The sponsor developed the present formulation as an improvement to the presently approved ganciclovir regimens. It should provide the potential to avoid the morbidity associated with intravenous ganciclovir induction and maintenance as well as a simpler oral regimen that might improve adherence to long term oral maintenance treatment.

Many of the studies already carried out on ganciclovir were relied upon for the assessment of the nonclinical evaluation of the valganciclovir's toxicologic profile. The following studies were carried out using valganciclovir: a battery of safety pharmacology studies, bridging three month toxicology studies in rats and dogs, a six month bridging toxicology study in mice, a primary irritation study in rabbits and a battery of genetic toxicology studies. The toxicities seen in the bridging studies and the genetic toxicology studies were similar to those seen with ganciclovir alone and most of the information in the label was taken from the existing ganciclovir label. The studies submitted to the NDA are sufficient for the assessment of the toxicological profile and the information placed into the label is a good assessment of the toxicities of valganciclovir.

Ganciclovir is a nucleoside analog, the monophosphate of which is capable of entering the growing DNA chain (and producing structural damage) so it is not surprising that it is a mutagen as well as a carcinogen. It is particularly toxic to the male and female reproductive system but it is not clear whether its toxicities to these systems stems from the fact that it is a nucleoside analog. Since valganciclovir is rapidly hydrolyzed to ganciclovir, it is reasonable to consider the toxicities of the one to be identical to those of the other.

NONCLINICAL SAFETY PHARMACOLOGY STUDIES

Study Summaries:

Effects of RS-79070-194 on gross behavior and symptomatology in male mice (Irwin Profile) (Study no. 53-M-95). RR AT6961 (P-180278). 1995

Effects of RS-79070-194 on responses to autonomic agents in anesthetized, instrumented dogs (Study no. 55-D-95). RR AT6965 (P-180280). 1995

Effects of RS-79070-194 on hemodynamic and cardiovascular parameters in anesthetized, instrumented dogs (Study no. 54D-95). RR AT6960 (P-180277). 1995

Effects of RS-79070-194 on intestinal meal progression in male rats (Study no. 51-R-95). RR AT6959 (P-180276). 1995

Effects of RS-79070-194 on urine volume and electrolyte output in male rats (Study no. 55-R-95). RR AT6964 (P-180279). 1995

Study Reviews

Effects of RS-79070-194 on gross behavior and symptomatology in male mice (Irwin Profile) (Study no. 55-M-95). RR AT6961 (P-180278). 1995.

Vol. 11; Pages: 61-125; **Conducting Laboratory:** Syntex Preclinical Research and Development, Preclinical Product Safety and Analysis

Date of Initiation: 2/16/1995; **GLP Compliance:** Yes (X); **Drug Lot:** #7090-127

Formulation: Aqueous vehicle and RS-79070 formulations contained sodium phosphate and sodium benzoate. The pH was adjusted to 3.3 with HCl or NaOH. The RS-79070 formulations contained 3, 30, or 100 mg/ml of RS-79070

This study was conducted to evaluate the effects of orally administered RS-79070 on gross behavior and the Irwin Profile in male mice.

Methods

Groups of six male mice (CrI:CD-1(ICR)BR VAF/Plus; 4 to 5 weeks old; body weight: 18 to 24 g) were administered single oral doses of 0, (vehicle), 15, 150, or 500 mg/kg of RS-79070 by gavage (dose volume: 5 ml/kg). Clinical observations and behavioral tests were conducted on mice according to procedures similar to those described by Irwin (Re: Irwin S. Gordon research conference on medicinal chemistry, 1959: 133. In: Turner RA, Screening Methods in Pharmacology. Academic Press, New York, 1965, pp 24-34). Core body temperature, behavioral changes including pinna reflex, cornea reflex, induced activity, analgesia, ataxia, orientation, grip strength, passivity, righting reflex, and muscle tone, were recorded before dosing, and 15 minutes after dosing.

Results

Increased activity with aggressive posturing and vocalization were seen in one animal at 150 mg/kg, which was not considered attributable to RS-79070 treatment. No other treatment-related clinical or gross behavioral changes were seen at any dose.

1008-Effects of RS-79070-194 on responses to autonomic agents in anesthetized, instrumented dogs (Study no. 55-D-95). RR AT6965 (P-180280). 1995

Vol. 11; Pages: 126-167; **Conducting Laboratory:** Syntex Preclinical Research and Development, Preclinical Product Safety and Analysis

Date of Initiation: 2/15/1995; **GLP Compliance:** Yes (X); **Drug Lot:** #7090-127

Formulation: Aqueous vehicle and RS-79070 formulations contained sodium phosphate and sodium benzoate. The pH was adjusted to 3.3 with HCl or NaOH. The RS-79070 formulations contained 3, 30, or 100 mg/ml of RS-79070

The study was conducted to evaluate the effects of RS-79070-194 (RS-79070) on responses to autonomic agents in anesthetized, instrumented dogs.

Methods

Beagle dogs were anesthetized with isoflurane gas and surgically instrumented in this study. Animals in the vehicle control group (1 animal/sex/group) and the 50-mg/kg group (2 animals/sex/group) were then intravenously administered norepinephrine (3 µg/kg), isoproterenol (0.3 µg/kg), and acetylcholine (10 µg/kg) with approximately 10 minutes between each dose, before dosing with the test article. ECG, the aortic blood pressure, and blood gas parameters, as well as the heart rate responses were monitored. Approximately thirty minutes after the administration of the autonomic agents, dogs were administered 0 (vehicle) or a single dose of 50 mg/kg RS-79070 via an intraduodenal cannula. The blood pressure was continuously recorded approximately 1, 2, and 3 hours after dosing with RS-79070.

Results

Responses to norepinephrine: No test article treatment-related changes were present in the mean aortic pressure increases between the control and drug treatment animals.

Responses to isoproterenol: No treatment-related differences between predose and postdose responses to isoproterenol were present in diastolic aortic pressure.

Responses to acetylcholine: No treatment-related differences between predose and postdose responses to acetylcholine were present in diastolic aortic pressure.

Comments

In this study, only blood pressure responses to autonomic agents were evaluated before dosing and approximately 1, 2, and 3 hours after dosing with RS-79070. No treatment related changes were present in responses to autonomic agents. Note that the Sponsor did not report the ECG and heart rate responses to autonomic agents before and after dosing with RS-79070.

Effects of RS-79070-194 on hemodynamic and cardiovascular parameters in anesthetized dogs (Study no. 54-D-95). RR AT6960 (P-180277). 1995

Vol. 12; Pages: 1-43; **Conducting Laboratory:** Syntex Preclinical Research and Development, Preclinical Product Safety and Analysis

Date of Initiation: 2/15/1995; **GLP Compliance:** Yes (X); **Drug Lot:** #7090-127

Formulation: Aqueous vehicle and RS-79070 formulations contained sodium phosphate and sodium benzoate. The pH was adjusted to 3.3 with HCl or NaOH. The RS-79070 formulations contained 3, 30, or 100 mg/ml of RS-79070

The study was conducted to evaluate the effects of RS-79070-194 (RS-79070) on hemodynamic and cardiovascular parameters in anesthetized, instrumented dogs.

Methods

Two groups of beagle dogs (age: 6-30 months; body weights: not specified) were administered single intraduodenal doses of 0 (vehicle) or 50 mg/kg of RS-79070 (Dose volume: 0.5 ml/kg). Animals in the vehicle control group (1 animal/sex/group) and the RS-79070-treated group (2 animals/sex/group) were surgically instrumented while anesthetized with sodium pentobarbital. Blood pressure, cardiac function, blood pH and blood gases, and ECG were evaluated before dosing and approximately 1, 2, and 3 hours after dosing.

Results

Hemodynamic parameters: No treatment-related effects were seen in blood pressure, cardiac function, blood pH and blood gases, and ECG.

Effects of RS-79070-194 on intestinal meal progression in male rats (Study no. 51-R-95). RR AT6959 (P-180276).1995

Vol. 12; Pages: 44-78; Conducting Laboratory: Syntex Preclinical Research and Development, Preclinical Product Safety and Analysis

Date of Initiation: 2/17/1995; **GLP Compliance:** Yes (X); **Drug Lot:** #7090-127
Formulation: Aqueous vehicle and RS-79070 formulations contained sodium phosphate and sodium benzoate. The pH was adjusted to 3.3 with HCl or NaOH. The RS-79070 formulations contained 3, 30, or 100 mg/ml of RS-79070

The study was conducted to evaluate the effects of RS-79070-194 (RS-79070) on intestine motility in male rats.

Methods

Four groups of rats (10/sex/group; Crl:CD®(SD)BR VAF/Plus; age: 7 weeks; body weights: 202-275 g) were administered single oral doses of 0 (vehicle), 15, 150, or 500 mg/kg of RS-79070 by gavage (Dose volume: 5 ml/kg). A charcoal test meal was given orally by gavage to each rat 10 minutes after administration of the test article. Animals were sacrificed approximately 90 minutes after administration of the test article. The length of the small intestine and the length that the test meal traveled within the small intestine were measured.

Results

No test article-related changes in charcoal mean progression was seen. The mean distance traveled by the charcoal test meal as a percentage of the total small intestine length was 89.4%, 89.9%, 84%, and 83.9% for the vehicle-control, 15-, 150-, and 500 mg/kg groups, respectively.

Comment

Administration of single oral doses of 15-, 150-, or 500 mg/kg of RS-79070 by gavage did not change the intestinal motility in rats. Note that no positive control and no female rats were included in this study.

Effect of RS-79070-194 on urine volume and electrolyte output in male rats (Study no. 55-R-95). RR AT6964 (P-180279). 1995

Vol. 12; Pages: 79-121; **Conducting Laboratory:** Syntex Preclinical Research and Development, Preclinical Product Safety and Analysis **Date of Initiation:** 2/14/1995; **GLP Compliance:** Yes (X); **Drug Lot:** #7090-127 **Formulation:** Aqueous vehicle and RS-79070 formulations contained sodium phosphate and sodium benzoate. The pH was adjusted to 3.3 with HCl or NaOH. The RS-79070 formulations contained 3, 30, or 100 mg/ml of RS-79070

The study was conducted to evaluate the effects of RS-79070-194 (RS-79070) on urine volume and electrolyte output in male rats.

Methods

Four groups of rats (10/sex/group; Crl:CD®(SD)BR VAF/Plus; age: 7 weeks; body weights: not specified) were administered single oral doses of 0 (vehicle), 15, 150, or 500 mg/kg of RS-79070 by gavage (Dose volume: 5 ml/kg). Saline (0.9% NaCl; 20 mL/kg) was administered by oral gavage to each rat 30 minutes after administration of the test article. Urine was collected from 0 to 5 hours and from 5 to 24 hours after dosing. Urine volume, sodium, potassium, and chloride were measured for both collecting periods.

Results

Urine volume: urine volume was increased in the 5- to 24- hour postdosing intervals in rats given 150 mg/kg and in both the 0- to 5-hour and 5- to 24-hour postdosing intervals in rats at 500 mg/kg. No test article-related changes in urine volume were seen in rats at 15 mg/kg.

Urine electrolyte output: urine potassium output was increased in the 0- to 5- hour postdosing intervals in rats at 150 mg/kg or greater. Urine sodium output was increased in the 0- to 5- hour postdosing intervals and decreased in the 5- to 24-hour postdosing interval for rats at 500 mg/kg. Chloride output was increased in the 5- to 24-hour postdosing interval for rats at 500 mg/kg. No test article-related changes in urine electrolyte output were seen in rats at 15 mg/kg. The results are shown in Table 1.

Comment

Administration of single oral doses of 150-, or 500 mg/kg of RS-79070 by gavage increased urine volume and electrolyte output (sodium, potassium, and chloride) in rats. Note that no positive control and no female rats were included in this study.

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Table 1. Summary of urine volume and Electrolyte output

Variable	Dose mg/kg	No of rats	Mean urine volume or electrolyte output (0-5 hours)	Mean urine volume and electrolyte output (5-24 hours)
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Urine volume (mL)	0	10	2.7	9.6
	15	10	3.2	9.7
	150	10	4.7	12.7*
	500	10	6.6*	21.4*
Sodium (MEQx10⁻³)	0	10	240	1539
	15	10	272	1501
	150	10	427	1354
	500	10	731*	1142*
Potassium (MEQ x10⁻³)	0	10	77	2715
	15	10	111	2795
	150	10	142*	2797
	500	10	125	2660
Chloride (MEQ x10⁻³)	0	10	274	2312
	15	10	290	2338
	150	10	525	2383
	500	10	855*	2366

* P < 0.05

Comment

Administration of single oral doses of 150-, or 500 mg/kg of RS-79070 by gavage increased urine volume and electrolyte output (sodium, potassium, and chloride) in rats. Note that no positive control and no female rats were included in this study.

NONCLINICAL TOXICOLOGY STUDIES**Study Summary:**

Acute oral toxicity study of RS-79070-194 in mice (Study no. 13- M-95). RR AT6884 (P-180268). 1995

Acute oral toxicity study of RS-79070-194 in beagle dogs (Study no.12-D-95). RR AT6883 (P-180268). 1995

RS-79070-194: a 14-day intravenous toxicity and toxicokinetic study in the mouse (Study no. HRE/36/96). Revised Report – Supercedes Report No. W-142870, 18 February 1998; RR W-1000523, 2000

One-month oral toxicity study of RS-79070-194 in mice. RR AT6952 (P-180270). 1995

RS-79070-194: A 26 week oral toxicity and toxicokinetic study in the mouse (26 week data: Study no. HRE/25/97/rK). RR W142872. 1998

RS-79070-194: A 13-week oral toxicity and toxicokinetic study in the rat (study no. HRE/37/97). RR W-143160. 1999

Three-month oral toxicity study in beagle dogs with ganciclovir prodrug RS-79070-194, followed by a 9-week recovery period (GLP study 049P96). RR B-164596. 1996

Ro 107-9070:194: Primary Skin Irritation Study in Rabbits. Study No. 607D98. RR B170-570.2000

L5178Y/TK mouse lymphoma mutagenesis assay (study no. 912Y-95). RR AM456. 1995

Salmonella/Escherichia coli preincubation mutagenicity assay (study no. 911- Y-95)

Mutagenicity test on RS-79070-194 in an in vivo mouse micronucleus assay (study no. 913-M-95). RR AM458. 1995

Study Review:

Acute oral toxicity study of RS-79070-194 in mice (Study no.13-M-95). RR AT6884 (P-180268). 1995

Vol. 13; Pages: 1-60; **Conducting Laboratory:** Syntex Preclinical Research and Development, Preclinical Product Safety and Analysis

Date of Initiation: 8/23/1994; **GLP Compliance:** Yes (X); **Drug Lot:** #79070-194

Formulation: Aqueous vehicle and RS-79070 formulations contained sodium phosphate and sodium benzoate. The pH was adjusted to 3.3 with HCl or NaOH. The RS-79070 formulations contained 100 mg/ml of RS-79070

Methods

RS-79070-194 was evaluated for acute oral toxicity in male and female mice (CrI:CFW®(SW)BR VAF/Plus; 8-week old, Charles River, Portage, MI; body weight: 21-31 g for males and 18-25 g for females). A single dose of RS-79070-194 was administered to groups of 5 male and 5 female mice in single doses of 0 (vehicle), 1000, or 2000 mg/kg, followed by 14 days of observation (dose volume: 10 -20 ml/kg). Mice were weighed before dosing, on the day of treatment and 2, 7, and 14 days postdosing. Food consumption was recorded weekly. Mice that died prematurely were necropsied. Surviving mice were necropsied at the end of the 14-day observation period.

Results

One mouse was found dead on the day after dosing. The cause of the death was undetermined. No other clinical signs were seen in mice at all doses. No treatment-related body weight changes and pathologic changes were seen. The NOEL for this study was 2000 mg/kg.

Acute oral toxicity study of RS-79070-194 in beagle dogs (Study no.12-D-95). RR AT6883 (P-180268). 1995

Vol. 13; Pages: 60-122; **Conducting Laboratory:** Syntex Preclinical Research and Development, Preclinical Product Safety and Analysis

Date of Initiation: 8/23/1994; **GLP Compliance:** Yes (X); **Drug Lot:** #79070-194

Formulation: Aqueous vehicle and RS-79070 formulations contained sodium phosphate and

sodium benzoate. The pH was adjusted to 3.3 with HCl or NaOH. The RS-79070 formulations contained 100 mg/ml of RS-79070

Methods

RS-79070-194 was evaluated for acute oral toxicity in male and female beagle dogs (age: 12 to 23-months old; body weight: 9.6-12.7 kg for males and 8.6-11.5 kg for females). A single dose of RS-79070-194 was administered to groups of one male and one female dog in single doses of 0 (vehicle), 500, or 1000 mg/kg by oral gavage, followed by 14 days of observation (dose volume: 10 -20 ml/kg). Mice were weighed before dosing, on the day of treatment and 2, 7, and 14 days postdosing. Food consumption was recorded weekly. Blood samples for clinical pathology analyses were collected once before dosing, on the day after dosing, and 7 and 14 days postdosing. Animals were necropsied at the end of the 14-day observation period.

Results

No deaths were seen during the study period. Emesis was seen within 3-hours postdosing in all dogs given RS-79070. No other clinical signs were seen in dogs at any dose. No treatment-related body weight changes were seen at any dose. At one week postdosing, decreases in leukocyte and neutrophil counts were seen in dogs at 500 mg/kg or greater. The blood urea nitrogen level was increased in a male dog at 1000 mg/kg on day 1 postdosing, which returned to the predose range at the end of the study period. Decreases in the platelet counts were also seen for dogs at 500 mg/kg or greater. No other treatment-related gross pathologic changes were seen. Mottled-white thyroid due to multifocal mineralization of thyroid follicles and interdigital cysts of the forefeet with ulceration of the skin were seen in one dog at 1000 mg/kg. The NOEL for this study was less than 500 mg/kg.

RS-79070-194: a 14-day intravenous toxicity and toxicokinetic study in the mouse (Study no. HRE/36/96). Revised Report – Supercedes Report No. W-142870, 18 February 1998; RR W-1000523, 2000

Vol. 14; Pages: 1-333; Conducting Laboratory: _____

Sponsor: Pre-clinical Drug Safety, Drug Metabolism and Kinetics, Roche Discovery Welwyn, Broadwater Road, Wylwyn Garden City, Herts, AL7 3AY **Date of Initiation:** 8/21/1996; **GLP Compliance:** Yes (X); **Drug Lot:** #1487201; 1487051 **Formulation:** Aqueous vehicle and RS-79070 formulations contained sodium phosphate and sodium benzoate. The pH was adjusted to 3.3 with HCl or NaOH. The RS-79070 formulations contained 100 mg/ml of RS-79070

Methods

Groups of Ctrl: CD-1 (ICR) BR mice (10/sex/group) (age: about 6 weeks old, 21-34g; Charles River, Portage, MI) were intravenously administered with RS-79070-194 at doses of 0 (vehicle), 20, or 100 mg/kg/day for 14 consecutive days (dose volume: 10 ml/kg/day for animals at 20 mg/kg/day and 5 ml/kg for those dosed at 10 and 100 mg/kg/day). Mice were observed daily during the treatment period for survival and clinical signs. Food consumption was measured once pretreatment and weekly during the treatment period. Body weights were recorded at baseline, and on days 4, 8, and 11 of treatment, and at study termination. Hematology and clinical

chemistry were evaluated during the 2nd week of treatment (note that urinalysis was not performed in this study). Ophthalmoscopy was performed on all animals before the treatment, and again on animals of the control and high dose group only during the week 2 of treatment. All animals were subjected to a gross necropsy, and external body features and internal organs were carefully examined and any alterations or gross lesions were recorded. Wet tissue weights were obtained from the following organs: adrenals, brain, epididymides, heart, kidneys, liver, gall bladder, lungs, ovaries, pituitary, prostate, spleen, testes, thymus and uterus. The following tissues were collected and examined histologically by a pathologist (Addendum 2).

Results

Clinical signs and mortality. No test article-related mortality and clinical signs were seen at any dose. However, physical damage at the injection site was seen in mice where a dose volume of 10 mg/kg/day was used.

Body weights and food consumption. No test article treatment -related changes in mean body weights and body weight gain were seen in mice at any dose. No test article treatment-related changes in feed consumption were seen at any dose level.

Ophthalmology. No test article treatment-related ophthalmologic changes in were seen in mice at any dose level.

Hematology. No test article treatment-related changes in hematological parameters were seen in mice at any dose.

Clinical Chemistry. Increases in blood urea nitrogen (BUN: 48.9 mg %; reference range: 18.6-28.2 mg %) was seen in one male mouse at 100 mg/kg/day. Increases in serum calcium, inorganic phosphate, and potassium levels were seen in one male at 100 mg/kg/day, which was associated with minimal renal cortical tubular degeneration and generation. No other test article treatment-related changes in clinical chemistry were seen in mice at any dose. Note that urinalysis was not performed in this study.

Histopathology. No test article treatment-related organ weight and macroscopic findings were seen in mice at any dose at necropsy. Renal cortical tubular degeneration and regeneration were seen in mice at 20 mg/kg/day or greater. Partial degeneration of the germinal epithelium was seen in all males at 20 mg/kg/day. Acinar degeneration in the preputial or clitoral glands was seen in males and females at 100 mg/kg/day, respectively. The clitoral changes were also seen in females at 20 mg/kg/day.

Comment

Note that no histopathological findings were reported in the Sponsor's original report (GCR W-142870). However, the re-evaluation of the histopathological findings following a review of the study by the Sponsor (Re: Report Amendment dated 18th February 1998) identified histopathological changes in the kidneys, testes, preputial glands and clitoral glands at 20 mg/kg/day or greater. The Sponsor, therefore, substantially revised the original report and gave a new Report number, GCR W-1000523.

Comment

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volume throughout the study. Ophthalmoscopy was carried out on day one in each animal and at the end of treatment or recovery. Samples for clinical chemistry, urinalysis and hematology evaluations were collected at the end of treatment or recovery.

At the end of dosing, all animals were submitted to a complete necropsy including gross and histopathologic evaluations. The tissues weighed and those submitted to histologic examination are listed in the Histology Table in Addendum 1. Tissues from the control and high dose and selected tissues from the intermediate doses were examined.

Results

Three males and three female mice at the high dose died during the study and mice at the high dose were pale, inactive, wasting and had rough coats. Five were found dead and one was killed in extremis. Cause of death was considered to be because of decreased bone marrow cellularity. There were some decreases in body weights at the high dose in both males and females but body weights returned to normal after the recovery period. Mice at the high dose had decreased food intake during the first week only. At the end of the treatment period, mice at the high dose exhibited pale eyes, indicating anemia. The pale eyes were not seen at the end of the recovery period. Red blood cell parameters were affected in both males and females at the high dose.

Lower erythrocyte counts, as well as hemoglobin and hematocrit measurements were significantly lower at the end of the treatment period and only partially resolved at the end of the recovery period. There were general rises in MCV, MCH and MCHC at the high dose, especially in the males and remained higher in males and females at the end of the recovery period.

Eosinophil counts were reduced and platelet counts were increased in males and females at the end of the dosing period but returned to normal at the end of recovery. There were increases at the high dose in males and females in blood urea nitrogen levels at the end of dosing but these, in general, returned to normal after recovery.

At the end of dosing, testes weights were lower at all doses relative to the controls and remained lower at the end of the recovery period. Uterus (females) and thymus (males and females) weights were lower at the high dose at the end of dosing and the uterus weights remained lower after recovery.

Testicular tubular atrophy and thymus gland lymphoid atrophy were present at all doses. At the two higher doses, lymph node, preputial gland and renal tubular atrophy (as well as necrosis in the renal tubules) were seen. Decreased numbers of epididymal spermatozoa were seen at the two higher doses. At the high dose, decreased bone marrow cellularity affecting both the erythroid and myeloid series, small intestinal crypt and large intestinal gland necrosis, and splenic lymphoid, ovarian and uterine atrophy were recorded.

At the end of the recovery period, males at the three highest doses still had testicular tubular atrophy and decreased numbers of epididymal spermatozoa. Mice administered the two high doses had renal tubular atrophy, dilation and necrosis.

Toxicology summary: The major toxicological effects were seen in the male reproductive system with some effects on other systems such as bone marrow, renal, intestinal and female reproductive organs.

Toxicology conclusions: The effects on the male reproduction system are toxicities that will be placed into the label.

RS-79070-194: A 26 week oral toxicity and toxicokinetic study in the mouse (26 week data: Study no. HRE/25/97/TK). RR W142872. 1998, Volume 1.18-1.19 inclusive, Conducting

laboratory and location: _____, Date of study initiation: April 24, 1996, GLP compliance: U.K. GLP compliant, QA report: yes, Drug, lot 30349-P100, Formulation/vehicle: phosphate buffer

Methods

Four groups of Crl:CD-1 (ICR) BR strain (VAF+) mice comprising 30 males and 30 females per group were dosed by gavage at dose levels of 0 (vehicle control), 1, 10 or 100 mg/kg/day. The animals were 5-6 weeks at the beginning of dosing and weighed 21-34 g. The dosing volume was 5 ml/kg and the animals were dosed once a day for 26 weeks. Of these animals, ten per group were allowed a recovery period of four weeks. In an additional arm of the study, forty animals per dose group (no control) were dosed identically and used for a toxicokinetic study. Clinical signs, including mortality were recorded daily. Body weights were recorded on day one and weekly after that. Food consumption was recorded weekly and used to adjust the dosing volume throughout the study. Ophthalmoscopy was carried out on day one in the control and high dose group and on week 13 and 25 of treatment. Samples for clinical chemistry and hematology evaluations were carried out on 20 animals per group (10 for chemistry and 10 for hematology) during week 13 and 26 of treatment. Toxicokinetic evaluations were carried out on day one and weeks 4, 13, and 26 of dosing. On day one, three animals per dose per group were bled at 15 minutes, 30 minutes, five hours and 24 hours post dosing. The animals were discarded. On weeks 4, 13 or 26, six animals per group were bled at the same schedule as above and discarded.

At the end of dosing, all animals were submitted to a complete necropsy including gross and histopathologic evaluations. The tissues weighed and those submitted to histologic examination are listed in the Histology Table in Addendum I.

Results

The toxicity of major importance to labeling for this drug is toxicity to male reproduction. Low testes weights were observed at all doses and low epididymal weights at the two higher doses. After the recovery period, only the low testes weights reverted to normal. At the intermediate and high dose there was marked to severe atrophy of the testicular seminiferous epithelium in most of the males. Toxicity was also found in the Leydig cells with vacuolation of Sertoli cells accompanied with severe oligospermia in the epididymides in the majority of the males. Even after the recovery period, the severe oligospermia in the epididymides remained. Minimal to slight hypertrophy/hyperplasia of Leydig cells with vacuolation of Sertoli cells remained upon recovery with some lessening of the effect at the intermediate dose. The finding of oligospermia and possible effects on fertility will be placed into the label.

There were some sporadic deaths at all doses related to blood collection. At the high dose, there were a number of deaths (three males and four females) that the sponsor did not consider a result of treatment but there was no evidence that the deaths were not related to treatment.

There was a statistically significant decrease in RBC levels in the males that was still slightly reduced after the recovery phase. Small, but statistically significant recoverable decreases in hemoglobin levels and packed cell volume was also seen in the males. All the above blood changes were seen at 100 mg/kg/day dose group.

Also seen in the study was preputial gland inflammation in males and salivary glands in females. In carcinogenicity studies carried out on ganciclovir, tumors of the preputial gland in males were reported.

In the toxicokinetics studies, the levels of ganciclovir as well as the parent compound (RS-79070-194) were evaluated by an ~~_____~~ method. The limit of detection was ~~_____~~. Table 2 shows the pharmacokinetic parameters of ganciclovir in this study.

Treatment Mg/kg	Cmax (µg/ml)			Tmax (Hr)			AUC _{0-24h} (mg.hr/liter)		
	Day 1	Day 28	Week 26	Day 1	Day 28	Week 26	Day 1	Day 28	Week 26
1	0.28	0.23	0.25	0.5	0.5	0.5	0.78	0.67	0.85
10	2.65	2.83	2.45	0.5	0.5	0.5	6.72	7.17	6.35
100	25.53	28.63	22.28	0.5	0.5	0.5	64.38	72.44	59.51

Toxicology summary: The major toxicological effects were seen in the male reproductive system with some effects on red blood cell parameters.

Toxicology conclusions: The finding of oligospermia and the possible effects of the drug on human fertility will be placed into the label.

RS-79070-194: A 13-week oral toxicity and toxicokinetic study in the rat (study no. HRE/37/97). RR W-143160. 1999, Research Report W-143160, Volume 1.20-21 inclusive, Conducting laboratory and location: _____

GLP compliance:
U.K. GLP compliant, QA report: yes, Study start date, October 3, 1997, Drug, Lot 30349-P100, Formulation/vehicle: water

The purpose of this study was to determine the proper dosing MTD for a two-year carcinogenicity study.

Methods

Ten male and ten female HsdBrl: (Wistar Hannover) rats (males weighing 114-143 g and females, 99-130g) were dosed with 2, 20 or 200 mg/kg/day of RS-79070-194 (volume 10 ml/kg) for 13 weeks. Separate groups of eight males and eight females were dosed identically for a toxicokinetic study. Clinical signs, including mortality were recorded daily. Body weights were recorded on day -7, one and weekly after that. Food consumption was recorded weekly and used to adjust the dosing volume throughout the study. Ophthalmoscopy was carried out on day one on all animals and in the control and high dose group and on week 12 of treatment. Samples for clinical chemistry and hematology evaluations were carried out on week 4 and 13 of treatment. Toxicokinetic evaluations were carried out on day one and weeks 4 and 13 of dosing at 15 minutes, and at 4 and 24 hours of dosing.

At the end of dosing, all animals were submitted to a complete necropsy including gross and histopathologic evaluations. The tissues weighed and those submitted to histologic examination are listed in the Histology Table in Addendum 1.

Results

No deaths and no clinical signs related to treatment were recorded. There was a significant loss in body weight gain at the end of 13 weeks in animals at the high dose group. This came to 83% in males and 90% for females compared with controls. Females at the intermediate dose only

recovery period of nine weeks. Clinical symptoms were recorded daily and body weights were recorded on day one and weekly thereafter. Food consumption was recorded weekly and used to adjust the dosing volume throughout the study. Ophthalmoscopy was carried out on day one in all animals and on week 14 and 22 of treatment. Samples for clinical chemistry were collected on days 26, 58 and 89, and on recovery animals, on day 159. Hematology evaluations were carried out on days 16, 26, 40, 58, 68 and 89 and on recovery animals on days 124 and 159. Additional blood samples were collected on days 20 and 35 from mid and high dose animals to further investigate the development of hematological parameters. Toxicokinetic evaluations on each dog were carried out on day 0, day 34 and day 91 just before dosing and at 0.5, 1, 2, 5 and 24 hours following dosing. Plasma concentrations of ganciclovir and RS-79070-194 were determined by a ~~method~~ method.

At termination of the study, a bone marrow differential was carried out on all animals and sperm taken from the left ductus epididymidis of all males (including recovery animals but excepting animals with aspermia) were examined for the number of immobile sperm. Changes in the sperm velocity were noted. All animals were submitted to a complete necropsy including gross and histopathologic evaluations. The tissues weighed and those submitted to histologic examination are listed in the Histology Table in Addendum I.

Results:

One female animal dosed at 20 mg/kg/day was sacrificed in moribund condition on day 19 with a body weight loss of approximately 20% and severe leukopenia and was replaced on day 20. Histopathologic evaluation showed a respiratory infection that was worsened by treatment. There were no additional deaths during the study.

The most prominent clinical symptoms seen in the study was significant weight loss and poor condition in the females dosed at 20 mg/kg/day and in two of the females dosed at 2 mg/kg/day. Upon decrease of the high dose to 10 mg/kg/day on day 26, little effect on weight was seen for the remainder of the study.

White blood cell counts were decreased in the high dose dogs (when dosing was carried out at 10 mg/kg/day as well as at 20 mg/kg/day) throughout the dosing period but returned to normal during the recovery period. In the high dose animals, there was also a mild decrease in platelet counts during the course of the treatment. This returned to normal during the recovery phase of the study.

Aspermia was noted in the epididymides in all males dosed with 2 mg/kg/day or higher even after the recovery period. At the lowest dose, there was a trend towards immobile sperm and in one animal there was aspermia at the end of treatment. At the end of the recovery period, the sperm had returned to normal at the lower dose.

In the testes, severe tubular atrophy was seen in all males treated at the high dose and marked to slight degeneration of the tubules was observed in all males dosed with 2 mg/kg/day.

Additionally, moderate vacuolation of the seminiferous epithelium and slight interstitial cell hypoplasia was observed at all doses. One low-dose animal presented with the lesions seen in the intermediate and high dose groups. The lesions seen in the testes correlated with lowered testicular weight.

In the epididymides, aspermia and some vacuolation of the ducts were recorded at the two higher doses. One animal at the low dose had slight oligospermia and some cellular debris in the epididymides. After the recovery period, the lesions at the low dose group were shown to be reversible. However, even though there was some evidence of reversibility in the two higher dose groups (marked tubular regeneration in the testes), oligospermia was still observed in the epididymides.

There was moderate to marked thymic cortical atrophy in the high dose animals and slight effects at the intermediate dose group. After the end of the recovery period, minimal to moderate cortical atrophy was still present.

In the toxicokinetics studies, the levels of ganciclovir as well as the parent compound (RS-79070-194) were evaluated by an ~~method~~ method. The limit of detection was ~~_____~~ Table 4 shows the pharmacokinetic parameters of ganciclovir in this study.

	Ester	Ester	Ester	Ganciclovir	Ganciclovir	Ganciclovir
Treatment Mg/kg·d	C _{ss} min µg/ml	C _{ss} max µg/ml	AUC _{0-τ} Mg·h/l	C _{ss} min µg/ml	C _{ss} max µg/ml	AUC _{0-τ} Mg·h/l
0.2 mg/kg/d	<0.04	<0.04	-	<0.04	0.09	1.20
2.0 mg/kg/d	0.041	0.083	<0.10	<0.04	1.09	8.42
10 mg/kg/d	0.061	0.36	0.34	<0.04	5.88	39.02
20 mg/kg/d	0.95	1.00	0.71	<0.04	12.267	65.08

Toxicology summary: The major toxicological effects were seen in the male reproductive system with some effects on white blood cells, platelets and thymus.

Toxicology conclusions: The finding of oligospermia and the possible effects on human fertility will be placed into the label. Mention will be made in the label that the effects elicited by valganciclovir occurred in mice rats and dogs.

Ro 107-9070/194: Primary Skin Irritation Study in Rabbits. Study No. 607D98. RR B170-570.2000, (Study no. 717772). 2000, Volume 1.26 pp 133-153, Conducting Laboratory: ~~_____~~, Date of study initiation: January 12, 1999, GLP compliance: OECD compliant, QA report: yes, Drug, lots 356-103, Formulation/vehicle: water

The primary skin irritation test was carried out on three young adult New Zealand white rabbits (two females and one male). In the study, the fur on the left flank was shaved and 0.5 g of test article was applied to an area of 6 cm², after which it was covered with a semi-occlusive dressing for four hours. After removal of the dressing, the skin was evaluated for erythema, eschar and edema at 1, 24, 48 and 72 hours.

Dermal exposure to RO 107-9070/194 caused no signs of irritation.

L5178Y/TK mouse lymphoma mutagenesis assay (study no. 912Y-95). RR AM456. 1995

Volume # 1.26, page 5, Completion date, March 15, 1995, Performing Laboratory, ~~_____~~ Sponsor Syntex Research, Palo Alto, CA 94303, Test Article and (Drug lot), RS-79070-194 (7090-127), GLP, yes

L5178Y/TK cells were tested for four hours for mutagenicity in the presence of solvent and nine concentrations of test article ranging from ~~_____~~ in the presence and absence of S-9 prepared from Araclor-1254 treated Sprague Dawley rats. In the non-activated study, the test

article was positive at doses of 2000 µg/ml and above. In the activated arm of the study, the test article was positive at concentrations of 250 and 500 µg/ml.

Salmonella/Escherichia coli preincubation mutagenicity assay (study no. 911- Y-95) 1995

Volume # 1.26, page 40, Completion date, February 6, 1995, Performing Laboratory, ~~_____~~ Sponsor Syntex Research, Palo Alto, CA 94303, Test Article and (Drug lot), RS-79070-194 (7090-127), GLP, yes

A Salmonella and E. coli mutagenicity assay was carried out on test article in the presence and absence of S-9 prepared from Araclor-1254 treated Sprague Dawley rats. The tester strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 and WP2 uvr A strains were used in the assay. The assay was carried out using the preincubation method.

A dose range-finding study was carried out with the maximum dose tested being 5000 µg/plate, the dose being delivered to the assay as a clear solution in water. At the highest dose, there was no precipitate or toxicity and based on the results, the highest dose delivered to the test system was 5000µg per plate.

In the mutagenicity assay, no positive responses were observed between 100 and 5000 µg/plate in the presence or absence of an S-9 activation system. Positive controls elicited a positive response on the presence and absence of activation.

Mutagenicity test on RS-79070-194 in an in vivo mouse micronucleus assay (study no. 913-M-95). RR AM458. 1995

Volume # 1.26, page 93, Completion date, January 13, 1995, Performing laboratory, ~~_____~~ Sponsor Syntex Research, Palo Alto, CA 94303, Test Article and (Drug lot), RS-79070-194 (1131661), GLP, yes

Five male (weight 29.7-38.1g) and five female (weight 21.8-28.9g) CD-1 (ICR) strain mice per group were administered RS-79070-194 by gavage at 60, 300 or 1500 mg/kg (dose volumes 20, 10 and 15 ml/kg). A separate group of males and females were administered deionized water (control) and an additional group of males and females were administered cyclophosphamid at 80 mg/kg (dose volume 20 ml/kg). The animals were killed at 24, 48 or 72 hours (the positive control animals were killed at 24 hours), the marrow of both tibiae was removed and processed to be stained on slides by May-Grunwald solution followed by Giemsa stain. The slides were coded and scored for micronuclei and the polychromatic (PCE) to normochromatic (NCE) cell ratio. One thousand PCEs were scored.

At the 1500 mg/kg dose, RS-79070-194 induced significant increases in micronuclei in bone marrow PCEs in females and at 48 hours dosing in males and females. The positive control gave the expected result. Thus, the test article was considered to be positive in the bone marrow micronucleus test.

NONCLINICAL PHARMACOKINETIC STUDY

Study Summary:

In vitro evaluation of the metabolism of the ester prodrug valganciclovir, in man, mouse and dog. Research Report W-143167. 1999

Study Review:

In vitro evaluation of the metabolism of the ester prodrug valganciclovir, in man, mouse and dog. Research Report W-143167. 1999

Volume # 1.30, page 78-104, Start date, July 14, 1998, Performing Laboratory, Roche Discovery Welwyn, Hertfordshire, U.K., Test Article and (Drug lot), RS-79070-194 (1654661), GLP, no

The objective of this study was to determine the tissue location and the rate of hydrolysis of valganciclovir to ganciclovir in man, dog and mouse liver fractions. In the presence of liver S9 fractions from human, mouse and dog, valganciclovir was hydrolyzed to ganciclovir most rapidly by human liver S9. Mouse S9 hydrolyzed valganciclovir somewhat more rapidly than dog S9. On the other hand, mouse blood was more efficient than dog or human in carrying out the hydrolysis. No metabolites, other than ganciclovir, were detected in the studies.

Toxicology Summary:

The toxicities to the target organs and systems are described below.

Reproductive Toxicity

In general, toxicities to the sperm and testes were seen in the bridging studies carried out on valganciclovir. The general reproductive toxicology battery was carried out on ganciclovir and it is the results of the latter studies that have supplied the data that have been placed into the label (although the toxicity to sperm upon the administration of valganciclovir in mice, rats and dogs has also been placed into the label). The following toxicities have been seen in the above studies. Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryoletality in female mice following intravenous doses. Ganciclovir also caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg. Valganciclovir caused similar effects on spermatogenesis in mice, rats, and dogs. It is considered likely that ganciclovir (and valganciclovir) could cause inhibition of human spermatogenesis.

Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (2x the human exposure based on AUC comparisons), respectively. Effects observed in rabbits included: fetal growth retardation, embryoletality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryoletality.

Daily intravenous doses of 90 mg/kg administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach. The drug exposure in mice as estimated by the AUC was approximately 1.7x the human AUC.

Genetic Toxicity

Valganciclovir increased mutations in mouse lymphoma cells and was positive in the mouse micronucleus assay. Valganciclovir was not mutagenic in the Ames Salmonella assay. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro and was also active in the mouse micronucleus assay. Ganciclovir was not mutagenic in the Ames Salmonella assay. The similarity in the results of the genetic toxicity studies on ganciclovir and valganciclovir are convincing in the argument that carcinogenicity studies on ganciclovir will mimic the outcome of the same studies using valganciclovir as the test article.

Carcinogenicity

Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day (approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following the recommended intravenous dose of 5 mg/kg, based on area under the plasma concentration curve [AUC] comparisons). At the dose of 1000 mg/kg/day there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the dose of 20 mg/kg/day, a slightly increased incidence of tumors was noted in the preputial and Harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (estimated as 0.01x the human dose based on AUC comparison). Ganciclovir (and valganciclovir) should be considered a potential carcinogen in humans.

Hematologic Toxicity

Hematologic toxicities were seen in the mouse and dog studies and were similar to those seen in the clinic and placed into the black box warning. In the mouse, decreased bone marrow cellularity was noted. Red blood cell parameters were affected in the mouse with the statement that the eyes were particularly light (which was a clinical sign of anemia). In the dog, decreases in white blood cell parameters and decreases in platelet counts were also noted.

Kidney

Renal tubular degeneration and necrosis was seen in the mouse.

Intestines

Small and large intestinal necrosis was seen in the mouse.

Addendum list:

1. Histopathology inventory in mouse, rat and dog studies.
2. Histopathology inventory in 14 day i.v. mouse study.

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ADDENDUM 1: Histopathology Inventory for NDA # 21-087.ori

Study	26 week	26 week	13 week	One month		
Species	Mouse	Dog	Rat	Mouse		
Adrenals	X*	X*	*	X		
Aorta	X	X		X		
BoneMarrow smear	X	X	X	X		
Bone	X	X	X	X		
Brain	X*	X*	*	X*		
Cecum	X	X				
Cervix	X			X		
Colon	X	X	X	X		
Duodenum	X	X		X		
Epididymis	X*	X	X	X		
Esophagus	X	X		X		
Eye	X	X		X		
Fallopian tube						
Gall bladder	X	X		X		
Gross lesions	X	X	X	X		
Harderian gland				X		
Heart	X*	X*	*	X*		
Tonsils		X				
Ileum	X	X	X			
Injection site						
Jejunum	X	X				
Kidneys	X*	X*	X*	X*		
Lachrymal gland						
Larynx						
Liver	X*	X*	X*	X*		
Lungs	X*	X	X*	X		
Lymph nodes mediastinal		X				
Lymph nodes submandibular	X					
Lymph nodes, mesenteric	X	X	X	X		
Mammary Gland	X	X		X		
Nasal cavity						
Optic nerves						
Ovaries	X*	X*	X*	X		
Pancreas	X	X		X		
Parathyroid	X	X		X		
Peripheral nerve		X				
Pharynx						
Pituitary	X*	X	X*	X		

Prostate	X*	X	X*	X*		
Rectum	X	X				
Salivary gland	X	X	*	X		
Sciatic nerve	X	X		X		
Seminal vesicles	X	X	X*	X*		
Skeletal muscle	X	X		X		
Skin	X	X		X		
Spinal cord	X	X		X		
Spleen	X*	X	X*	X*		
Sternum	X	X	X	X		
Stomach	X	X		X		
Testes	X*	X*	X*	X*		
Thymus	X*	X	X*	X*		
Thyroid	X	X	*	X		
Tongue	X					
Trachea	X	X				
Urinary bladder	X	X		X		
Uterus	X*	X	X*	X*		
Vagina	X			X		
Preputial gland	X		X	X		
Clitoral glands	X		X	X		

* organ weight obtained

Addendum 2. Histopathology performed in 14 day i.v. study in mice with RS-79070-194

Tissue	0 (mg/kg)	Treatment (mg/kg)
Eye	X	X
Brain	X	X
Pituitary gland	X	X
Sternebrae	X	X
Bone marrow	X	X
Lungs	X	X
Heart	X	X
Aorta	X	X
Thyroid	X	X
Parathyroid	X	X
Trachea,	X	X
Esophagus	X	X
Thymus	X	X
Salivary gland	X	X
Liver	X	X
Adrenal glands	X	X
Spleen	X	X
Pancreas	X	X
Lymph node(s)	X	X
Mesenteric	X	X
Submandibular	X	X
Sciatic nerve	X	X

Testes	X	X
Epididymides	X	X
Seminal vesicles	X	X
Prostate gland	X	X
Ovaries	X	X
Uterus	X	X
Vagina	X	X
Stomach	X	X
Duodenum	X	X
Jejunum	X	X
Ileum	X	X
Colon	X	X
Cecum	X	X
Urinary bladder	X	X
Spinal cord	X	X
<i>Thoracic</i>	X	X
<i>Lumbar</i>	X	X
Skeletal muscle	X	X
Skin with Mammary gland	X	X

Histopathologic examination of gallbladder was performed in dogs.

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Label

There are a number of sections of the label that include pharmacology and toxicology information. They will be listed in turn and the suggested wording put into the review.

WARNINGS:**Impairment of Fertility:**

Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses (see PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility). It is considered probable that in humans, valganciclovir at the recommended doses may cause temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

Teratogenesis, Carcinogenesis and Mutagenesis:

Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during, and for at least 90 days following, treatment with _____ tablets (see PRECAUTIONS: Carcinogenesis, Mutagenesis and Pregnancy: Category C).

In animal studies, ganciclovir was found to be mutagenic and carcinogenic. Valganciclovir should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see DOSAGE AND ADMINISTRATION: Handling and Disposal).

PRECAUTIONS:**Information for patients:**

Patients should be advised that ganciclovir has caused decreased sperm production in animals and may cause decreased fertility in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Women of childbearing potential should be advised to use effective contraception during treatment with _____ tablets. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with _____ tablets.

Carcinogenesis, Mutagenesis and Impairment of Fertility[†]:

No long-term carcinogenicity studies have been conducted with valganciclovir. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir. Therefore, like ganciclovir, valganciclovir is a potential carcinogen.

Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day (approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following the recommended intravenous dose of 5 mg/kg, based on area under the plasma concentration curve [AUC] comparisons). At the dose of 1000 mg/kg/day there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the dose of 20 mg/kg/day, a slightly increased incidence of tumors was noted in the preputial and Harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (estimated as 0.01x the human dose based on AUC comparison). Ganciclovir should be considered a potential carcinogen in humans.

Valganciclovir increases mutations in mouse lymphoma cells. In the mouse micronucleus assay, valganciclovir was clastogenic at a dose of 1500 mg/kg (60x human mean exposure for ganciclovir based upon AUC). Valganciclovir was not mutagenic in the Ames Salmonella assay. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (IV) (2.8 to 10x human exposure based on AUC) but not 50 mg/kg (exposure approximately comparable to the human based on AUC). Ganciclovir was not mutagenic in the Ames Salmonella assay.

Valganciclovir is converted to ganciclovir and therefore is expected to have similar reproductive toxicity effects as ganciclovir (see WARNINGS: Impairment of Fertility). Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryoletality in female mice following intravenous doses of 90 mg/kg/day (approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1x the AUC of the recommended human intravenous dose. Valganciclovir caused similar effects on spermatogenesis in mice, rats, and dogs. It is considered likely that ganciclovir (and valganciclovir) could cause inhibition of human spermatogenesis.

Pregnancy:**Category C[†]:**

Valganciclovir is converted to ganciclovir and therefore is expected to have reproductive toxicity effects similar to ganciclovir. Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (2x the human exposure based on AUC comparisons), respectively. Effects observed in rabbits included: fetal growth retardation, embryoletality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/micropthalmia, aplastic organs (kidney and pancreas),

hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality.

Daily intravenous doses of 90 mg/kg administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see Teratogenesis, Carcinogenesis and Mutagenesis). The drug exposure in mice as estimated by the AUC was approximately 1.7x the human AUC.

Data obtained using an ex vivo human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1 to 10 mg/mL and occurred by passive diffusion.

Valganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women ~~Valcyte~~ tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

[‡]Footnote: All dose comparisons presented in the Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy subsections are based on the human AUC following administration of a single 5 mg/kg infusion of intravenous ganciclovir as used during the maintenance phase of treatment.

Nursing Mothers:

Nursing Mothers: It is not known whether ganciclovir or valganciclovir is excreted in human milk. Because valganciclovir caused granulocytopenia, anemia and thrombocytopenia in clinical trials and ganciclovir was mutagenic and carcinogenic in animal studies, the possibility of serious adverse events from ganciclovir in nursing infants is possible (see Warnings). Because of potential for serious adverse events in nursing infants, **mothers should be instructed not to breastfeed if they are receiving Valcyte tablets.** In addition, the Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

CONCLUSIONS:

The nonclinical information submitted to this NDA are sufficient to recommend approval of Valcyte.

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James G. Farrelly, Ph.D.
Reviewing Pharmacologist

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