PRODUCT MONOGRAPH

[Pr]TEVA-ACYCLOVIR

Acyclovir Tablets, USP

200 mg, 400 mg and 800 mg

(Acyclovir, as Acyclovir Hydrate)

ANTIVIRAL AGENT

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PrTEVA-ACYCLOVIR TABLETS

(Acyclovir, as Acyclovir Hydrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet / 200, 400 and 800 mg acyclovir (as acyclovir hydrate)	Colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, sodium starch glycolate, FD&C Blue#2, FD&C Yellow #6, FD&C Blue #1 and D&C Red #7

INDICATIONS AND CLINICAL USE

TEVA-ACYCLOVIR (acyclovir) is indicated for the following conditions:

- The treatment of initial episodes of herpes genitalis.
- The suppression of unusually frequent recurrences of herpes genitalis (6 or more episodes per year).
- The acute treatment of herpes zoster (shingles) and varicella (chickenpox).

The results of clinical studies suggest that some patients with recurrent genital herpes may derive clinical benefit from the administration of oral acyclovir if taken at the first sign of an impending episode. Those most likely to benefit are patients who experience severe, prolonged recurrences; such intermittent therapy may be more appropriate than suppressive therapy when these recurrences are infrequent.

Early treatment of acute herpes zoster (shingles) in immunocompetent individuals with oral acyclovir resulted in decreased viral shedding; decreased time to healing; less dissemination; and alleviation of acute pain.

Treatment of varicella (chickenpox) in immunocompetent patients with oral acyclovir reduced the total number of lesions, accelerated the progression of lesions to the crusted and healed stages, and decreased the number of residual hypopigmented lesions. In addition, acyclovir decreased fever and constitutional symptoms associated with chickenpox.

The prophylactic use of acyclovir in chickenpox has not been established.

Geriatrics: (≥ 65 years of age): Use in the geriatric population may be associated with differences in safety due to age-related changes in renal function and a brief discussion can be found in the appropriate sections (see WARNINGS AND PRECAUTIONS).

Pediatrics (< 2 years old): No data is available.

CONTRAINDICATIONS

TEVA-ACYCLOVIR (acyclovir) is contraindicated for patients who develop hypersensitivity or who are hypersensitive to acyclovir, valacyclovir or any other components of the formulations of TEVA-ACYCLOVIR. For a complete listing, see Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Care should be taken to maintain adequate hydration in patients receiving high oral doses of acyclovir.

Suppressive therapy of herpes genitalis with acyclovir should be considered only for severely affected patients. Periodic evaluation of the need for continued suppressive therapy is recommended. In some patients, there is a tendency for the first recurrent episode to be more severe following cessation of suppressive therapy.

In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses associated with infections which may not respond. Thrombotic thrombocytopenic purpura/haemolytic uremic syndrome (TTP/HUS), which has resulted in death, has occurred in immunocompromised patients receiving acyclovir therapy.

The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION). The decision to prescribe a course of suppressive therapy should be weighed in the light of our present knowledge about the long-term effects of acyclovir and must clearly relate to the condition of the patient.

Whereas cutaneous lesions associated with herpes simplex infections are often pathognomonic, Tzanck smears prepared from lesion exudate or scrapings may assist in the diagnosis. Positive cultures for herpes simplex virus offer the only absolute means for confirmation of the diagnosis. Appropriate examinations should be performed to rule out other sexually transmitted diseases. All patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding.

The clinical status of the patient and the adverse event profile of acyclovir should be borne in mind when considering the patient's ability to drive or operate machinery. There have been no studies to investigate the effect of acyclovir on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that treatment of chickenpox with acyclovir would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life.

Carcinogenesis and Mutagenesis

Acyclovir has caused mutagenesis in some acute studies at high concentrations of the drug (see Part II, TOXICOLOGY).

Renal

Renal insufficiency or acute renal failure has been observed in patients taking acyclovir at the recommended dosage and/or with no previous renal conditions and may be associated with renal pain (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Acyclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see DOSAGE AND ADMINISTRATION, Patients with Acute or Chronic Renal Impairment). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see ADVERSE REACTIONS).

Caution should be exercised when administering to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

Sexual Function/Reproduction

In a study of 20 male patients with normal sperm count, oral acyclovir administered at doses of up to 1 g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology. There is no information on the effect of acyclovir oral formulations on human female fertility.

Special Populations

Pregnant Women: Teratology studies carried out to date in animals have been negative in general. However, in a non-standard test in rats, there were fetal abnormalities such as head and tail anomalies, and maternal toxicity; since such studies are not always predictive of human response, acyclovir should not be used during pregnancy unless the physician feels the potential benefit justifies the risk of possible harm to the fetus. The potential for high concentrations of acyclovir to cause chromosome breaks *in vitro* should be taken into consideration in making this decision.

A post-marketing acyclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of acyclovir. The registry findings have not shown an increase in the number of birth defects amongst subjects exposed to acyclovir compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a

common cause.

Nursing Women: Acyclovir concentrations have been documented in breast milk in 2 women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg per day. Caution should therefore be exercised when TEVA-ACYCLOVIR is administered to a nursing woman.

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

Geriatrics: The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see WARNINGS AND PRECAUTIONS, Renal, and DOSAGE AND ADMINISTRATION, Patients with Acute or Chronic Renal Impairment). Adequate hydration of elderly patients taking high oral doses of acyclovir should be maintained.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequent adverse reactions associated with the use of acyclovir are headache and nausea.

Neurological side effects have also been reported in rare instances. Elderly patients and patients with a history of renal impairment are at increased risk of developing these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see WARNINGS AND PRECAUTIONS; and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Treatment of Herpes Simplex: Short-term administration (5-10 days): The most frequent adverse reactions reported during clinical trials of treatment of genital herpes with oral acyclovir in 298 patients are listed in Table 1.

Table 1 Adverse Reactions Reported in Clinical Trials of Treatment of Genital Herpes with Acyclovir

Adverse Reactions	Total	%
Nausea and/or vomiting	8	2.7

Suppression of Herpes Simplex: Long-term administration: The most frequent adverse events

reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily are listed in Table 2.

Table 2 Adverse Reactions Reported in a Clinical Trial for the Prevention of Recurrences of Genital Herpes with Acyclovir

Adverse Reactions	1st Year (n=586) %	2nd Year (n=390) %	3rd Year (n=329) %
Nausea	4.8		
Diarrhea	2.4		
Headache	1.9	1.5	0.9
Rash	1.7	1.3	
Paresthesia		0.8	1.2
Asthenia			1.2

Evidence so far from clinical trials suggests that the severity and frequency of adverse events is unlikely to necessitate discontinuation of therapy.

Herpes Zoster: The most frequent adverse reactions reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 or 10 days or placebo are listed in Table 3.

Table 3 Adverse Reactions Reported in Clinical Trials of Treatment of Herpes Zoster

Adverse Reactions	Acyclovir (n=323) %	Placebo (n=323) %
Malaise	11.5	11.1
Nausea	8.0	11.5
Headache	5.9	11.1
Vomiting	2.5	2.5
Diarrhea	1.5	0.3

Chickenpox: The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir or placebo are listed in Table 4.

Table 4 Adverse Reactions Reported in Clinical Trials of Treatment of Chickenpox

Adverse Reactions	Acyclovir (n=495) %	Placebo (n=498) %
Diarrhea	3.2	2.2

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Other adverse reactions reported in less than 1% of patients receiving acyclovir in any clinical trial included: abdominal pain, anorexia, constipation, dizziness, edema, fatigue, flatulence, inguinal adenopathy, insomnia, leg pain, medication taste, skin rash, sore throat, spasmodic hand movement and urticaria.

Abnormal Hematologic and Clinical Chemistry Findings
No clinically significant changes in laboratory values have been observed in clinical trials for the treatment of chickenpox and zoster, and for the treatment and suppression of genital herpes with acyclovir.

Post-Market Adverse Drug Reactions
The following events have been reported voluntarily during post-market use of acyclovir in clinical practice. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to acyclovir or a combination of these factors. Post-market adverse events are reported spontaneously from a population of unknown size, thus estimates of frequency cannot be made.

General: Fever, headache, pain, and peripheral edema.

Nervous: Dizziness, paresthesia. Very rarely, agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy and coma have been reported. These events are generally reversible and usually reported in patients with renal impairment, or with predisposing factors (see WARNINGS AND PRECAUTIONS). These symptoms may be marked, particularly in older adults.

Digestive: Diarrhea, gastrointestinal distress, nausea.

Haematogical and Lymphatic: Very rarely anaemia, leukopenia, lymphadenopathy and thrombocytopenia.

Hypersensitivity and Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, rashes including photosensitivity, pruritus, urticaria, and rarely dyspnoea, angioedema and anaphylaxis.

Hepatobiliary Tract and Pancreas: Reports of reversible hyperbilirubinemia and elevated liver related enzymes. Hepatitis and jaundice.

Musculoskeletal: Myalgia.

Special Senses: Visual abnormalities.

Urogenital: Elevated blood creatinine and blood urea nitrogen (BUN). Acute renal failure, renal pain and hematuria have been reported. Renal pain may be associated with renal failure (see WARNINGS AND PRECAUTIONS).

DRUG INTERACTIONS

Drug-Drug Interactions
No clinically significant interactions have been identified.

Acyclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase acyclovir plasma concentrations. Probenecid and cimetidine increase the area under the curve (AUC) of acyclovir by this mechanism, and reduce acyclovir renal clearance. Similarly increases in plasma AUCs of acyclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients have been shown when the drugs are coadministered. However, no dosage adjustment is necessary because of the wide therapeutic index of acyclovir.

Drug-Food Interactions
There is no known interaction with food (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
- The dosage of TEVA-ACYCLOVIR (acyclovir) should be reduced in patients with impaired renal function.
- Therapy should be initiated as soon as possible after a diagnosis of chickenpox or herpes zoster, or at the first sign or symptoms of an outbreak of genital herpes.
- The recommended dose and duration of use is dependent on the indication.

Recommended Dose and Dosage Adjustment

Treatment of Initial Infection of Herpes Genitalis: 200 mg every 4 hours, 5 times daily for a total of 1 gram daily for 10 days. Therapy should be initiated as early as possible following onset of signs and symptoms.

Suppressive Therapy for Recurrent Herpes Genitalis: The initial recommended dose is 200 mg three times daily. This can be increased if breakthrough occurs up to a dosage of one 200 mg tablet, five times daily. If necessary, a dose of 400 mg (one 400 mg tablet or two 200 mg tablets) given twice daily may be considered. Periodic re-evaluation of the need for therapy is recommended.

Administration of TEVA-ACYCLOVIR for intermittent therapy is 200 mg every 4 hours 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Treatment of Herpes Zoster: 800 mg every 4 hours, 5 times daily for 7 to 10 days. Treatment should be initiated within 72 hours of the onset of lesions. In clinical trials, the greatest benefit occurred when treatment was begun within 48 hours of the onset of lesions.

Treatment of Chickenpox: 20 mg/kg (not to exceed 800 mg) orally, 4 times daily for 5 days. Therapy should be initiated within 24 hours of the appearance of rash.

Patients With Acute or Chronic Renal Impairment: Caution is advised when administering acyclovir to patients with impaired renal function. Adequate hydration should be maintained.

Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment.

Based on these studies, dosage adjustments are recommended in Table 5 for genital herpes and herpes zoster indications.

Table 5 Dosage Modification for Renal Impairment

Normal Dosage Regimen	Creatinine Clearance ($mL/min/1.73m^2$)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval (hours)
200 mg every 4 hours	>10 0-10	200 200	every 4 hours, 5 x daily every 12 hours
400 mg every 12 hours	>10 0-10	400 200	every 12 hours every 12 hours
800 mg every 4 hours	>25 10-25 0-10	800 800 800	every 4 hours, 5 x daily every 8 hours every 12 hours

Hemodialysis: For patients who require hemodialysis, 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.

Peritoneal Dialysis: No supplement dose appears to be necessary after adjustment of the dosing interval.

Missed Dose

If a dose of TEVA-ACYCLOVIR is missed, the patient should be advised to take it as soon as he/she remembers, and then continue with the next dose at the proper time interval.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

Acyclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested of up to 20g acyclovir on a single occasion, with no unexpected adverse effects. In clinical studies, the highest plasma concentration observed in a single patient at these doses was 10.0 μg/mL. Accidental, repeated overdoses of oral acyclovir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion).

Intravenous doses administered to humans have been as high as 1200 mg/m^2 (28 mg/kg) 3 times daily for up to 2 weeks. Peak plasma concentrations have reached 80 μg/mL. Overdosage of intravenous acyclovir has resulted in elevations of serum creatinine, blood urea nitrogen and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with intravenous overdosage.

Patients should be observed closely for signs of toxicity. Hemodialysis significantly enhances the removal of acyclovir from the blood and may, therefore be considered a management option in the event of symptomatic overdose. Precipitation of acyclovir in renal tubules may occur if the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. In the event of renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Acyclovir, a synthetic acyclic purine nucleoside analog, is a substrate with a high degree of specificity for herpes simplex and varicella-zoster specified thymidine kinase. Acyclovir is a poor substrate for host cell-specified thymidine kinase. Herpes simplex and varicella-zoster specified thymidine kinase transform acyclovir to its monophosphate which is then transformed by a number of cellular enzymes to acyclovir diphosphate and acyclovir triphosphate. Acyclovir triphosphate is both an inhibitor of, and a substrate for, herpesvirus-specified DNA polymerase. Although the cellular α-DNA polymerase in infected cells may also be inhibited by acyclovir triphosphate, this occurs only at concentrations of acyclovir triphosphate which are higher than those which inhibit the herpesvirus-specified DNA polymerase. Acyclovir is selectively converted to its active form in herpesvirus-infected cells and is thus preferentially taken up by these cells. Acyclovir has demonstrated a very much lower toxic potential *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 has a lower sensitivity to the action of the active form of the drug. A combination of the thymidine kinase specificity, inhibition of DNA polymerase and premature termination of DNA synthesis results in inhibition of herpesvirus replication. No effect on latent non-replicating virus has been demonstrated. Inhibition of the virus reduces the period of viral shedding, limits the degree of spread and level of pathology, and thereby facilitates healing. During suppression there is no evidence that acyclovir prevents neural migration of the virus. It

aborts episodes of recurrent herpes due to inhibition of viral replication following reactivation.

Pharmacokinetics

The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients.

Absorption: In one study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection given acyclovir in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, the bioavailability was estimated to be 15 to 20%. In this study, steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the last 200 mg dose were 0.49 μg/mL (0.47 to 0.54 μg/mL) and 0.31 μg/mL (0.18 to 0.41 μg/mL), respectively and following the last 800 mg dose were 2.8 μg/mL (2.3 to 3.1 μg/mL) and 1.8 μg/mL (1.3 to 2.5 μg/mL). In another study, 20 immunocompetent patients with recurrent genital herpes simplex infections given acyclovir in dose of 800 mg every 6 hours, 4 times daily for 5 days, the mean steady-state peak and trough concentrations were 1.4 μg/mL (0.66 to 1.8 μg/mL) and 0.55 μg/mL (0.14 to 1.1 μg/mL).

In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20, 15 and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 μg/mL, 1.21 and 0.63 μg/mL, and 1.61 and 0.83 μg/mL for the 200, 400 and 800 mg dosage regimens, respectively.

In another study in 6 volunteers, the influence of food on the absorption of acyclovir was not apparent.

A single oral dose bioavailability study in 23 normal volunteers showed that acyclovir 200 mg capsules are bioequivalent to 200 mg acyclovir in aqueous solution. In a separate study in 20 volunteers, it was shown that acyclovir suspension is bioequivalent to acyclovir capsules. In a different single-dose bioavailability/bioequivalence study in 24 volunteers, one acyclovir 800 mg Tablet was demonstrated to be bioequivalent to four acyclovir 200 mg capsules.

Distribution: Plasma protein binding is relatively low (9 to 33%) and drug interactions involving binding site displacement are not anticipated.

Elimination: Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6 to 19.8%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-[(carboxymethoxy) methyl] guanine.

Special Populations and Conditions

Pediatrics: In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean

half-life after oral doses of 300 mg/m^2 and 600 mg/m^2 in children aged 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

Orally administered acyclovir in children less than 2 years of age has not yet been fully studied.

Geriatrics: In the elderly, total body clearance falls with increasing age, associated with decreases in creatinine clearance, although there is little change in the terminal plasma half-life. Dosage reduction may be required in geriatric patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The half-life and total body clearance of acyclovir are dependent on renal function.

A dosage adjustment is recommended for patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

Tablets should be stored at controlled room temperature (15° to 30°C) in a dry place and protected from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms:

TEVA-ACYCLOVIR is available as tablets containing 200 mg, 400 mg and 800 mg of acyclovir (on anhydrous basis).

TEVA-ACYCLOVIR 200 mg TABLETS are available in bottles of 100 tablets. Each blue, shield-shaped compressed tablet contains 200mg acyclovir, and is engraved with "N" on one side and "200" on the other side.

TEVA-ACYCLOVIR 400 mg TABLETS are available in bottles of 100 tablets. Each pink, shield-shaped compressed tablet contains 400mg acyclovir, and is engraved with "N" on one side and "400" on the other side.

TEVA-ACYCLOVIR 800 mg TABLETS are available in bottles of 100 tablets. Each blue, elongated, scored compressed tablet contains 800mg acyclovir, and is engraved with "N | N" on one side and "800" on the other side.

Composition:

TEVA-ACYCLOVIR tablet contains 200 mg, 400 mg or 800 mg acyclovir and the following non-medicinal ingredients, colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch and sodium starch glycolate.

In addition, 200 mg tablets contain FD&C Blue#2, 400 mg tablets contain FD&C Yellow #6, FD&C Blue #1, D&C Red #7 and 800 mg tablets contain FD&C Blue#2, FD&C Blue #1.

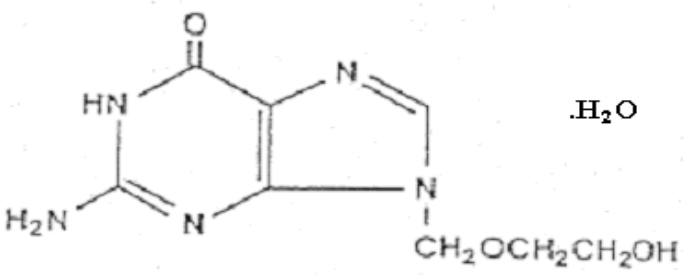
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	Acyclovir
Chemical name:	6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)-methyl]- 9-[(2-Hydroxyethoxy)methyl]guanine
Molecular formula:	$C_8H_{11}N_5O_3.H_2O$
Molecular Weight:	225.2 (acyclovir anhydrous) 243.2 (acyclovir hydrate)

Structural formula:



pKa: 2.27 and 9.25
pH: 5.96 (0.50 mg/mL solution in water)
Partition coefficient for octanol/water: 1.53

Physicochemical properties: Acyclovir is a white to almost white crystalline powder, slight soluble in water, very slightly soluble in alcohol, freely soluble in dimethylsulfoxide, soluble in dilute solutions of alkali hydroxides and mineral acids.

CLINICAL TRIALS

A single-dose, randomized, two-period, two-treatment, two sequence crossover study design was used on 35 healthy, non-smoking, male subjects, 18 to 55 years of age (inclusive), to evaluate the comparative bioavailability between TEVA-ACYCLOVIR Tablets, 200 mg (Teva Canada Limited, Canada) and Zovirax® 200 mg Tablets (GlaxoSmithKline Inc., Canada) when dosed (1x200 mg) under fasting conditions (Study #2004-745).

The pharmacokinetic data calculated for the two acyclovir formulations are tabulated below:

TABLE OF COMPARATIVE BIOAVAILABILITY DATA

Acyclovir (1 x 200 mg) From measured data **Geometric Mean Arithmetic Mean (CV %)**				
Parameter	**TEVA-ACYCLOVIR Tablets, 200mg**	**Zovirax® 200mg Tablets†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng*hr/ml)	1685.09 1802.65 (37.7%)	1581.98 1706.2 (40.2%)	107	96.5 - 118
AUC_I (ng*hr/ml)	1817.06 1927.33 (35.3%)	1712.63 1825.45 (37.2%)	106	96.7 - 116
C_{MAX} (ng/ml)	349.56 371.03 (34.53%)	348.56 371.27 (36.83%)	100	91.9 - 109
T_{MAX}‖ (hr)	1.700 (51.7%)	1.586 (41.7%)		
$T_{½}$‖ (hr)	3.553 (34.7%)	3.583 (32.6%)		

† Zovirax® 200mg Tablets, GlaxoSmithKline Inc., Canada

‖ Expressed as the arithmetic mean (CV%) only.

A single-dose, randomized, two-period, two-treatment, two sequence crossover study design was used on 36 healthy, non-smoking, male subjects, 18 to 55 years of age (inclusive), to evaluate the comparative bioavailability between TEVA-ACYCLOVIR Tablets, 200 mg (Teva Canada Limited, Canada) and Zovirax® 200 mg Tablets (GlaxoSmithKline Inc., Canada) when dosed (1x200 mg) under fed conditions (Study #2004-746).

The pharmacokinetic data calculated for the two acyclovir formulations are tabulated below:

TABLE OF COMPARATIVE BIOAVAILABILITY DATA

Acyclovir (1 x 200 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**TEVA-ACYCLOVIR Tablets, 200mg**	**Zovirax® 200mg Tablets†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng*hr/ml)	1904.08 1977.83 (28.3%)	1883.71 1961.57 (28.7%)	101	96.5 - 106
AUC_I (ng*hr/ml)	2016.92 2090.82 (27.6%)	1992.97 2070.89 (27.9%)	101	96.8 - 106
C_{MAX} (ng/ml)	402.47 417.30 (27.7%)	417.04 434.02 (27.9%)	96.5	92.0 - 101
T_{MAX}‖ (hr)	1.896 (44.4%)	1.861 (37.5%)		
$T_{½}$‖ (hr)	3.162 (21.4%)	3.179 (22.4%)		

† Zovirax® 200mg Tablets, GlaxoSmithKline Inc., Canada
‖ Expressed as the arithmetic mean (CV%) only.

Initial Genital Herpes

Double blind, placebo controlled studies have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection and duration of lesion healing. The duration of pain and new lesion formation was decreased in some patient groups.

Recurrent Genital Herpes

In a study of patients who received acyclovir 400 mg twice daily for 3 years, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively.

Serial analyses of the 3 month recurrence rates for the patients showed that 71% to 87% were recurrence free in each quarter.

Herpes Zoster Infections

In a double blind, placebo controlled study of immunocompetent patients with localized cutaneous zoster infection, acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.

In a similar double blind, placebo controlled study, acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain; and reduced the duration of new lesion formation.

Treatment was begun within 72 hours of rash onset and was most effective if started within the first 48 hours. Adults greater than 50 years of age showed greater benefit.

Chickenpox

Three randomized, double-blind, placebo controlled trials were conducted in 993 pediatric patients aged 2 to 18 years with chickenpox. All patients were treated within 24 hours after the onset of rash. In 2 trials, acyclovir was administered at 20 mg/kg 4 times daily (up to 3,200 mg per day) for 5 days. In the third trial, doses of 10, 15, or 20 mg/kg were administered 4 times daily for 5 to 7 days. Treatment with acyclovir shortened the time to 50% healing; reduced the maximum number of lesions; reduced the median number of vesicles; decreased the median number of residual lesions on day 28; and decreased the proportion of patients with fever, anorexia, and lethargy by day 2. Treatment with acyclovir did not affect varicella zoster virus specific humoral or cellular immune responses at 1 month or 1 year following treatment.

DETAILED PHARMACOLOGY

See Part I, ACTION AND CLINICAL PHARMACOLOGY.

VIROLOGY

The quantitative relationship between the *in vitro* susceptibility of herpes simplex virus (HSV) and varicella-zoster viruses (VZV) 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, the cell type employed, and the laboratory performing the test. The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 μg/mL (plaque reduction in Vero cells) to 5.9-13.5 μg/mL (plaque reduction in green monkey kidney [GMK] cells). The ID_{50} against HSV-2 ranges from 0.01 μg/mL to 9.9μg/mL (plaque reduction in Vero and GMK cells, respectively).

Using a dye-uptake method in Vero cells, which gives ID_{50} values approximately 5 to 10-fold higher than plaque reduction assays, 1417 HSV isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period. These assays found that 90% of HSV-1 isolates were sensitive to ≤0.9 μg/mL acyclovir and 50% of all isolates were sensitive to ≤0.2 μg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤2.2 μg/mL and 50% of all isolates were sensitive to ≤0.7 μg/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 HSV clinical isolates have been relatively deficient in the viral thymidine kinase (TK). Strains with alterations in viral TK or viral DNA polymerase have also been reported.

The ID_{50} against VZV ranges from 0.17-1.53 μg/mL (yield reduction, human foreskin fibroblasts) to 1.85-3.98 μg/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 μg/mL acyclovir. Cytomegalovirus (CMV) is relatively resistant to acyclovir with ID_{50} values ranging from 2.3-17.6 μg/mL (plaque reduction, HEF cells) to 1.82-56.8 μg/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.

Resistance

Prolonged exposure of HSV to subinhibitory concentrations (0.1 μg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir resistant strains. The emergence of resistant strains is believed to occur by "selection" of naturally occurring viruses with relatively low susceptibility to acyclovir. Such strains have been reported in pre-therapy isolates from several clinical studies.

Two resistance mechanisms involving viral thymidine kinase (required for acyclovir activation) have been described. These are: (a) selection of thymidine-kinase-deficient mutants that induce little or no enzyme activity after infection, and (b) selection of mutants possessing a thymidine kinase of altered substrate specificity that is able to phosphorylate the natural nucleoside thymidine but not acyclovir. The majority of less susceptible viruses arising *in vitro* are of the thymidine-kinase-deficient type which have reduced infectivity and pathogenicity and less likelihood of inducing latency in animals.

However, an acyclovir-resistant HSV infection in an immunosuppressed bone marrow transplant recipient on extended acyclovir therapy was found to be due to a clinical isolate which had a normal thymidine kinase but an altered DNA polymerase. This third mechanism of resistance involving herpes simplex virus DNA polymerase is due to the selection of mutants encoding an altered enzyme, which is resistant to inactivation by acyclovir triphosphate.

VZV appears to manifest resistance to acyclovir via mechanisms similar to those seen in HSV.

However, limited clinical investigation has revealed no evidence of a significant change *in vitro* susceptibility of VZV with acyclovir therapy, although resistant mutants of this virus can be isolated *in vitro* in a manner analogous to HSV. Analysis of a small number of clinical isolates from patients who received oral acyclovir or placebo for acute herpes zoster suggests that *in vivo* emergence of resistant VZV may occur infrequently. Prolonged acyclovir treatment of highly immunocompromised patients with acquired immunodeficiency syndrome and severe VZV may lead to the appearance of resistant virus.

Cross-resistance to other antivirals occurs *in vitro* in acyclovir-resistant mutants. HSV mutants which are resistant to acyclovir due to an absence of viral thymidine kinase are cross-resistant to other agents which are phosphorylated by herpesvirus thymidine kinase, such as bromovinyldeoxyuridine, ganciclovir and the 2'-fluoropyrimidine nucleosides, such as, 2'-fluoro-5-iodoarabinosyl-cytosine (FIAC).

The clinical response to acyclovir treatment has usually been good for patients with normal immunity from whom HSV having reduced susceptibility to acyclovir has been recovered either before, during or after therapy. However, certain patient groups, such as the severely immunocompromised (especially bone marrow transplant recipients) and those undergoing chronic suppressive regimens have been identified as being most frequently associated with the emergence of resistant herpes simplex strains, which may or may not accompany a poor response to the drug. The possibility of the appearance of less sensitive viruses must be recognized when treating such patients, and susceptibility monitoring of clinical isolates from these patients should be encouraged.

In summary, the quantitative relationship between the *in vitro* susceptibility of HSV and VZV to acyclovir and the clinical response to therapy has not been clearly established in man. Standardized methods of virus sensitivity testing are required to allow more precise correlations between *in vitro* virus sensitivity and clinical response to acyclovir therapy.

TOXICOLOGY

Acute Toxicity Studies

Adult Mice and Rats: The acute toxicity of oral acyclovir was determined as shown in Table 6.

Table 6 Acute Toxicology Studies

Species	Sex	Route	LD_{50}(mg/kg)	95% Conf. Level	Signs
Mouse	M	Oral	>10 000	-	None
Rat	M	Oral	>20 000	-	None

Neonatal, Immature, and Adult Rats: Groups of 10 male and 10 female Charles River CD (Sprague-Dawley) rats were given single large doses (5 different dose levels) of a solution (pH 11.0) of acyclovir by subcutaneous injection when they were 3, 10, 28 and 71 days of age. They were observed for 14 days after treatment and LD_{50} values were calculated by the Litchfield and Wilcoxon method (see Table 7 below). This study was done to determine if age at exposure affects the acute toxicity of acyclovir; there was no evidence that young rats were more sensitive than older rats to the acute toxic effects of acyclovir.

Table 7 LD_{50} in Rats

Age When Treated	**LD_{50} (mg/kg body weight)**	
	Males	**Females**
3 Days	1070	1281
10 Days	790	496
28 Days	678	750
71 Days	650	1477

There was no apparent relationship between length of survival after treatment and age at which treatment was given. Clinical signs for the rats treated at 3 and 10 days of age included red and purple cutaneous blisters, blue areas, scabs, scars, necrotic and sloughed skin, open wounds, body tremors and alopecia. Decreased activity, lacrimation, closed eyelids, red-brown or brown material around the eyes, nose and mouth, ataxia, prostration, body tremors, urine stains around the abdomen or genital area, scabbed or necrotic areas and alopecia were observed in rats treated at 28 and 71 days of age.

Subchronic Oral Toxicity Study

Mice: Four groups each consisting of 28 male and 28 female Charles River CD-1 (ICR) mice were orally dosed by stomach tube for 33 days with suspensions of acyclovir. Daily dose levels were 0, 50, 150 and 450 mg/kg. Hematology and clinical chemistry measurements were made on an additional 8 male and 8 female mice per group (dosed in the same manner) after the first and fourth weeks of dosing and during the 3rd postdose week.

Plasma drug concentrations were measured in pooled samples from an additional 4 male and 4 female mice per group on dose days 1, 15 and 30.

Based on preliminary experiments with rats and mice, the high dose of 450 mg/kg was selected to produce the highest drug plasma levels attainable, in a practical manner, by oral dosing in a rodent species. Averaged drug plasma concentrations ranged from approximately 3.4 (at the low dose) to 11.0 (at the high dose) μg/mL of plasma one hour after oral dosing.

No changes in health, growth rate, hematology and clinical chemistry measurements occurred that could be definitely attributed to dosing with acyclovir. Gross and histopathologic

examinations of 16 male and 16 female rats from the high-dose and control groups at the end of the dose period revealed nothing remarkable.

Chronic Toxicity Studies

Lifetime Oral Toxicity Study in Rats Given Acyclovir by Gastric Intubation:
Charles River CD (Sprague-Dawley) rats were given suspensions of acyclovir by gavage. There were 50 male and 50 female rats at each of the following dose levels: 0, 50, 150 and 450 mg/kg. After 30 and 52 weeks of treatment, 10 male and 10 female rats from each group were necropsied. The remaining rats were dosed each day until natural mortality decreased a group size to approximately 20% of the number of animals of that sex present in the test groups when the study was started. All remaining rats were killed and necropsied when the 20% cut-off point was reached. This was during week 110 for the male rats and week 122 for the female rats. Tissues from control rats and those in the high-dose group were evaluated by light microscopy. Tissues from rats in the low and mid-dose groups having masses, nodules or unusual lesions were also examined by light microscopy. Fixed tissues from rats that were found dead during the first 52 weeks of the study were also evaluated by light microscopy.

No signs of toxicosis were observed. Plasma samples were collected 1.5 hours after dosing on days 7, 90, 209, 369, 771 (males only) and 852 (females only). Mean plasma levels found in high-dose males (450 mg/kg/day) at the times indicated above were as follows: 1.54, 1.63, 1.39, 1.60 and 1.70 μg/mL (6.84, 7.26, 6.17, 7.10 and 7.56 μM). Corresponding mean plasma levels for the high-dose females for the corresponding time periods were 1.76, 2.38, 2.12, 1.71 and 1.81 μg/mL (7.82, 10.58, 9.44, 7.62 and 8.03 μM). Plasma levels in both males and females at all dose levels after one year of treatment were generally comparable to plasma levels obtained at earlier samplings. Values for laboratory tests including hematology, clinical chemistry and ophthalmoscopy were all within the normal range. There were no drug-induced gross or microscopic lesions and there was no evidence that acyclovir affected survival.

Lifetime Oral Carcinogenicity Study in Rats: There were no signs of toxicosis in Charles River CD (Sprague-Dawley) rats (100 rats/sex/dose group) given acyclovir by oral gavage at 50, 150 and 450mg/kg in a lifetime oral carcinogenicity study. Mean plasma levels obtained in high-dose males 1.5 hours after dosing at various sampling times during the study were as follows: 1.54, 1.63, 1.39, 1.60 and 1.70μg/mL (6.84, 7.26, 6.17, 7.10 and 7.56 μM) at days 7, 90, 209, 369 and 771, respectively. Corresponding mean values for the high-dose females were 1.76, 2.38, 2.12, 1.71 and 1.81 μg/mL (7.82, 10.58, 9.44, 7.62 and 8.03 μM) at days 7, 90, 209, 369 and 852, respectively.

Values for clinical laboratory tests including hematology, clinical chemistry, urinalysis, body weight, food consumption and ophthalmoscopy were all within normal ranges. There were no drug-induced gross or microscopic lesions and there was no evidence that acyclovir affected survival, temporal patterns of tumor incidence or tumor counts for benign or malignant

neoplasms.

Most of the relatively few rats found dead or moribund during the first 52 weeks of this study suffered dosing accidents as evidenced by postmortem findings of esophageal perforation causing pleural effusion, pneumonia, or mediastinitis.

Lifetime Oral Carcinogenicity Study in Mice: There were no signs of toxicosis in Charles River CD-1 (ICR) mice (115 mice/sex/dose group) given acyclovir by oral gavage at 50, 150 and 450 mg/kg/day in a lifetime oral carcinogenicity study. Mean plasma levels obtained in high-dose males 1.5 hours after dosing at various sampling times during the study were as follows: 2.83, 3.17 and 1.82 μg/mL (12.59, 14.10 and 8.10 μM) at days 90, 365 and 541, respectively. Corresponding mean values for the high-dose females were 9.81, 5.85 and 4.0 μg/mL (43.60, 26.0 and 17.79 μM).

Values for clinical laboratory tests including hematology, body weight and food consumption were all within normal ranges. There were no drug-induced gross or microscopic lesions. Female mice given 150 and 450 mg/kg acyclovir survived significantly longer than control female mice; survival of treated males was comparable to survival of control males. Patterns of tumor incidence and tumor counts for benign or malignant neoplasms were not affected by treatment with acyclovir.

Chronic 12-Month Oral Toxicity Study in Dogs: Purebred Beagle dogs were given 0, 15, 45 or 150 mg/kg/day of acyclovir each day for the first two weeks of a 1-year study. There were 9 male and 9 female dogs in each test group. The dogs were given gelatin capsules that contained the appropriate dose. They were treated t.i.d., hence the dosages administered at each of three equally spaced dose periods were 0, 5, 15 and 50 mg/kg. The 45 and 150 mg/kg dose levels induced diarrhea, emesis, decreased food consumption and weight loss in both male and female dogs during the first two weeks of the study. For this reason, during the third week of the study the decision was made to decrease the mid- and high-dosage levels to 30 and 60 mg/kg/day (10 and 20 mg/kg t.i.d.). The low dose of 15 mg/kg/day (5 mg/kg t.i.d.) was unchanged. Dogs given 60 mg/kg/day occasionally vomited and occasionally had diarrhea but did well for the duration of the test, and values for body weight gain and food consumption were comparable to control values.

During the toxicosis induced by the larger doses of acyclovir, plasma levels of the drug were likely very high (as indicated by initial mean values of 24.0 μg/mL (106.6 μM) for high-dose males and 17.4 μg/mL (77.2 ⎵M) for high-dose females when determined 1 hour after the third dose on day 1 of the study). When measured on day 15, plasma levels of acyclovir in high-dose dogs (150 mg/kg/day) were still very high but they decreased later when the dosages were decreased. Values for plasma levels after 12 months of treatment were generally comparable to values recorded after 1, 3 and 6 months of treatment. Thus, there was no indication of enhanced metabolism of acyclovir as a result of chronic treatment.

During the 13th week, some male and female dogs at both the mid- and high-dosage levels had the following signs: tenderness in forepaws, erosion of footpads, and breaking and loosening of nails. Regeneration of lost nails began a few weeks later. Nails regenerated by 6 months (when 3 males and 3 females from each group were killed for an interim sacrifice) and by the end of the study were of generally good quality. There were never any signs of an effect on paws or nails in dogs in the low dose group (15 mg/kg/day).

It is accepted that injury of the corial epithelium that produces nail keratin can result in arrested production of keratin and production of abnormal keratin. The transient toxicosis induced by the large doses (45 and 150 mg/kg/day) of acyclovir given during the first two weeks of the study may have affected the corial epithelium. If there was a transient effect on the corial epithelium (possibly related to direct effects or secondary to drug-induced illness during the first two weeks of the study) later loss of the nail could be a sequella. No discernible effects upon other keratin-producing or keratin-containing tissues were observed. It should be emphasized that the alterations in the nails appeared to be related to the transient toxicosis induced by dose levels of 50 and 150 mg/kg/day tested during the first two weeks of the study and not to the 30 and 60 mg/kg/day dose levels tested subsequently.

There were no important drug-induced alterations in values for serum biochemical tests, urinalyses and electrocardiographic tests done at appropriate intervals during this study. Values for serum albumin and total protein were slightly decreased in dogs treated at 30 and 60 mg/kg/day for 6 and 12 months. However, all values for these parameters remained within limits accepted as normal.

With the exception of residual alterations in old keratin at the tips of the claws, there were no signs of treatment-related effects in any of the tissues examined by light microscopy. Nor were there meaningful alterations in values for the organs weighed at necropsy. Thus, dose levels up to 60 mg/kg/day were well tolerated for one year. The "no dose effect" dose level of acyclovir was 15 mg/kg/day (5 mg/kg t.i.d.); however, the only adverse effects at 30 or 60 mg/kg/day were changes in nails and footpads (30 and 60 mg/kg/day) and mild gastrointestinal signs (60 mg/kg/day).

Reproduction Studies

Teratology – Rats: Acyclovir was administered to pregnant A.R.S. Sprague-Dawley female rats by subcutaneous injection during the period of organogenesis (day 6 through day 15 of gestation) at dose levels of 0.0, 6.0, 12.5 and 25.0 mg/kg body weight twice daily.

Criteria evaluated for compound effect included maternal body weights, weight gains, appearance and behavior, survival rates, eye changes, pregnancy rates, and reproduction data. Offspring viability and development were also evaluated.

In addition to the above measurements, designated animals were sacrificed 1 hour after the first

dose on day 15 in order to collect samples of maternal blood, amniotic fluid and fetuses for measurements of drug concentration. Mean values from these samples are listed in Table 8.

Table 8 Acyclovir Concentrations in a Teratology Study in Rats

Dose mg/kg bid., s.c.		**Plasma (μg/mL)**	**Acyclovir Concentrations**		
			Amniotic Fluid (μg/mL)	**Fetal Homogenate**	
				μg/mL	**(nmoles/g wet wt)**
6	N=7	0.26±0.09	0.39±0.06	0.70	(3.13±0.50)
12.5	N=5	0.69±0.20	1.13±0.22	0.96	(4.28±0.67)
25	N=5	1.59±0.55	2.0±0.53	1.95	(8.64±2.33)

The values obtained for plasma would represent about 30% of initial plasma levels as judged by the plasma half-life in rodents.

No effects attributable to the administration of acyclovir were noted in comparisons of maternal body weight values, appearance and behavior, survival rates, pregnancy rates, or implantation efficiencies. In addition, no compound-related differences were noted in evaluations of fetal size, sex, and development.

Although the incidences of resorption and fetal viability were within the range of normal variability in all of the groups, slightly greater incidences of resorptions were noted in the high-dose animals sacrificed on days 15 and 19 of gestation; however, clear dose-related trends did not eventuate.

Therefore, acyclovir was not considered teratogenic or embryotoxic when administered to rats at levels up to 50.0 mg/kg of body weight per day during organogenesis.

Teratology – Rabbits: A teratology study was done in New Zealand White rabbits using essentially the same experimental design as in the rat, except that dosing was from day 6 through day 18 of gestation. Also, collection of fetuses, amniotic fluid and samples of maternal blood occurred on day 18 rather than day 15.

No signs of maternal toxicity were observed at any dose, but there was a statistically significant ($p<0.05$) lower implantation efficiency in the high-dose group. While there were a few terata observed in the study (in both control and treated animals), there was no apparent association with drug treatment. There was, however, an apparent dose-related response in the number of fetuses having supernumerary ribs. No similar effect was noted in the rat teratology study (see above) or in a reproduction-fertility experiment in mice.

Concentrations of acyclovir were detected in plasma and amniotic fluid samples, as well as in homogenates of fetal tissues. All samples were taken one hour after the first dose on day 18 of

gestation. Drug concentrations in amniotic fluid were substantially higher than that of plasma (see Table 9).

Table 9 Acyclovir Concentrations in a Teratology Study in Rabbits

Dose mg/kg bid., s.c.		Plasma (μg/mL)	Acyclovir Concentrations (Mean and S.E.)		
			Amniotic Fluid (μg/mL)	Fetal Homogenate	
				μg/mL	(nmoles/g wet wt)
6	N=4	0.25±0.03	0.89±0.18	0.16	(0.69±0.13)
12.5	N=5	0.25±0.05	8.03±6.37	0.21	(0.92±0.14)
25	N=4	0.39±0.12*	6.16±4.25	0.32	(1.40±0.19)

*N=5

Reproduction – Fertility: Acyclovir was shown not to impair fertility or reproduction in groups of 15 male and 30 female mice in a two-generation fertility study. The mice in this study were given acyclovir by gastric intubation at dosage levels of 50, 150 and 450 mg/kg/day. Males were dosed for 64 consecutive days prior to mating and females for 21 days prior to mating.

In a rat fertility study where groups of 20 male and 20 female rats were given 0, 12.5, 25.0 and 50.0 mg/kg/day by subcutaneous injection, acyclovir was shown not to have an effect on mating or fertility. The males were dosed for 60 days prior to mating and until their mating schedule was completed. Female rats were dosed for 14 days prior to mating and until day 7 of pregnancy. At 50 mg/kg/day s.c. there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size.

In 25 female rabbits treated subcutaneously with 50 mg/kg/day acyclovir on days 6 to 18 of gestation, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size. There was also a dose-related increase in the number of fetuses with supernumerary ribs in all drug-treated groups. This increase was not dose-related when the incidence of supernumerary ribs per litter was examined.

In 15 female rabbits treated intravenously with 50 mg/kg/day acyclovir on days 6 to 18 of gestation, there was no effect on either implantation efficiency or litter size.

In a rat peri- and postnatal study (20 female rats per group), acyclovir was given subcutaneously at 0, 12.5, 25 and 50 mg/kg/day from 17 days of gestation to 21 days postpartum. At 50 mg/kg/day s.c. there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F1 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.

In a dose-range finding study with 5 female rabbits the intravenous administration of acyclovir at a dose of 100 mg/kg/day from days 6 to 8 of pregnancy, a dose known to cause obstructive

nephropathy, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. At a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits there were no drug-related reproductive effects.

In a subchronic toxicity study where groups of 20 male and 20 female rats were given intraperitoneal doses of acyclovir at 0, 20, 80 or 320mg/kg/day for one month, and followed for a one-month postdose period, there was testicular atrophy. Some histologic evidence of recovery of sperm production was evident 30 days postdose, but this was insufficient time to demonstrate full reversibility.

Groups of 25 male and 25 female rats were administered intraperitoneal doses of acyclovir at 0, 5, 20 or 80 mg/kg/day for 6 months. Ten male and 10 female rats in each group were continued undosed for 13 weeks. Testicular atrophy was limited to high-dose rats given 80 mg/kg/day for 6 months. Organ weight data and light microscopy defined full reversibility of the testicular atrophy by the end of the postdose recovery period.

In a 31 -day dog study (16 males and 16 females per group) where acyclovir was administered intravenously at levels of 50, 100 and 200 mg/kg/day, testicles were normal in dogs at 50 mg/kg. Doses of 100 or 200 mg/kg/day caused death of some dogs due to cytostatic effects (bone marrow and gastrointestinal epithelium) and aspermic testes or testes with scattered aspermic tubules. It cannot be ruled out that the testicular change may have been primary, however, similar changes can be observed secondary to severe stress in moribund dogs.

Developmental Toxicity Studies

Neonatal Rats - Subchronic Study: Acyclovir dissolved in 0.4% sterile saline was given by subcutaneous injection to Charles River CD (Sprague-Dawley) neonatal rats for 19 consecutive days, beginning on the 3rd post-partum day. The dose levels tested were 0, 5, 20 and 80 mg/kg body weight. There were 12 litters (each consisting of 5 male and 5 female neonates nursing the natural dam) at each dose level. The dams were not treated. Neonates were removed from each group for necropsy and microscopic evaluation of a wide variety of tissues, including eyes and multiple sections of brain, after they had been treated for 5, 12 or 19 days and after a 3-week postdose drug-free period (at which time they were 45 days of age). Hematologic (hemoglobin, packed cell volume, RBC, WBC and differential cell counts) and clinical chemistry (BUN) tests were done after 16 days of treatment and repeated 18 days after the last (19th) dose was given.

Blood was collected from some neonates 30 minutes after treatment on day 1, on day 9 and at the end of the dose period for the determination of concentrations of acyclovir in plasma. The largest concentration of acyclovir in plasma was 99.1 μg/mL (440.5 μM) found in pooled plasma collected from 6 female high-dose (80 mg/kg) neonates 30 minutes after the first dose was given. Treatment with acyclovir did not increase mortality in the neonatal period.

Rats in the low-dose group gained as much body weight as the respective control rats. Significant ($p<0.05$) reductions in mean body weight values were observed in mid- and high-dose group

male and female neonates during the treatment period. Rats in the high-dose group partially compensated by gaining significantly more body weight than the controls during the post-dose recovery period. There was a minimal but significant increase in BUN for male ($p<0.01$) and female (<0.05) neonates in the high-dose group on dose day 16. This finding may be of biological importance because there were minimal accumulations of nuclear debris in renal collecting ducts and loops of Henle in kidney sections taken from high-dose neonates after 19 days of treatment and examined by light microscopy. This was the only time period (and the kidney was the only organ) in which minimal effects on developing organ systems were detected. Thus, 5 mg/kg was clearly a no effect dose level and 20 mg/kg caused only minimal decreases in body weight gain.

Eye examinations and light microscopy did not reveal adverse effects on ocular development. It should be emphasized that there was no morphologic or functional evidence of adverse effects on developing brain or other portions of the central nervous system. Thus, acyclovir is distinctly different than cytosine arabinoside which was reported to produce prominent cerebellar and retinal dysplasia in neonatal rats.

Mutagenicity and Other Short-Term Studies

Acyclovir has been tested for mutagenic potential in a number of *in vitro* and *in vivo* systems:

Microbial: Acyclovir was tested for mutagenic activity in the Ames Salmonella plate assay; in a preincubation modification of the Ames assay; in the Rosenkrantz E. coli $polA^+/polA^-$ DNA repair assay; and in the eukaryote S. cerevisiae, D-4. All studies were performed both in the presence and absence of exogenous mammalian metabolic activation. Acyclovir gave no positive responses in any of these systems.

The previous Salmonella studies were extended to extremely high concentrations in order to achieve toxicity. No positive effects were observed either in the presence or absence of exogenous mammalian metabolic activation, at concentrations of acyclovir up to 300 mg/plate or 80 mg/mL.

Mammalian Systems: Acyclovir was tested for mutagenic activity in cultured L5178Y mouse lymphoma cells, heterozygous at the thymidine kinase (TK) locus, by measuring the forward mutation rate to TK-deficiency ($TK^{+/-} \rightarrow TK^{-/-}$) additional studies were performed at the HGPRT locus and at the Ouabain-resistance marker in these same cells. All studies were performed in the presence and in the absence of exogenous mammalian metabolic activation. The test compound was mutagenic at the TK locus at high (400-2400 ⌋g/mL) concentrations. (By comparison, the upper limit of acyclovir peak plasma levels following oral dosing of 200 mg q4h is 0.9 μg/mL). It was negative at the HGPRT locus and Ouabain-resistance marker. Identical results were obtained with and without metabolic activation.

Inconclusive results with no apparent dose-related response were obtained when acyclovir mutagenicity was studied at each of 3 loci (APRT, HGPRT and Ouabain-resistance) in Chinese

hamster ovary (CHO) cells, both in the presence and absence of exogenous metabolic activation.

Acyclovir, at a concentration of 50 μg/mL (222 μM) for a 72-hour exposure, has been shown to cause a statistically significant increase in the incidence of morphologically-transformed foci resulting from treating BALB/C-3T3 cells *in vitro* in the absence of exogenous metabolic activation. The morphologically transformed foci have been shown to grow as tumors following transplantation into immunosuppressed, syngeneic, weanling mice. Tumour tissues were diagnosed as being either undifferentiated sarcomas or lymphosarcomas.

Acyclovir at concentrations between 8 μg/mL and 64 μg/mL for 18 hours' exposure did not induce any morphologically-transformed foci among C3H/10T 1/2 cells treated *in vitro* in the absence of exogenous metabolic activation.

Acyclovir, at concentrations of 62.5 and 125μg/mL for a 48-hour exposure, did not induce any chromosome aberrations in cultured human lymphocytes in the absence of exogenous metabolic activation. At higher concentrations - 250 and 500 μg/mL for 48 hours exposure - acyclovir caused a significant increase in the incidence of chromosome breakage. There was also a significant dose-related decrease in mitotic index with exposure to acyclovir.

Acyclovir, at doses of 25 and 50 mg/kg/day i.p. for 5 consecutive days, did not produce a dominant lethal effect in male BKA (CPLP) mice. Further, there was no evidence of a dominant lethal effect on Charles River CD-1 (ICR) male and female mice treated orally at dose levels of 50, 150 and 450 mg/kg/day as summarized for the Two Generation Reproduction/Fertility Study.

Acyclovir, at single intraperitoneal doses of 25, 50 and 100 mg/kg, failed to induce chromosome aberrations in bone marrow cells of Chinese hamsters when examined 24 hours after dosing. At higher nephrotoxic doses (500 and 1000 mg/kg), a blastogenic effect was seen. (An intraperitoneal dose of 500 mg/kg produces mean peak plasma levels in Chinese hamsters of 611 μg/mL (2.72 mM) which is 680 times higher than the upper limit of human peak plasma levels during oral dosing of 200 mg q4h).

Acyclovir, at single intravenous doses of 25, 50 and l00 mg/kg, failed to induce chromosome aberrations in bone marrow cells of male and female rats when examined at 6, 24 and 48 hours after treatment.

Thus, all these studies showed that acyclovir does not cause single-gene mutations but is capable of breaking chromosomes.

Immunotoxicology Studies

Acyclovir was subjected to a number of *in vitro* and *in vivo* immunological tests.

In two *in vivo* tests, lymphocyte-mediated cytotoxicity and neutrophil chemotaxis, acyclovir showed no inhibitory effects at concentrations as high as 135 μg/mL (600 μM). The compound

inhibited rosette formation approximately 50% at 0.9 μg/mL(4 μM).

In four *in vivo* tests in mice which measured cell-mediated immunity (complement-dependent cellular cytotoxicity, complement-independent cellular cytotoxicity, delayed hypersensitivity and graft vs. host reaction) acyclovir showed no inhibitory effects at single doses up to 200 mg/kg given on day 2 after antigenic stimulation.

Four daily doses of l00 mg/kg/day had no significant effect on Jerne hemolysin plaques or circulating antibody on day 7 after antigenic stimulation. When the Jerne hemolysin plaques and antibody titers were examined four days after antigenic challenge and one day after the last drug dose, l00 mg/kg showed only a slight suppressive effect. However, 200 mg/kg produced some weight loss (-2.2 g), a moderate reduction in the number of Jerne hemolysin plaques (PFC/spleen were reduced to 33% of control, PFC/107 WBC to 46.5% of control). However, there was only a small reduction in the circulating hemagglutinin titer (from 8.3 to 6.5) and the circulating hemolysin titer (from 9.5 to 8.3) at 200 mg/kg.

In experiments in mice designed to test whether acyclovir would potentiate the immunosuppressive effect of azathioprine on antibody formation, it was found that the effects of the two drugs were no more than additive. Only the 200 mg/kg dose of acyclovir showed an increased suppression of antibody response when given in combination with azathioprine at doses above 25 mg/kg.

Studies were carried out to evaluate the influence of acyclovir *in vitro* on human lymphocyte function. Inhibitory effects on blastogenesis were seen only in assays examining peak concentrations of potent mitogens, phytohemagglutinin (PHA) and concanavalin A (Con A), and only at concentrations of drug above 50 μg/mL (222 ⎦M) and were much less with monilia and tetanus toxoid antigens, where the blastogenic response is characteristically less vigorous. There was very little effect on cytotoxicity or LIF production except at concentrations of 200 μg/mL (890 μM) where there has already been demonstrated to be a direct cytotoxic effect. These inhibitory concentrations are far in excess of anticipated levels from doses selected for clinical application and over 1000-fold higher than the concentration required to inhibit herpesvirus multiplication *in vitro*.

The effect of acyclovir on human cells was measured. A concentration of 11.2-22.5 μg/mL (50-100 μM) inhibits the division of fibroblasts to a variable extent, depending on the experimental design and the confluency of the monolayer. The magnitude of this effect was less than that caused by adenine arabinoside or human leukocyte interferon when these three antiviral agents were compared at clinically relevant concentrations. Acyclovir also inhibited thymidine incorporation by peripheral blood mononuclear cells stimulated by PHA or three different herpesvirus antigens. A linear dose-response curve was observed with these cells, and their proliferation was 50% inhibited by 22.5 μg/mL (100 μM) acyclovir. Inhibition was exerted on T-cell proliferation without apparent effect on the release of lymphokines or on monocyte function.

It should also be mentioned that there was no evidence of adverse effects on the immune system in the detailed subchronic and chronic animal tests covered earlier in this summary except at excessively high doses (50 to 100 mg/kg b.i.d.) in dogs where marked lymphoid hypoplasia occurred.

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CONSUMER INFORMATION

[Pr]TEVA-ACYCLOVIR TABLETS
(Acyclovir, as Acyclovir Hydrate)

This leaflet is part III of a three-part "Product Monograph" published when TEVA-ACYCLOVIR TABLETS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-ACYCLOVIR TABLETS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for and what it does:
TEVA-ACYCLOVIR is an antiviral medicine.

Treatment of shingles (herpes zoster)
TEVA-ACYCLOVIR is used to treat shingles (herpes zoster) infections. Shingles is caused by the varicella-zoster virus. The virus multiplies in and eventually destroys affected skin cells. TEVA-ACYCLOVIR stops the virus from multiplying and therefore from spreading to neighbouring healthy cells. It cannot replace a cell which has been damaged by the multiplying virus, but it will facilitate the process of healing.

Treatment of chickenpox (varicella)
TEVA-ACYCLOVIR is used to treat chickenpox (varicella) which is caused by the varicella-zoster virus and is highly contagious. The disease is most contagious shortly before the rash appears, through the early stages of the rash and until all the blisters have dried. A patient is not contagious once all the blisters have become scabs.

Treatment and suppression of genital herpes
TEVA-ACYCLOVIR is used to treat initial episodes of genital herpes.

Genital herpes is a sexually transmitted infection caused by the herpes simplex virus (HSV). HSV causes small, fluid-filled blisters in the genital area which break down into ulcers/sores which may be itchy or painful. The fluid in these blisters contains the virus which causes the disease. It is a feature of all herpes viruses that once in the body, they stay throughout life alternating between active (outbreak) and inactive states.

When taken on a daily basis, TEVA-ACYCLOVIR can also be used to prevent the HSV infection from coming back. This type of treatment is called suppressive therapy.

When it should not be used:
You should not use TEVA-ACYCLOVIR if you are allergic to or react badly to acyclovir or valacyclovir or any other components of the formulation of TEVA-ACYCLOVIR (see "What the non-medicinal ingredients are" section). Tell your doctor if you have ever had an allergic reaction to any of these ingredients.

What the medicinal ingredient is:
Acyclovir

What the non-medicinal ingredients are:

TEVA-ACYCLOVIR 200 mg TABLETS contain the non-medicinal ingredients colloidal silicon dioxide, FD&C Blue#2, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch and sodium starch glycolate.

TEVA-ACYCLOVIR 400 mg TABLETS contain the non-medicinal ingredients colloidal silicon dioxide, FD&C Yellow #6, FD&C Blue #1, D&C Red #7 , lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch and sodium starch glycolate.

TEVA-ACYCLOVIR 800 mg TABLETS contain the non-medicinal ingredients colloidal silicon dioxide, FD&C Blue#2, FD&C Blue #1, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch and sodium starch glycolate.

What dosage forms it comes in:
TEVA-ACYCLOVIR 200mg TABLETS are blue, shield-shaped compressed tablets contain 200mg acyclovir, and are engraved with "N" on one side and "200" on the other side.

TEVA-ACYCLOVIR 400mg TABLETS are pink, shield-shaped compressed tablets contain 400mg acyclovir, and are engraved with "N" on one side and "400" on the other side.

TEVA-ACYCLOVIR 800mg TABLETS are blue, elongated, scored compressed tablets contain 800mg acyclovir, and are engraved with "N|N" on one side and "800" on the other side.

WARNINGS AND PRECAUTIONS

Before using TEVA-ACYCLOVIR, tell your doctor if:

- You have kidney problems or if you are 65 years of age or older. Your doctor may give you a lower dose of TEVA-ACYCLOVIR and/or ask you to stay hydrated.
- You are severely immunocompromised (e.g. suffering a severe disease or have recently undergone an organ transplant, and are taking immunosuppressant drugs for either of these conditions).
- You are pregnant, planning to become pregnant, breastfeeding or planning to breastfeed

The safety and effectiveness in children less than 2 years of age are not known.

You must make sure you **drink plenty of liquids such as water** while you are being given Teva-Acyclovir.

Feeling drowsy or sleepy may impair your ability to concentrate and react. Make sure you are not affected before you drive or operate machinery.

When using TEVA-ACYCLOVIR for suppression of genital herpes, your doctor may periodically stop your drug therapy in order to reassess your need for continuous treatment. The effect of long-term use in humans has not been fully assessed. Prudence is therefore suggested when choosing continuous, long term therapy with TEVA-ACYCLOVIR. Suppression of recurrent genital herpes is therefore, only recommended in those who are severely affected. Some patients experience increased severity of the first episode of genital herpes after stopping treatment.

Genital herpes is passed from one person to another through direct intimate contact. To reduce the risk of transmission, wash your hands immediately if you touch your skin sores, and do not touch other parts of your body until you have done so. Especially avoid intimate contact with others when the disease is visible. Herpes virus particles may also be released when you do not have blisters or sores. For this reason, it is safest to believe that you can spread the infection to your partner even when sores are not present.

Although decreased sperm counts were observed in animals treated with high doses, these effects did not occur in humans.

PROPER USE OF THIS MEDICATION

Medication should not be shared with others. The prescribed dosage should not be exceeded.

Tablets should be swallowed whole, with water.

Usual dose for shingles:
For the treatment of shingles (herpes zoster), the usual dose of TEVA-ACYCLOVIR is 800 mg every 4 hours, 5 times daily for 7 to 10 days. TEVA-ACYCLOVIR must be taken as early as possible within 72 hours after the onset of the lesions.

Usual dose for chickenpox:
For the treatment of chickenpox (varicella), the usual dose of TEVA-ACYCLOVIR is 20 mg/kg (not to exceed 800 mg) 4 times daily for 5 days. TEVA-ACYCLOVIR must be taken as early as possible within 24 hours after the appearance of rash.

Usual dose for genital herpes:
For the treatment of an initial episode of genital herpes, the usual dose of TEVA-ACYCLOVIR is 200 mg every 4 hours, 5 times daily (maximum 1 g daily) for 10 days. TEVA-ACYCLOVIR must be taken as early as possible following onset of signs and symptoms.

For the suppression of genital herpes, the usual dose of TEVA-ACYCLOVIR is 200 mg 3 to 5 times daily or 400 mg twice daily. You should follow dosing instructions carefully. The objective is to keep enough of the drug in the body at all times to prevent the herpes virus from multiplying. Your doctor will try to prescribe the minimum dose required to do this in your case and may therefore increase or decrease your dose during the first few weeks. Follow your doctor's instruction carefully to ensure that you get the best possible response to treatment

For the treatment of recurrent episodes of genital herpes, the usual dose of TEVA-ACYCLOVIR is 200 mg every 4 hours 5 times daily for 5 days. TEVA-ACYCLOVIR must be taken at the earliest sign or symptom (prodrome) of recurrence.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take a dose, take it as soon as you remember. Then continue with the next dose at the proper time interval. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with any widely prescribed medication, adverse events in association with the use of TEVA-ACYCLOVIR are reported from time to time.
Common side effects may affect up to 1 in 10 people:

- Headache
- Nausea, diarrhea, upset stomach, vomiting
- Feeling unwell
- Weakness, lack of energy
- Skin tingling, itching

Other side effects include: dizziness; high temperature (fever); itchy, bumpy rash; skin reaction after exposure to light (photosensitivity); hair loss; unusual bruising or bleeding; shortness of breath; effects on blood and urine tests; swelling of the face, lips, mouth, tongue or throat; increases in the enzymes that work in the liver; feeling agitated or confused; feeling shaky, unsteady and a lack of co-ordination; difficulty speaking or hoarseness; seeing or hearing things that are not really there; feeling drowsy or sleepy; inability to think or judge clearly or concentrate; disturbances of behaviour, speech and eye movements; unconsciousness; yellowing of the skin and whites of the eyes**,** inflammation of the liver; and changes to blood test results (reduced numbers of red blood cells, white blood cells, or blood platelets).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency	**Sympton / Effect**	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Unknown	**Severe allergic reaction:** itchy, bumpy rash; swelling, sometimes of the face or mouth causing difficulty in breathing; collapse			✓
	Kidney failure: pain in the side (between ribs and hip) or kidney area of your back			✓
	Blood disorders: unusual bruising or bleeding			✓

This is not a complete list of side effects. For any unexpected effects while taking Teva-Acyclovir, contact your doctor or pharmacist.

HOW TO STORE IT

Tablets should be stored at room temperature (15°C to 30°C) in a dry place and protected from light.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:
- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited at:

1-800-268-4127 ext. 1255005 (English);
1-877-777-9117 (French)
or druginfo@tevacanada.com

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