PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pms-VALACYCLOVIR

Valacyclovir tablets

Tablets, 500 mg and 1000 mg (as valacyclovir hydrochloride), oral

House Standard

Antiviral Agent

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Date of Initial Authorization:
MAY 15, 2008

Date of Revision:
MAY 10, 2023

Submission Control Number: 270106

RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

pms-VALACYCLOVIR, valacyclovir tablets (as valacyclovir hydrochloride), is indicated:

- For the treatment of herpes zoster (shingles) in adult patients.
- For the treatment or suppression of genital herpes in immunocompetent adult patients and for the suppression of recurrent genital herpes in HIV infected adult patients.
- To reduce the risk of transmission of genital herpes with the use of suppressive therapy in adult patients. Safer sex practices should be used with suppressive therapy.
- For the treatment of cold sores (herpes labialis) in adult patients and adolescent patients ≥ 12 years of age.

1.1 Pediatrics

Pediatrics (< 12 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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 7 WARNINGS AND PRECAUTIONS, Renal)

2 CONTRAINDICATIONS

pms-VALACYCLOVIR is contraindicated in patients with a known hypersensitivity or intolerance to valacyclovir, acyclovir, or any component of the formulation. For a complete listing of ingredients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The dosage of pms-VALACYCLOVIR should be reduced in patients with impaired renal function (see Table 1).

- Therapy should be initiated as soon as possible after a diagnosis of herpes zoster, or at the first sign or symptoms of an outbreak of oral or genital herpes.

- The recommended dose and duration of use is dependent on the indication.

- The safety and tolerability of valacyclovir hydrochloride 500 mg once daily has been established for up to 20 months (see 14 CLINICAL TRIALS and 8.1 Adverse Drug Reaction Overview).

4.2 Recommended Dose and Dosage Adjustment

Pediatrics (< 12 years of age): Health Canada has not authorized an indication for pediatric use (see 1.1 INDICATIONS, Pediatrics).

pms-VALACYCLOVIR tablets may be given without regard to meals.

Herpes Zoster (shingles): The recommended dosage of pms-VALACYCLOVIR tablets for the treatment of herpes zoster is 1000 mg orally three times daily for 7 days. Treatment with pms-VALACYCLOVIR should be initiated within 72 hours of the onset of rash.

Initial Episode of Genital Herpes: The recommended dosage of pms-VALACYCLOVIR tablets for the treatment of an initial episode of genital herpes is 1000 mg orally twice daily for 10 days. There are no data on the effectiveness of treatment with valacyclovir hydrochloride when initiated more than 72 hours after the onset of signs and symptoms. Therapy was most effective when administered within 48 hours of the onset of signs and symptoms.

Recurrent Episodes of Genital Herpes: The recommended dosage of pms-VALACYCLOVIR tablets for the treatment of recurrent episodes of genital herpes is 500 mg orally twice daily for 3 days. Therapy should be initiated at the earliest sign or symptom of recurrence. pms-VALACYCLOVIR can prevent lesion development when taken at the first signs and symptoms of a genital herpes recurrence.

Suppression of Genital Herpes: The recommended dosage of pms-VALACYCLOVIR tablets for chronic suppressive therapy of recurrent genital herpes is 1000 mg orally once daily in patients with normal immune function. The safety and efficacy of valacyclovir hydrochloride 1000 mg once daily beyond 1 year have not been established. In patients with a history of 9 or fewer recurrences per year, an alternative dose is 500 mg orally once daily. The safety and tolerability of valacyclovir hydrochloride 500 mg once daily have been established for up to 20 months (see 14 CLINICAL TRIALS and 8.1 Adverse Drug Reaction Overview).

In patients with HIV infection with CD4 cell count > 100 cells/mm^3, the recommended dosage of pms-VALACYCLOVIR tablets for chronic suppressive therapy of recurrent genital herpes is 500 mg orally twice daily. The safety and efficacy of therapy with valacyclovir hydrochloride beyond 6 months in patients with HIV infection have not been established.

Reduction of Transmission of Genital Herpes: The recommended dosage of pms-VALACYCLOVIR tablets for reduction of transmission of genital herpes in patients with a history of 9 or fewer recurrences per year is 500 mg orally once daily for the source partner. The efficacy of reducing transmission beyond 8 months in couples discordant for HSV-2 infection has not been established. The safety and tolerability of valacyclovir hydrochloride 500 mg once daily has been established for up to 20 months (see 14 CLINICAL TRIALS and 8.1 Adverse Drug Reaction Overview).

Cold Sores (Herpes Labialis): The recommended dosage of pms-VALACYCLOVIR for the treatment of cold sores (herpes labialis) is 2000 mg orally twice daily for 1 day (24-hour period). The second dose should be taken approximately 12 hours after the first dose, but not less than 6 hours after

the first dose. Therapy should be initiated at the earliest symptom of a cold sore (e.g., tingling, itching, or burning). There are no data on the efficacy of treatment initiated after the development of clinical signs of a cold sore (e.g., papule, vesicle or ulcer).

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

Pharmacokinetic and safety evaluations following administration of oral valacyclovir hydrochloride have been performed in patients with renal impairment and volunteers with end-stage renal disease (ESRD) managed by hemodialysis. Based on these studies and extensive experience with acyclovir, the following dosage adjustments are recommended (data are not available for the use of pms-VALACYCLOVIR in pediatric patients with a creatinine clearance less than 50 mL/min/1.73m^2):

Table 1 Dosage Adjustments for Adults Renal Insufficiency

	Creatinine Clearance(mL/min)			
	≥ 50	**30 to <50**	**10 to <30**	**< 10**
Herpes Zoster	1000 mg every 8 hours†	1000 mg every 12 hours	1000 mg every 24 hours	500 mg every 24 hours
Recurrent Episodes of Genital Herpes	500 mg every 12 hours†	500 mg every 12 hours†	500 mg every 24 hours	500 mg every 24 hours
Suppression of Genital Herpes				
Immunocompetent patients	1000 mg every 24 hours†	1000 mg every 24 hours†	500 mg every 24 hours	500 mg every 24 hours
Alternate dose for immunocompetent patients with less than or equal to 9 recurrences/year	500 mg every 24 hours†	500 mg every 24 hours†	500 mg every 48 hours	500 mg every 48 hours
HIV-infected patients	500 mg every 12 hours†	500 mg every 12 hours†	500 mg every 24 hours	500 mg every 24 hours
Initial Episode of Genital Herpes	1000 mg every 12 hours†	1000 mg every 12 hours†	1000 mg every 24 hours	500 mg every 24 hours
Cold Sores (Herpes Labialis)§	Two 2000 mg doses taken 12 hours apart†	Two 1000 mg doses taken 12 hours apart	Two 500 mg doses taken 12 hours apart	500 mg single dose

† Standard dose - adjustment not necessary

§ Do not exceed one day of treatment.

Intermittent Hemodialysis: During hemodialysis, the half-life of acyclovir after administration of valacyclovir hydrochloride is approximately 4 hours. About 1/3 of acyclovir in the body is removed by dialysis during a 4-hour hemodialysis session. These patients should receive the daily dose of pms-

VALACYCLOVIR recommended (Table 1), the dose administered after hemodialysis on the days it is performed.

Peritoneal Dialysis: There is no information specific to administration of valacyclovir hydrochloride. The effect of continuous ambulatory peritoneal dialysis (CAPD) and continuous arteriovenous hemofiltration/dialysis (CAVHD) on acyclovir pharmacokinetics has been studied. The removal of acyclovir after CAPD and CAVHD is less pronounced than with hemodialysis, and the pharmacokinetic parameters closely resemble those observed in patients with ESRD not receiving hemodialysis. Therefore, supplemental doses of pms-VALACYCLOVIR should not be required following CAPD or CAVHD.

4.5 Missed Dose

If a dose of pms-VALACYCLOVIR 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.

5 OVERDOSAGE

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

Acute renal failure and neurological symptoms, including confusion, hallucinations, agitation, decreased consciousness and coma, have been reported in patients receiving overdoses of valacyclovir hydrochloride. Nausea and vomiting may also occur. Caution is required to prevent inadvertent overdose. Many of the reported cases involved renally impaired and geriatric patients receiving repeated overdoses, due to lack of appropriate dosage reduction (see 7 WARNINGS AND PRECAUTIONS, Renal; and 8.5 Post- Market Adverse Reactions, Renal).

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. However, it is known that precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Acute or Chronic Renal Insufficiency).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Route of Administration, Dosage Forms, Strengths, Non-medical Ingredients

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Tablets, 500 mg and 1000 mg valacyclovir (as valacyclovir hydrochloride)	Crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate, titanium dioxide. In addition, the 500 mg tablets also contain: FD&C blue #2 aluminum lake.

pms-VALACYCLOVIR 500 mg tablets are blue, coated, capsule-shaped tablet (caplet), debossed with "VC" followed by "500" on one side and nothing on the other side. Available in bottles of 100 tablets.

pms-VALACYCLOVIR 1000 mg tablets are white, coated, capsule-shaped tablet (caplet), debossed with "VC" and "1G" on one side, and 2 dashes debossed perpendicularly to the tablet's length on each side, at mid-length of the tablet. Available in bottles of 100 tablets and blister packs of 21 tablets.

7 WARNINGS AND PRECAUTIONS

General

Care should be taken to ensure adequate fluid intake in patients who are at risk of dehydration particularly in geriatric patients.

The safety and efficacy of valacyclovir hydrochloride have not been established for the treatment of disseminated herpes zoster.

The safety and efficacy of valacyclovir hydrochloride have not been established in immunocompromised patients other than for the suppression of ano-genital herpes in HIV-infected patients. The safety and efficacy of valacyclovir hydrochloride for the suppression of recurrent ano-genital herpes in patients with advanced HIV disease (CD4 cell count < 100 cells/mm^3) have not been established.

Patients should be informed that pms-VALACYCLOVIR is not a cure for genital herpes.

Safer sex practices should be used in combination with suppressive therapy. pms-VALACYCLOVIR alone should not be used for reducing the risk of transmitting genital herpes. Because genital herpes is a sexually transmitted infection, patients should, in order to further reduce the risk of infecting partners, avoid contact with lesions, damaged skin/mucosa, and also avoid intercourse when lesions and/or symptoms are present. Genital herpes is frequently transmitted in the absence of symptoms through asymptomatic viral shedding; therefore, patients should be counselled to use safer sex practices. The effect of valacyclovir hydrochloride on transmission of sexually transmitted infections other than

herpes (including HIV, gonorrhea, syphilis and Chlamydia) is unknown.

The efficacy of valacyclovir hydrochloride for reducing transmission of genital herpes has not been established in individuals with multiple partners, non-heterosexual couples, and couples not counselled to use safer sex practices.

Driving and Operating Machinery
Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hepatic/Biliary/Pancreatic
Dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dosage adjustment. There are no data available on the use of higher doses of valacyclovir hydrochloride (4 g or more per day) in patients with liver disease. Caution should therefore be exercised when administering higher doses of pms-VALACYCLOVIR to these patients.

Immune
Drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, has been reported in association with valacyclovir treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of DRESS appear, valacyclovir should be withdrawn immediately and an alternative treatment considered (as appropriate). If a patient has developed DRESS with the use of valacyclovir, treatment with valacyclovir must not be restarted in this patient at any time.

Neurologic
Psychiatric and central nervous system adverse reactions (e.g., agitation, hallucinations, confusion, and encephalopathy): May occur in both adult and pediatric (≥ 12 years of age) patients (with or without reduced renal function) and in patients with underlying renal disease who receive higher than recommended doses of pms-VALACYCLOVIR for their level of renal function. Elderly patients are more likely to have central nervous system adverse reactions. Use with caution in elderly patients and reduce dosage in patients with renal impairment.

Renal
Renal insufficiency or acute renal failure has been observed in patients taking valacyclovir hydrochloride at the recommended dosage and/or with no previous renal conditions and may be associated with renal pain (see 8.5 Post-Market Adverse Reactions).

Acyclovir, the active metabolite of valacyclovir, is eliminated by renal clearance, therefore the dose of pms-VALACYCLOVIR must be reduced in patients with renal impairment (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Acute or Chronic Renal Insufficiency). Geriatric patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both geriatric patients and patients with a history of 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 8.5 Post-Market Adverse Reactions, Central Nervous System Symptoms).

Cases of acute renal failure have been reported in patients without adequate hydration. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. Adequate hydration should be maintained for all patients.

Caution should be exercised when administering pms-VALACYCLOVIR to patients with significant renal impairment or those receiving potentially nephrotoxic agents, since this may increase the risk of renal dysfunction (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Acute or Chronic Renal Insufficiency) and/or the risk of reversible central nervous system symptoms such as those that occur infrequently in patients treated with intravenous acyclovir.

Given the dosage recommendations for treatment of cold sores, special attention should be paid when prescribing pms-VALACYCLOVIR for cold sores in patients who are geriatric or who have impaired renal function (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Acute or Chronic Renal Insufficiency, Table 1). Treatment should not exceed 1 day (2 doses of 2000 mg in 24 hours). Therapy beyond 1 day does not provide additional clinical benefit.

In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored.

Thrombotic Thrombocytopenic Purpura/ Hemolytic Uremic Syndrome (TTP/HUS)

Thrombotic Thrombocytopenic Purpura/ Hemolytic Uremic Syndrome (TTP/HUS), in some cases resulting in death, has occurred in patients with advanced HIV-1 disease, and also in allogenic bone marrow transplant and renal transplant recipients participating in clinical trials of valacyclovir hydrochloride at a dose of 8000 mg per day. Treatment with pms-VALACYCLOVIR should be stopped immediately if clinical signs, symptoms, and laboratory abnormalities consistent with TTP/HUS occur.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies with either acyclovir or valacyclovir hydrochloride in pregnant women. In a study of the pharmacokinetics of valacyclovir and acyclovir during late pregnancy, the steady-state daily acyclovir AUC (area under plasma concentration-time curve) following valacyclovir 1000 mg was approximately 2 times greater than that observed with oral acyclovir at 1200 mg daily. pms-VALACYCLOVIR tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy registries have documented the pregnancy outcomes in women exposed to valacyclovir hydrochloride or to any formulation of acyclovir (the active metabolite of valacyclovir); 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy), respectively, were obtained from women prospectively registered. The findings of the acyclovir pregnancy registry have not shown an increase in the number of birth defects amongst acyclovir-exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause. Given the small number of women enrolled into the valacyclovir pregnancy registry, reliable and definitive conclusions could not be reached regarding the safety of valacyclovir hydrochloride in pregnancy.

Valacyclovir hydrochloride was not teratogenic in rats or rabbits given 400 mg/kg (which results in 10 and 7 times human plasma levels, respectively) during the period of major organogenesis. However, in a non-standard test in rats given three subcutaneous doses of 100 mg/kg acyclovir (20 times human plasma levels) on gestation day 10, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.

7.1.2 Breast-feeding

Acyclovir, the principal metabolite of valacyclovir, is excreted in breast milk. Following oral administration of a 500 mg dose of valacyclovir, peak acyclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 (median 1.4) times the corresponding maternal acyclovir serum concentrations. The acyclovir breast milk to maternal serum AUC ratios ranged from 1.4 to 2.6 (median 2.2).

The median acyclovir concentration in breast milk was 2.24 µg/mL (9.95 µM). With a maternal valacyclovir dosage of 500 mg twice daily, this level would expose a nursing infant to a daily oral acyclovir dosage of about 0.61 mg/kg/day. The elimination half-life of acyclovir from breast milk was similar to that for serum.

Unchanged valacyclovir was not detected in maternal serum, breast milk, or infant urine.

Caution should be exercised when pms-VALACYCLOVIR is administered to a nursing woman. Consideration should be given to temporary discontinuation of nursing, as the safety of valacyclovir hydrochloride has not been established in infants.

7.1.3 Pediatrics

Pediatrics (< 12 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Of the total number of patients included in clinical studies of valacyclovir hydrochloride, more than 800 were age 65 or older, and more than 300 were age 75 or older. A total of 34 volunteers age 65 or older completed a pharmacokinetic trial of valacyclovir hydrochloride. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of valacyclovir hydrochloride tablets in geriatric volunteers varied with renal function. The possibility of renal impairment in geriatric patients must be considered and the dosage should be adjusted accordingly (see 7 WARNINGS AND PRECAUTIONS, Renal, and 4.2 Recommended Dose and Dosage Adjustment, Patients with Acute or Chronic Renal Insufficiency). Adequate hydration should be maintained.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following serious adverse reactions are discussed in greater detail in 7 WARNINGS AND PRECAUTIONS:

- Thrombotic Thrombocytopenic Purpura/ Hemolytic Uremic Syndrome
- Acute Renal Failure
- Central Nervous System Effects

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

Neurological side effects have also been reported in rare instances. Geriatric 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 7 WARNINGS AND PRECAUTIONS; and 8.5 Post-Market Adverse Reactions).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Herpes Zoster: Adverse drug reactions were not significantly different in recipients of valacyclovir hydrochloride compared to placebo or acyclovir in the two double-blind, randomized clinical trials of treatment of herpes zoster (shingles) in immunocompetent patients. The most frequent adverse drug reactions reported in recipients of valacyclovir hydrochloride are listed in Table 3.

Table 3 Incidence (%) of Drug-Related Adverse Reactions Occurring in ≥ 1 % of Patients Receiving valacyclovir hydrochloride in Two Clinical Trials of Treatment of Herpes Zoster

Adverse Drug Reaction	Herpes Zoster			
	18-50 Years		> 50 Years	
	Valacyclovir hydrochloride (n=202) (%)	Placebo (n=195) (%)	Valacyclovir hydrochloride (n=765) (%)	Acyclovir (n=376) (%)
Nausea	8	6	12	14
Headache	11	8	8	7
Diarrhea	4	4	4	4
Vomiting	2	2	4	3
Asthenia	1	3	3	2
Constipation	< 1	< 1	3	3
Abdominal pain	< 1	1	2	1
Anorexia	< 1	2	2	2
Dizziness	1	1	2	2
Dry Mouth	< 1	0	2	1
Dyspepsia	0	< 1	2	1
Flatulence	0	0	1	1
Pruritus	1	0	< 1	0

Genital Herpes: In two double-blind, randomized trials of treatment of recurrent genital herpes in immunocompetent patients, adverse drug reactions were not significantly different in recipients of

valacyclovir hydrochloride compared to placebo. The most frequent adverse reactions are listed in Table 4.

Table 4 Incidence (%) of Drug-Related Adverse Reactions Occurring in ≥ 1 % of Patients Receiving valacyclovir hydrochloride in two Clinical Trials of Treatment of Recurrent Genital Herpes

Adverse Drug Reaction	Valacyclovir hydrochloride (n=1235) (%)	Placebo (n=439) (%)
Headache	11	9
Nausea	5	6
Diarrhea	4	4
Dizziness	2	2
Abdominal pain	2	1
Asthenia	1	3

In two recurrent genital herpes suppression studies of immunocompetent patients, adverse drug reactions were not significantly different in recipients of valacyclovir hydrochloride 1000 mg once daily or valacyclovir hydrochloride 500 mg once daily, compared to placebo or acyclovir 400 mg twice daily. The most frequent adverse reactions are reported in Table 5.

Table 5 Incidence (%) of Drug-Related Adverse Reactions Occurring in ≥ 1 % of Patients Receiving valacyclovir hydrochloride in Two Clinical Trials for Suppression of Recurrent Genital Herpes

	Trial 123-026 (52 Weeks)				Trial 123-037 (16 Weeks)	
Adverse Drug Reaction	Valacyclovir hydrochloride 1000 mg q.d. (n=269) (%)	Valacyclovir hydrochloride 500 mg q.d. (n=266) (%)	Acyclovir 400 mg b.i.d. (n=267) (%)	Placebo (n=134) (%)	Valacyclovir hydrochloride 500 mg q.d. (n=288) (%)	Placebo (n=94) (%)
Headache	13	13	12	11	7	6
Nausea	8	8	6	5	6	9
Abdominal pain	4	2	3	3	2	2
Diarrhea	4	3	5	7	2	0
Dyspepsia	3	< 1	3	2	< 1	0
Dizziness	2	2	1	1	< 1	1
Pain	2	2	< 1	< 1	< 1	1
Acne	1	< 1	< 1	0	< 1	0
Arthralgia	1	0	0	0	0	0
Constipation	1	< 1	1	0	< 1	0
Flu syndrome	1	< 1	< 1	< 1	0	0
Vomiting	1	< 1	1	0	< 1	2
Depression	< 1	1	< 1	1	< 1	0
Insomnia	< 1	2	< 1	< 1	0	0
Migraine	< 1	< 1	< 1	1	1	1
Paresthesia	< 1	1	< 1	< 1	0	0
Rash	< 1	2	1	1	1	0
Asthenia	0	2	1	< 1	0	1
Dry mouth	0	3	< 1	< 1	< 1	1

Eczema	0	1	< 1	0	< 1	1
Pruritis	0	1	1	0	< 1	0
Vasodilatation	0	< 1	0	0	1	0

In one multicenter, double-blind, randomized study of immunocompetent patients for the treatment of an initial episode of genital herpes, the frequency of adverse events, regardless of attributability to study medication, was similar in both treatment groups: Valacyclovir hydrochloride 1000 mg twice daily (n=318) compared to acyclovir 200 mg five times a day (n=318). The most frequent adverse events were headache (13% with valacyclovir hydrochloride versus 10% with acyclovir) and nausea (6% with both treatments). All other adverse events were reported by 3% or less of patients.

In a 6-month study of suppression of recurrent genital herpes in HIV-infected patients, adverse drug reactions were similar in nature and incidence in the groups receiving valacyclovir hydrochloride 500 mg twice daily and placebo when duration of exposure was considered. Adverse reactions reported with an incidence ≥ 1% during the double-blind phase are detailed in Table 6.

Table 6 Incidence (%) of Drug-Related Adverse Reactions Occurring in ≥ 1% of Patients Receiving valacyclovir hydrochloride in a Clinical Trial for Suppression of Recurrent Genital Herpes in HIV-Infected Patients

Adverse Drug Reaction	**Valacyclovir 500 mg b.i.d. (n=194) (%)**	**Placebo (n=99) (%)**
Headache	5	3
Diarrhea	3	2
Nausea	2	5
Constipation	1	0
Dizziness	1	0

Adverse reactions reported by patients receiving valacyclovir hydrochloride 500 mg once daily (n=743) or placebo once daily (n=741) in a clinical study for the reduction of transmission of genital herpes are listed below in Table 7.

Table 7 Incidence (%) of Drug-Related Adverse Reactions Occurring in ≥ 1% of Patients Receiving valacyclovir hydrochloride in a Clinical Trial for the Reduction of Transmission of Genital Herpes

Adverse Drug Reaction	**Valacyclovir hydrochloride (n=743) (%)**	**Placebo (n=741) (%)**
Headache	6	4
Diarrhea	2	1
Nausea	2	2
Dyspepsia	1	1

Of the 1484 patients enrolled in the reduction of transmission study, 1018 entered the open-label phase of the study (≤ 12 months), 499 from the placebo group and 519 from the valacyclovir hydrochloride group. The nature and incidence of events in the open-label phase were similar to those observed during the double-blind phase of the study (Table 8).

Table 8 Incidence (%) of Drug-Related Adverse Reactions Occurring in ≥ 1% of Patients Receiving valacyclovir hydrochloride in the Double-Blind, Open-Label, and Combined Double-Blind + Open-Label Phases of a Clinical Trial for the Reduction of Transmission of Genital Herpes

	Double-Blind Phase (≤ 8 months)		Open-Label Phase (≤ 12 months)	Combined Double-Blind + Open-Label Phases (≤ 20 months)
Adverse Drug Reaction	**Valacyclovir hydrochloride (n=519[1]) (%)**	**Placebo (n=499[2]) (%)**	**Valacyclovir hydrochloride (n=1018[3]) (%)**	**Valacyclovir hydrochloride (n=519[4]) (%)**
Headache	5	4	2	6
Diarrhea	2	2	< 1	2
Nausea	1	3	< 1	1
Dyspepsia	1	< 1	< 1	2
Abdominal pain, upper	1	0	< 1	1

[1] Number of patients from the valacyclovir hydrochloride group of the double-blind phase who entered the open-label phase of the study.

[2] Number of patients from the placebo group of the double-blind phase who entered the open-label phase of the study.

[3] Total number of patients (valacyclovir hydrochloride + placebo groups) from the double-blind phase who entered the open-label phase of the study. All patients in the open-label phase received valacyclovir hydrochloride 500 mg once daily

[4] Number of patients who received valacyclovir hydrochloride during the double-blind phase followed by open-label valacyclovir hydrochloride suppressive therapy.

Cold Sores: Adverse drug reactions reported by patients receiving valacyclovir hydrochloride 2000 mg twice daily for one day (n=609) or placebo (n=609) in clinical studies for the treatment of cold sores are listed below in Table 9.

Table 9 Incidence (%) of Drug-Related Adverse Reactions Occurring in ≥ 1% of Patients Receiving valacyclovir hydrochloride in Two Clinical Trials for the Treatment of Cold Sores

Adverse Drug Reaction	**Valacyclovir hydrochloride (n=609) (%)**	**Placebo (n=609) (%)**
Headache	9	5
Nausea	4	5
Diarrhea	3	3
Dyspepsia	1	1

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

In herpes zoster trials, the frequencies of white blood cells abnormality (< 0.75 times the lower limit of normal) were 1.3% for patients receiving valacyclovir hydrochloride compared with 0.6% for patients receiving placebo. This difference was not clinically or statistically significant.

In studies of suppression of genital herpes in HIV-infected patients and of reduction of transmission of genital herpes, there were no clinically significant changes from baseline in laboratory parameters in patients receiving valacyclovir hydrochloride compared to placebo.

In clinical studies for the treatment of cold sores, the frequencies of abnormal ALT values (> 2 times the upper limit of normal) were 1.8% for patients receiving valacyclovir hydrochloride at the recommended clinical dose and 0.8% for placebo. Other laboratory abnormalities (hemoglobin, white blood cells,

alkaline phosphatase, and serum creatinine) occurred with similar frequencies in the 2 groups.

8.5 Post-Market Adverse Reactions

The following events have been reported voluntarily during post-approval use of valacyclovir hydrochloride in clinical practice. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, causal connection to valacyclovir hydrochloride, 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.

Allergic: Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnea, pruritus, rash and urticaria.

Central Nervous System Symptoms: Headache. Reports of neurological reactions including dizziness, confusion, hallucinations (auditory and visual), aggressive behaviour, decreased consciousness, tremor, ataxia, dysarthria, convulsions, encephalopathy, coma, mania, and seizures. Agitation and psychotic symptoms have also been reported. These events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

Gastrointestinal: Nausea, abdominal discomfort, vomiting and diarrhea.

General: Facial edema, hypertension, tachycardia.

Hematological: Reports of thrombocytopenia, aplastic anemia, leukocytoclastic vasculitis, thrombotic thrombocytopenic purpura / hemolytic uremic syndrome (TTP/HUS). Leukopenia, mainly reported in immunocompromised patients.

Hepatobiliary Tract and Pancreas: Reports of reversible increases in liver function test, hepatitis.

Immune: Drug reaction with eosinophilia and systemic symptoms (DRESS) (see 7 WARNINGS AND PRECAUTIONS).

Ophthalmologic: Visual abnormalities.

Renal: Reports of renal impairment, elevated blood creatinine and blood urea nitrogen (BUN) Acute renal failure, renal pain and hematuria. Renal pain may be associated with renal failure (see 7 WARNINGS AND PRECAUTIONS, Renal).

Respiratory, thoracic and mediastinal disorders: Dyspnea.

Skin: Erythema multiforme, rashes including photosensitivity.

Other: There have been reports of renal insufficiency, microangiopathic hemolytic anemia and thrombocytopenia (sometimes in combination) in severely immunocompromised patients, particularly those with advanced HIV disease, receiving high doses (8000 mg daily) of valacyclovir for prolonged periods in clinical trials. These findings have also been observed in patients not treated with

valacyclovir who have the same underlying or concurrent conditions.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

No clinically significant interactions have been identified.

No dosage adjustment is recommended when pms-VALACYCLOVIR is co-administered with digoxin, antacids, thiazide diuretics, cimetidine, or probenecid in subjects with normal renal function (see 10.3 Pharmacokinetics).

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 following valacyclovir administration.

Following administration of valacyclovir 1000 mg, cimetidine and probenecid increase the area under the curve (AUC) of acyclovir by this mechanism, and reduce acyclovir renal clearance. However, no dosage adjustment is necessary at this dose because of the wide therapeutic index of acyclovir (see 10.3 Pharmacokinetics).

Care is also required (with monitoring for changes in renal function) if administering higher-doses of pms-VALACYCLOVIR (4 g or more/day) with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

9.5 Drug-Food Interactions

There is no known interaction with food (see 10.3 Pharmacokinetics).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Valacyclovir hydrochloride is the L-valyl ester and a pro-drug of the antiviral drug acyclovir. Valacyclovir hydrochloride is rapidly converted to acyclovir, which has *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), and varicella-zoster virus (VZV).

The inhibitory activity of acyclovir is highly selective due to its unique affinity for the thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. *In vitro*, acyclovir triphosphate terminates growing chains of viral DNA. Once incorporated, acyclovir irreversibly binds to viral DNA polymerase, effectively inactivating the enzyme. Acyclovir triphosphate is a potent inhibitor of all of the human herpes virus DNA polymerases studied.

Acyclovir is virtually inactive in uninfected cells, since it is preferentially taken up and selectively converted to the active triphosphate form by herpes virus-infected cells. Additionally, the enzyme thymidine kinase of uninfected cells does not effectively use acyclovir as a substrate and cellular α-DNA polymerase is less sensitive than viral DNA polymerase to the effects of acyclovir.

A combination of the thymidine kinase specificity, competitive inhibition of DNA polymerase and incorporation and termination of the growing viral DNA chain results in inhibition of herpes virus replication. No effect on latent non-replicating virus has been demonstrated. Inhibition of viral replication reduces the period of viral shedding, limits the degree of spread and level of pathology, and thereby facilitates healing. The pain of shingles is related to viral damage to neurons which takes place during viral replication.

10.3 Pharmacokinetics

The pharmacokinetics of valacyclovir and acyclovir after oral administration of valacyclovir hydrochloride have been investigated in 12 volunteer studies involving 253 adults.

Absorption

After oral administration, valacyclovir hydrochloride is rapidly absorbed from the gastrointestinal tract and nearly completely converted to acyclovir and *L*-valine by first-pass intestinal and/or hepatic metabolism. The absolute bioavailability of acyclovir after administration of valacyclovir hydrochloride is 54.5% ± 9.1% as determined following a 1000 mg oral dose of valacyclovir hydrochloride and a 350 mg intravenous acyclovir dose to 12 healthy volunteers. Acyclovir bioavailability from the administration of valacyclovir hydrochloride is not altered by administration with food [30 minutes after an 873 Kcal (3654 Kj) breakfast, which included 51 grams of fat].

Valacyclovir hydrochloride pharmacokinetics are not dose-proportional. The rate and extent of absorption decreases with increasing dose, resulting in a less than proportional increase in C_{max} over the therapeutic dose range and a reduced bioavailability at doses above 500 mg**.** After single-dose administration of 100 to 1000 mg of valacyclovir hydrochloride, in eight healthy volunteers, the mean C_{max} (± S.D.) ranged from 0.83 (± 0.14) to 5.65 (± 2.37) μg/mL, and the mean AUC (± SD) ranged from 2.28 (± 0.40) to 19.52 (± 6.04) hr•μg/mL. After multiple-dose administration of 250 to 1000 mg of valacyclovir hydrochloride administered four times daily for 11 days in parallel groups in eight healthy volunteers, the mean C_{max} (± SD) ranged from 2.11 (± 0.33) to 4.96 (± 0.64) μg/mL, and the mean AUC (± SD) ranged from 5.66 (± 1.09) to 15.70 (± 2.27) hr•μg/mL.

Acyclovir pharmacokinetics are unaltered after multiple-dose administration. There is no accumulation of acyclovir after the administration of valacyclovir at the recommended dosage regimens in healthy

volunteers with normal renal function.

Distribution
The binding of valacyclovir to human plasma proteins ranged from 13.5% to 17.9%.

Metabolism
Following absorption by the gastrointestinal tract, valacyclovir is rapidly and nearly completely hydrolyzed to acyclovir and *L*-valine, an essential amino acid, by first-pass metabolism. This hydrolysis is mediated primarily by the enzyme valacyclovir hydrolase, and occurs predominantly in the liver. Acyclovir is converted to a small extent to inactive metabolites by aldehyde oxidase and by alcohol and aldehyde dehydrogenase. Neither valacyclovir nor acyclovir metabolism is associated with liver microsomal enzymes. Plasma concentrations of unconverted valacyclovir are low and transient, generally less than 0.5 µg/mL at all doses. After single-dose administration of 1000 mg of valacyclovir hydrochloride, average plasma valacyclovir concentrations observed were 0.5, 0.4 and 0.8 µg/mL in patients with hepatic dysfunctions, renal insufficiency, and in healthy volunteers who received concomitant cimetidine and probenecid, respectively.

Elimination
The pharmacokinetic disposition of acyclovir delivered by valacyclovir is consistent with previous experience from intravenous and oral acyclovir. Acyclovir is eliminated primarily by urinary excretion of unchanged drug. In all studies of valacyclovir hydrochloride, the half-life of acyclovir typically averages 2.5 to 3.3 hours in subjects with normal renal function. Following the oral administration of a single 1000 mg dose of radiolabeled valacyclovir to four healthy subjects, 45.6% and 47.1% of

administered radioactivity was recovered in urine and feces over 96 hours, respectively. Acyclovir accounted for 88.6% of the radioactivity excreted in the urine. Renal clearance of acyclovir following the administration of a single 1000 mg dose of valacyclovir hydrochloride to 12 healthy volunteers was approximately 255 ± 86 mL/min, which represents 41.9% of the total acyclovir apparent plasma clearance.

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of valacyclovir hydrochloride have not been evaluated in pediatric patients.
- **Geriatrics:** The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of valacyclovir hydrochloride tablets in geriatric volunteers varied with renal function. Dosage reduction may be required in geriatric patients with reduced renal function (see 4.2 Recommended Dose and Dosage Adjustment). Following administration of valacyclovir hydrochloride, the half-life of acyclovir in geriatric patients is slightly longer and a 35% to 50% increase in AUC is observed relative to estimates in young healthy volunteers. These differences are consistent with the age-related decline in renal function. Population pharmacokinetic results obtained in efficacy trials are consistent with these observations.
- **Hepatic Insufficiency:** Administration of valacyclovir hydrochloride to patients with moderate or severe liver disease indicated that the rate but not the extent of conversion of valacyclovir to acyclovir is reduced, and the acyclovir half-life is not affected.
- **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

4.2 Recommended Dose and Dosage Adjustment, Patients with Acute or Chronic Renal Insufficiency). The elimination of acyclovir is correlated to renal function, and exposure to acyclovir will increase with increased renal impairment. In patients with end-stage renal disease, the average elimination half-life of acyclovir after valacyclovir administration is approximately 14 hours, compared with about 3 hours for normal renal function. During hemodialysis, the acyclovir half-life is approximately 4 hours. Approximately 1/3 of acyclovir in the body is removed by dialysis during a 4-hour hemodialysis session.

- **HIV Disease:** In patients with advanced HIV disease (CD4 cell counts < 150 cells/mm^3) who received a dose of valacyclovir hydrochloride of 1000 mg or 2000 mg four times daily for 30 days, the pharmacokinetics of valacyclovir and acyclovir are not different from that observed in healthy volunteers (see 7 WARNINGS AND PRECAUTIONS, General).

Drug Interactions

- **Cimetidine and Probenecid:** Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean elimination half-life, and the AUC of acyclovir. Urinary excretion and renal clearance of acyclovir were correspondingly reduced. The administration of cimetidine and probenecid, separately or together, reduced the rate but not the extent of conversion of valacyclovir to acyclovir. Reductions in the renal clearance of acyclovir were observed, resulting in higher acyclovir plasma concentrations. In volunteers with normal renal function, the renal clearance of acyclovir was reduced by approximately 22% and 33%, respectively, with concomitant cimetidine or probenecid administration. Renal clearance of acyclovir was reduced by approximately 46% in patients receiving cimetidine, probenecid, and valacyclovir hydrochloride.

  An additive increase in acyclovir AUC with concomitant administration of valacyclovir hydrochloride, cimetidine, and probenecid has also been observed. Acyclovir C_{max} was increased 8.4% ± 27.8%, 22.5% ± 25.3%, and 29.6% ± 27.5% by cimetidine, probenecid, and combination treatment (concomitant cimetidine and probenecid administration), respectively. Acyclovir AUC (0 to 24 hours) was increased 31.9% ± 22.9%, 49.0% ± 27.9%, and 77.9% ± 38.6% by cimetidine, probenecid, and combination treatment, respectively.
- **Digoxin:** The pharmacokinetics of digoxin (two 0.75 mg doses, 12 hours apart) were not affected by multiple dose administration of valacyclovir hydrochloride (1000 mg every 8 hours for 8 days beginning 12 hours before digoxin dosing) in a study with 12 volunteers. Acyclovir pharmacokinetics after single dose administration of valacyclovir hydrochloride (1000 mg) remained unchanged when the same dose was administered immediately after the second of two 0.75 mg doses of digoxin given 12 hours apart.
- **Antacids:** The administration of an aluminum hydroxide and magnesium hydroxide containing antacid either 30 minutes before or 65 minutes after administration of valacyclovir hydrochloride 1000 mg had no effect on the pharmacokinetics of acyclovir in a study with 18 volunteers.
- **Thiazide diuretics:** Thiazide diuretics do not affect acyclovir pharmacokinetics after administration of valacyclovir hydrochloride in a geriatric population.

11 STORAGE, STABILITY AND DISPOSAL

pms-VALACYCLOVIR should be stored between 15° and 30°C and protected from light.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

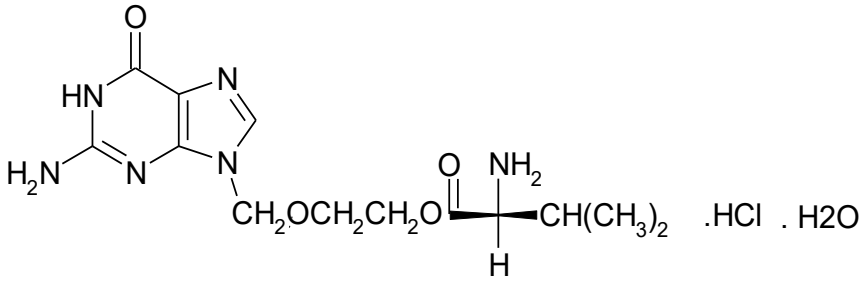
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Valacyclovir hydrochloride monohydrate
Chemical name: [USAN]	*L*-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl) methoxy]ethyl ester, monohydrochloride
Molecular formula:	$C_{13}H_{20}N_6O_4.HCl\ .\ H_2O$
Molecular mass:	378.80 g/mol

Structural formula:



Physicochemical properties: Valacyclovir hydrochloride is a white to off-white powder with a maximum solubility in water of 300 mg/mL at 25°C. Valacyclovir hydrochloride monohydrate starts melting at 150°C (solid shrinks) followed by a color change to pale yellow at 170°C, followed by decomposition with color change to dark brown above 195°C. A saturated solution (4.82×10^{-1}) of valacyclovir HCl in distilled water has a pH of 3.5 at 25°C. The pKa values of valacyclovir are $pKa_1 = 1.90$, $pKa_2 = 7.47$ and $pKa_3 = 9.43$.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Herpes Zoster

Two randomized double-blind clinical trials in 1540 immunocompetent adult patients with localized herpes zoster were conducted. In patients less than 50 years of age, valacyclovir hydrochloride 1000 mg three times daily for 7 days was compared to placebo. In patients greater than 50 years of age, valacyclovir hydrochloride 1000 mg three times daily for 7 days or 14 days was compared to acyclovir 800 mg five times daily for 7 days. All patients were treated within 72 hours of appearance of zoster rash.

In patients less than 50 years of age, the median time to cessation of new lesion formation was shorter for those treated with valacyclovir hydrochloride (2 days) compared with those treated with placebo (3 days, p=0.03). In patients greater than 50 years of age, the median time to cessation of new lesion formation was three days in patients treated with either valacyclovir hydrochloride or acyclovir.

In both studies, the median time to at least 50% crusting or healing was 5 days for all treatment groups.

These trials also included assessment of pain. The primary endpoint for pain was time to complete cessation of zoster-associated pain. Zoster-associated pain, as defined in these trials, combined acute pain (pain associated with zoster lesions) and post-herpetic neuralgia (pain after 100% crusting/healing of lesion rash), a definition that is not universally accepted; most experts consider each pain component to have different pathogenesis and different morbidity. The clinical trials were not designed to look specifically at post-herpetic neuralgia. However, a post-hoc analysis for post-herpetic neuralgia was requested and carried out.

In patients greater than 50 years of age, the median time to resolution of post-herpetic neuralgia for the study population (including those with zero post-herpetic neuralgia) was significantly shorter in patients treated with valacyclovir hydrochloride compared with patients treated with acyclovir (9 and 4 days shorter for patients treated with valacyclovir hydrochloride for 7 days and 14 days respectively, $p < 0.05$). In patients greater than 50 years of age, the incidence of chronic pain after 100% crusting/healing of lesion rash was not significantly different among the three treatment groups (79% and 80% in patients treated with valacyclovir hydrochloride for 7 or 14 days and 85% in patients treated with acyclovir). In patients less than 50 years of age, there was no statistically significant difference in the median time to cessation of post-herpetic neuralgia between the recipients of valacyclovir hydrochloride and placebo.

There were no significant differences in secondary endpoints, such as use of analgesics or quality of life, for patients treated with valacyclovir hydrochloride compared to placebo or acyclovir. In addition, no significant differences were found among the three groups with respect to intensity of pain.

Initial Episode of Genital Herpes

643 immunocompetent adults with first episode of genital herpes who presented within 72 hours of symptom onset were randomized in a double-blind trial to receive 10 days of valacyclovir hydrochloride 1000 mg twice daily (n=323) or acyclovir 200 mg five times a day (n=320). For both treatment groups: the median time to lesion healing was 9 days, the median time to cessation of pain

was 5 days, the median time to viral shedding was 3 days.

Recurrent Episodes of Genital Herpes
Three randomized, double-blind trials (2 of them placebo-controlled) in immunocompetent adult patients with recurrent genital herpes were conducted. Patients self-initiated therapy within 24 hours of the first sign or symptom of a recurrent genital herpes episode.

In one study (004), adult patients were randomized to receive five days of treatment with either valacyclovir hydrochloride 1000 mg twice daily, acyclovir 200 mg five times daily, or placebo. In a second study (028), adult patients were randomized to receive either valacyclovir hydrochloride 1000 mg, valacyclovir hydrochloride 500 mg, or placebo, administered twice daily for 5 days.

Valacyclovir hydrochloride significantly accelerated lesion healing and resolved episodes faster compared to placebo in both studies (p=0.0001). The median time to lesion healing was 4.8 days and 4.1 days for the groups receiving valacyclovir hydrochloride versus 6.0 days and 6.0 days for the placebo groups, for studies 004 and 028 respectively. The median length of an episode was 4.8 days and 4.0 days for the groups receiving valacyclovir hydrochloride versus 5.9 days and 5.9 days for the placebo groups, for studies 004 and 028, respectively (p=0.0001). There were no differences between active treatment groups in both studies.

In study 028, there was a significantly higher proportion of adult patients with aborted episodes in the groups receiving valacyclovir hydrochloride 1000 mg (28%) and 500 mg (31%) compared to placebo (21%) (p=0.042 and p=0.005 respectively). In study 004, the proportion of patients with aborted episodes was higher in the group receiving valacyclovir hydrochloride (25.9%) than in the placebo group (19.8%), although this was not statistically significant (p=0.097).

The duration of lesion pain/discomfort was significantly shorter in the groups receiving valacyclovir hydrochloride compared to placebo (p=0.0014 for study 004 and p=0.0001 for study 028). In study 028, the median time to cessation of pain was 2.8 days in the group treated with valacyclovir hydrochloride 500 mg versus 3.9 days for the placebo group. There were no differences between active treatments groups in either study.

In studies 028 and 004, valacyclovir hydrochloride significantly shortened the duration of viral shedding compared to placebo (p=0.0001). The median time to cessation of viral shedding in patients with at least one positive culture was two days in the groups receiving valacyclovir hydrochloride versus four days in the placebo group, for both studies. There were no differences between active treatments groups in either study.

In a third study, adult patients were randomized to receive valacyclovir hydrochloride 500 mg twice daily for 5 days (n = 398) or valacyclovir hydrochloride 500 mg twice daily for 3 days (and matching placebo twice daily for 2 additional days) (n = 402). The median time to lesion healing was about 4.5 days in both treatment groups. The median time to cessation of pain was about 3 days in both treatment groups.

Suppression of Genital Herpes
Two randomized, double blind trials for the suppression of recurrent genital herpes were conducted in

immunocompetent adult patients. In one study, 1479 immunocompetent adult patients received suppressive therapy daily for 1 year. This study included three once-daily regimens of valacyclovir hydrochloride (250 mg, 500 mg, and 1000 mg) and valacyclovir hydrochloride 250 mg twice daily which were compared with acyclovir (400 mg twice daily) and placebo. All regimens of valacyclovir hydrochloride were significantly better than placebo ($p < 0.0001$) in preventing or delaying recurrences of genital herpes during the 1-year study period. The once-daily regimens of valacyclovir hydrochloride showed a strong dose relationship in the efficacy parameters. Analysis of the time to first recurrence revealed that the 250 mg, 500 mg, and 1000 mg once-daily regimens and 250 mg twice daily regimen of valacyclovir hydrochloride prevented or delayed recurrences compared to placebo by 54%, 71%, 78%, and 79% respectively. The proportions of patients recurrence free at 1 year from a time-to-event analysis were 22%, 40%, 48% and 51% for the 250 mg, 500 mg, and 1000 mg once-daily doses and 250 mg twice daily dosing respectively. The proportion of patients recurrence free was 5% in the placebo group. In patients with a history of nine or fewer recurrences per year, valacyclovir hydrochloride 250 mg twice daily and 500 mg once daily provided comparable clinical efficacy (59% and 46% of patients were recurrence free at 1 year respectively). In patients with ten or more recurrences per year, 40% of patients receiving 250 mg twice daily were recurrence free at 1 year, while 30% of patients receiving 500 mg once daily were recurrence free at 1 year.

In the second study, 382 immunocompetent adult patients received daily suppressive therapy for 16 weeks. Valacyclovir hydrochloride 500 mg once daily was shown to prevent or delay 85% of the recurrences experienced by patients receiving placebo. At the end of the 16 weeks, the proportions of patients recurrence free were 69% for the patients receiving valacyclovir hydrochloride 500 mg once daily and 9.5% for those receiving placebo.

In an open-label suppression study, 1018 adult patients received valacyclovir hydrochloride 500 mg once daily suppressive therapy for 12 months after receiving either valacyclovir hydrochloride 500 mg or placebo during the 8 month double-blind phase of the study (see 14.1 Clinical Trials by Indication, Reduction of Transmission of Genital Herpes). During the 12 month open-label phase, 44% of source partners had a recurrence of genital HSV. This was similar to that observed in the valacyclovir hydrochloride group (39%) during the 8 month double- blind phase of the study. In the combined double-blind/open-label suppression phases, the median time to first recurrence of genital HSV was 49 days for source partners originally randomized to placebo and 405 days for source partners originally randomized to valacyclovir hydrochloride.

In a randomized, double-blind, placebo-controlled trial for the suppression of recurrent ano-genital herpes in subjects infected with Human Immunodeficiency Virus (HIV), a total of 293 adult subjects on stable antiretroviral therapy with a history of 4 or more recurrences of ano-genital herpes per year were randomized to receive either valacyclovir hydrochloride 500 mg twice daily (n=194) or matching placebo (n=99) for 6 months. The median pre-study HIV-1 RNA was 2.6 $\log_{10}$ copies/mL (range: 2.6 - 5.9 $\log_{10}$ copies/mL) in both treatment groups. Among the 194 subjects who received valacyclovir hydrochloride, the pre-study median CD4 cell count was 336 cells/mm^3; 11% had < 100 cells/mm^3, 16% had 100-199 cells/mm^3, 42% had 200-499 cells/mm^3, and 31% had > 500 cells/mm^3. The proportions of patients who were recurrence free at 6 months were 65% in the group receiving valacyclovir hydrochloride versus 26% in the placebo group. Any subject who experienced a breakthrough episode of genital herpes received valacyclovir hydrochloride 1000 mg twice daily for 5 to 10 days. Ten percent (10/99) of subjects receiving placebo compared to four percent (7/194) of subjects receiving

valacyclovir hydrochloride reported an oral HSV outbreak during the double-blind phase of the study. Time to first oral HSV outbreak was significantly shorter in the placebo group ($p < 0.001$).

Reduction of Transmission of Genital Herpes

A double-blind, placebo-controlled study to assess transmission of genital herpes was conducted in 1484 monogamous, heterosexual, immunocompetent adult couples. The couples were discordant for HSV-2 infection. The source partners had a history of 9 or fewer genital herpes episodes per year. Both partners were counselled on safer sex practices and supplied with condoms for use throughout the study period. Source partners were randomized to treatment with either valacyclovir hydrochloride 500 mg once daily or placebo once daily for 8 months.

In the double-blind phase of the study, transmission of genital herpes to the susceptible partner (as measured by the proportion of susceptible partners with clinical evidence of a first episode of genital herpes) was 2.2% (16/741) in the placebo group and 0.5% (4/743) in the group receiving valacyclovir hydrochloride, a reduction of 75%. The proportions of susceptible partners with acquisition of genital herpes infection were 3.6% (27/741) in the placebo group and 1.9% (14/743) in the group receiving valacyclovir hydrochloride, a reduction of 48%.

After successful completion of the 8 month double-blind phase of the study, 1018 patients (499 from the placebo group and 519 from the valacyclovir hydrochloride group) entered into an open-label phase of the study where they were treated with valacyclovir hydrochloride 500 mg once daily for up to 12 months. The 519 patients formerly in the valacyclovir hydrochloride group of the double-blind study received valacyclovir hydrochloride 500 mg once daily for a total of up to 20 months in the combined double-blind/open-label phases. The safety profile of valacyclovir hydrochloride in the open-label suppression phase of this study (12 months) was similar to that observed during the double-blind phase of this study (8 months). The safety and tolerability of valacyclovir hydrochloride 500 mg once daily has been established for up to 20 months.

Cold Sores (Herpes Labialis)

Two double-blind, placebo-controlled clinical trials were conducted in 1856 immunocompetent adults and adolescents (> 12 years old) with a history of cold sores. Patients were randomized to one of 3 treatment arms: valacyclovir hydrochloride 2000 mg twice daily on Day 1 followed by placebo on Day 2; valacyclovir hydrochloride 2000 mg twice daily on Day 1 followed by 1000 mg twice daily on Day 2; or, Placebo on Days 1 and 2. Patients self-initiated therapy at the earliest symptom of a cold sore (e.g., tingling, itching or burning). The majority of patients initiated treatment within two hours after onset of symptoms.

The mean duration of episode, measured as the time from initiation of treatment to the day the lesion was assessed as being healed (loss of crust in patients whose lesions progressed to the vesicular stage; return to normal skin and/or cessation of all signs and symptoms in patients whose lesions were not vesicular in nature) by the physician, was 1.1 days shorter (5.0 days vs. 6.1 days) in subjects treated with valacyclovir hydrochloride 2000 mg twice daily for 1 day (n=311) compared with subjects treated with placebo (n=292) in one study, and 1.0 days shorter (5.3 days vs. 6.3 days) in subjects treated with valacyclovir hydrochloride 2000 mg twice daily for 1 day (n=298) compared with subjects treated with placebo (n=317) in the second study. The 2-day regimen did not provide additional benefit overall.

There was no significant difference between subjects receiving valacyclovir hydrochloride or placebo

in the prevention of cold sore lesions beyond the papular stage.

For those patients whose lesions progressed to the vesicular stage (valacyclovir hydrochloride 2000 mg twice daily for 1 day, 53% in one study and 54% in the second study; placebo, 59% and 61%), the mean time to lesions healing (loss of crust) was 4.8 days vs. 6.1 days in one study, and 5.1 days vs. 6.4 days in the second study in patients treated with valacyclovir hydrochloride 2000 mg twice daily for 1 day (n=164 and n=161) compared with placebo (n=171 and n=192).

The mean time to cessation of pain/discomfort was 2.1 days vs. 2.9 days in one study, and 2.3 days vs. 3.1 days in the second study in patients treated with valacyclovir hydrochloride 2000 mg twice daily for 1 day (n=311 and n=298) compared with placebo (n=292 and n=317).

14.2 Comparative Bioavailability Studies

A randomized, two-treatment, two-period, crossover, single-dose (1 x 500 mg) bioequivalence study of pms-VALACYCLOVIR (Pharmascience Inc.) and VALTREX (GlaxoSmithKline Inc.) was conducted in healthy adult human male subjects under fasting conditions. A summary of the data from the 28 subjects that were included in the pharmacokinetic and statistical analyses are presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Valacyclovir (1 x 500 mg) From measured data **Geometric Mean Arithmetic Mean (CV %)**				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng.hr/mL)	136.1494 138.7 (18.89)	126.4631 129.7 (22.12)	107.66	103.22 – 112.29
AUC_I (ng.hr/mL)	138.4390 141.0 (18.88)	128.5046 131.7 (22.12)	107.73	103.36 – 112.28
C_{max} (ng/mL)	92.8710 97.7 (30.95)	98.9126 106 (38.82)	93.89	83.26 – 105.88
T_{max}[3] (h)	1.00 (0.35 – 2.50)	1.00 (0.33 – 2.50)		
$T_{½}$[4] (h)	0.56 (40.29)	0.51 (61.29)		

[1] pms-VALACYCLOVIR (valacyclovir (as valacyclovir hydrochloride)) tablets, 500 mg (Pharmascience Inc.).
[2] VALTREX (valacyclovir (as valacyclovir hydrochloride)) tablets, 500 mg (GlaxoSmithkline Inc., Canada).
[3] Expressed as median (range) only.
[4] Expressed as arithmetic mean (CV%) only.

15 MICROBIOLOGY

The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, 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 (IC_{50}), vary greatly depending upon the particular assay used, the cell type employed, and the laboratory performing the test. Using a plaque-reduction assay, the IC_{50} for acyclovir against VZV ranges from 0.12 to 4.0 µg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 µg/mL. The IC_{50} against herpes isolates ranges from 0.02 to 13.5 µg/mL for HSV-1 and from 0.01 to 9.9 µg/mL for HSV-2.

Resistance
Resistance of VZV to antiviral nucleosides analogues can result from qualitative or quantitative changes in the viral TK or DNA polymerase. Clinical isolates of VZV with reduced susceptibility to acyclovir have been recovered rarely from patients with AIDS. In these cases, the TK-deficient phenotype was predominantly responsible.

Resistance of HSV to antiviral nucleoside analogues occurs by the same mechanisms as resistance to VZV. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe disease in immunocompromised patients. The possibility of viral resistance to valacyclovir (and therefore acyclovir) should be considered in patients who show poor clinical response during therapy.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity
The acute toxicity of valacyclovir hydrochloride is low. Single oral doses give approximate lethal dose values > 2000 mg/kg for male mice, between 1000 and 2000 mg/kg for female mice and > 5000 mg/kg for male and female rats. All of the deaths occurred within 3 days of dose administration. The target organ in the acute studies was the kidney, as was expected. The valacyclovir hydrochloride tested produced obstructive nephropathy due to the precipitation of crystals of acyclovir in kidney tubules.

Long-Term Toxicity
Male and female rats were dosed with a single daily dose of 50, 150 and 300 mg/kg of valacyclovir hydrochloride for 97 days. Obstructive nephropathy, characterized by increased values for BUN and creatinine, dilated renal tubules, cellular debris and casts in renal collecting ducts, accumulations of a mixed population of inflammatory cells in the interstitium and the presence of crystals of precipitated acyclovir, was observed in rats given 150 and 300 mg/kg/day. Additional findings consisted of reversible decreases in values for erythrocyte counts, packed cell volume and hemoglobin at 150 mg/kg/day (minimal and inconsistent) and at 300 mg/kg/day. Reversible thymic involution and inconsistent, minimal atrophy of testes were limited to high dose males where renal damage was severe and not fully reversible. No toxicological effects were seen at 50 mg/kg/day valacyclovir

hydrochloride.

Monkeys given oral doses of valacyclovir hydrochloride for three months also had obstructive nephropathy. Male and female cynomolgus monkeys were dosed at 200, 400 and 600 mg/kg/day. The daily dose was divided into two equal doses given six hours apart. Reversible obstructive nephropathy was observed at 400 and 600 mg/kg/day. The no-effect level was 200 mg/kg/day.

No additional signs of toxicity occurred in rats and monkeys given daily oral doses of valacyclovir hydrochloride for 1 year. Although high-dose rats (120 mg/kg/day) had obstructive nephropathy, none of the doses of valacyclovir hydrochloride given to monkeys (125, 250 and 500 mg/kg/day) produced toxicity.

Carcinogenicity: Carcinogenicity bioassays were conducted in mice given 40, 80 and 120 mg/kg/day and in rats given 50, 75 and 100 mg/kg/day valacyclovir hydrochloride by gavage. The high doses were maximum tolerated doses and produced expected obstructive nephropathy. Both bioassays were negative for tumorigenic and carcinogenic potential. Dosing was for 20 months in female mice, 18 months in male mice, 23 months in female rats and 24 months in male rats. Except for expected effects on the kidney, there were no signs of chronic toxicity.

Genotoxicity: Five mutagenicity studies were performed with valacyclovir hydrochloride. An Ames test including pre-incubation was negative at concentrations up to 10,000 µg/plate (the highest concentration tested) with and without metabolic activation. An *in vitro* cytogenetic study in cultured human lymphocytes was negative at 500 µg/mL without metabolic activation and at 1000 µg/mL with metabolic activation. A mouse lymphoma assay was negative at 5000 µg/mL without metabolic activation and at 300 µg/mL with metabolic activation. Weak mutagenicity consistent with that previously encountered in testing acyclovir itself, occurred at 1000 µg/mL valacyclovir hydrochloride in the presence of metabolic activation where it was estimated that concentrations of acyclovir averaged 400 µg/mL over the 4-hour exposure period. There were no mutagenic effects at single doses up to and including 250 mg/kg (nephrotoxic) in a mouse micronucleus assay. Weak mutagenicity encountered at 500 mg/kg in this assay was fully explained by C_{max} acyclovir concentrations of 250 µg/mL for males and 128 µg/mL for females, as exposures in this range produced chromosomal damage when acyclovir itself was tested. These exposures also may have produced expected toxic effects on the bone marrow as there were decreased numbers of polychromatic erythrocytes in peripheral circulation. A rat cytogenetic study was negative at all doses including the highest one tested, 3000 mg/kg.

Reproductive and Developmental Toxicology: In reproductive toxicology studies, valacyclovir hydrochloride produced expected obstructive nephropathy in rats and rabbits. There were no teratogenic effects in either species. Embryotoxicity in rats consisted of post-implantation loss, decreased fetal body weight and length, and increased incidences of minor skeletal variations at the high dose. Maternal plasma levels of approximately 50 µg/mL acyclovir were achieved. This concentration of acyclovir is intermediate between that associated with an increased incidence of skeletal variations (but no embryolethality) in previous studies with acyclovir and that of 100 µg/mL producing overt fetal malformations in rats. Plasma levels of 50 µg/mL acyclovir are approximately 10 times those achieved in humans given the recommended oral dose (1000 mg 3 times per day) of valacyclovir to treat herpes zoster.

At high parenteral doses of acyclovir, testicular atrophy and aspermatogenesis have been observed in rats and dogs.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrVALTREX, (tablets, 500 mg and 1 g), submission control 259374, Product Monograph, GlaxoSmithKline Inc. (AUG 31, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-VALACYCLOVIR
valacyclovir tablets (as valacyclovir hydrochloride)

Read this carefully before you start taking **pms-VALACYCLOVIR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **pms-VALACYCLOVIR**.

What is pms-VALACYCLOVIR used for?
pms-VALACYCLOVIR is an antiviral medicine. It is used for the following:

Treatment of shingles (herpes zoster)
pms-VALACYCLOVIR is used to treat shingles (herpes zoster) infections. Shingles is caused by the varicella-zoster virus which damages nerves and skin. pms-VALACYCLOVIR helps stop the virus from multiplying, therefore reducing the damage.

Treatment or suppression of genital herpes
pms-VALACYCLOVIR is used to treat genital herpes which is 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 blisters contain many infectious HSV particles. pms-VALACYCLOVIR helps stop HSV from multiplying which helps to shorten the time that the virus is shed from the skin and mucous membranes. It reduces the number of painful blisters and also helps them to heal more quickly.

If you start taking pms-VALACYCLOVIR as soon as you feel an infection starting, you may actually prevent the blisters from developing. This type of treatment is called episodic therapy.

When taken every day, pms-VALACYCLOVIR can also be used to prevent the HSV infection from coming back. This type of treatment is called suppressive therapy.

With no visible symptoms, viral shedding can occur anywhere in the “boxer short” area (from just below the waistline down to the upper thighs, including the buttocks). This means it is possible to transmit genital herpes through skin-to-skin contact with the “boxer short” area, even in the absence of blisters.

pms-VALACYCLOVIR helps stop HSV from multiplying which helps to shorten the time that the virus is shed from the skin and mucous membranes.

Reduction of transmission of genital herpes
pms-VALACYCLOVIR taken every day and in combination with safer sex practices, including the use of condoms, can reduce the risk of transmitting genital herpes to your sexual partner. This type of treatment is for reduction of transmission.

Sometimes the herpes simplex virus (HSV) may be released to the skin at levels too low to cause blisters – this is called viral shedding.

Treatment of cold sores (herpes labialis)
pms-VALACYCLOVIR is used to treat cold sores (herpes labialis) which are caused by the herpes simplex virus (HSV).

Cold sores are small, fluid-filled blisters that you get in or around your mouth. The blisters then break down into ulcers/sores which may be itchy or painful. The blisters contain many infectious HSV particles. Cold sores may be spread by kissing or other physical contact with the infected area of the skin.

pms-VALACYCLOVIR helps stop HSV from multiplying which helps to shorten the time that the virus is released from the skin and mucous membranes. It reduces the number of painful blisters and also helps them to heal more quickly.

How does pms-VALACYCLOVIR work?
pms-VALACYCLOVIR works by lowering the ability of herpes viruses to multiply in your body. pms-VALACYCLOVIR does not cure herpes infections.

What are the ingredients in pms-VALACYCLOVIR?
Medicinal ingredients: pms-VALACYCLOVIR tablets contain valacyclovir 500 mg or 1000 mg as valacyclovir hydrochloride.

Non-medicinal ingredients:
Crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate, titanium dioxide. In addition to the above listed ingredients, pms-VALACYCLOVIR 500 mg tablets also contain: FD&C blue #2 aluminum lake.

pms-VALACYCLOVIR comes in the following dosage forms:
Tablets, 500 mg and 1000 mg.

Do not use pms-VALACYCLOVIR if:
You should not use pms-VALACYCLOVIR if you are allergic to or react badly to valacyclovir or acyclovir or any other components of the formulation of pms-VALACYCLOVIR (see "**What are the ingredients in pms-VALACYCLOVIR?**" section). Tell your healthcare professional if you have ever had an allergic reaction to any of these ingredients.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-VALACYCLOVIR. Talk about any health conditions or problems you may have, including if you:

- have kidney problems or you are 65 years of age or older. Your **healthcare professional** may give you a lower dose of pms-VALACYCLOVIR.
- have liver disease.
- have a weak immune system.
- are pregnant or planning to become pregnant. Your healthcare professional will consider the

benefit to you and the risk to your baby of taking pms-VALACYCLOVIR while you're pregnant.

- are breastfeeding or planning to breastfeed. You must check with your healthcare professional before taking pms-VALACYCLOVIR since the ingredients in this medication can pass into the breast milk.

Other warnings you should know about:

Driving and using machines
Be careful and see how you feel before driving or operating machinery while taking pms-VALACYCLOVIR.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take pms-VALACYCLOVIR:
You must take pms-VALACYCLOVIR as prescribed by your healthcare professional. If you are not sure how many tablets to take, or how often to take them, ask your healthcare professional.

You should not increase or decrease the prescribed dose or frequency unless advised by your healthcare professional.

For shingles, genital herpes (initial and recurrent episodes) and cold sores, for best effect, start taking your pms-VALACYCLOVIR tablets as soon as possible after your symptoms start.

Swallow the tablets whole with some water. It is important to drink enough water to prevent dehydration when you are taking pms-VALACYCLOVIR. It does not matter if you take them with or without food.

Usual dose:
Shingles (herpes zoster):
For the treatment of shingles, the usual dose of pms-VALACYCLOVIR is 1000 mg orally three times a day for 7 days. Most people take one dose when they get up in the morning, one dose mid-afternoon and one dose before they go to bed at night. Spreading the doses evenly throughout the day will help to shorten your rash and discomfort.

Genital herpes:

- **Episodic Therapy**

Episodic therapy involves taking pms-VALACYCLOVIR for a specific number of days during an outbreak to help speed the healing of blisters, shorten the duration of pain and discomfort, and reduce viral shedding (the stage during which herpes virus is secreted). If treatment with pms-VALACYCLOVIR is started before the appearance of any sores, it may prevent sores from occurring.

For the treatment of an initial (first) episode of genital herpes, the usual dose of pms-VALACYCLOVIR is 1000 mg orally two times a day. The treatment is usually taken for 10 days.

For the treatment of recurrent episodes of genital herpes, the usual dose of pms-VALACYCLOVIR is 500 mg orally two times a day for 3 days. Take one dose in the morning and one in the evening. Take your

pms-VALACYCLOVIR tablets as soon as you get the warning signs of an outbreak (i.e., itching, burning, swelling or pain in your genital area). This may actually prevent the blisters from developing.

- **Suppressive Therapy**

Suppressive therapy involves taking pms-VALACYCLOVIR every day to help prevent outbreaks of genital herpes. This will not cure genital herpes, but it may prevent genital herpes outbreaks before they start.

Suppressive therapy can significantly reduce the frequency of outbreaks, although results will vary from person to person. Many people can remain recurrence-free while on suppressive treatment.

For the suppression of genital herpes, the usual dose of pms-VALACYCLOVIR is 1000 mg orally once a day. If you have a history of 9 or fewer recurrences per year, your healthcare professional may prescribe an alternative dose of 500 mg orally once a day. You should continue to take this medicine every day and follow your healthcare professional instruction.

For the suppression of genital herpes in HIV-infected patients with CD4 cell count > 100 cells/mm^3, the recommended dosage of pms-VALACYCLOVIR is 500 mg orally two times a day.

- **Reduction of Transmission**

When taken every day, pms-VALACYCLOVIR in combination with safer sex practices can also reduce the risk of transmitting genital herpes to your sexual partner.

For the reduction of transmission of genital herpes in patients with a history of 9 or fewer recurrences per year, the usual dose of pms-VALACYCLOVIR is 500 mg once a day for the partner with the infection. Note that the efficacy of pms-VALACYCLOVIR for reducing transmission of genital herpes has not been established in individuals with multiple partners, non-heterosexual couples, and couples not counselled to use safer sex practices.

Cold sores (herpes labialis):

For the treatment of cold sores, the usual dose of pms-VALACYCLOVIR is 2000 mg orally two times a day for 1 day (24-hour period). The second dose should be taken around 12 hours after the first dose, but not less than 6 hours after the first dose. Do not exceed 1 day of treatment. Take your pms-VALACYCLOVIR tablets as soon as you get the warning signs of an outbreak (i.e., tingling, itching or burning).

Overdose:

If you think you, or a person you are caring for, have taken too much pms-VALACYCLOVIR, contact a healthcare professional, 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 and then continue with the next dose at the proper time interval. However, if it is nearly time for your next dose, skip the missed dose. Do not double dose.

What are possible side effects from using pms-VALACYCLOVIR?

These are not all the possible side effects you may have when taking pms-VALACYCLOVIR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Nausea
- Vomiting
- Diarrhea
- Stomach pain
- Mild headache

These side effects are generally mild and do not usually cause patients to stop taking pms-VALACYCLOVIR.

If you feel worse, or if you have taken all the tablets and do not feel better, tell your healthcare professional as soon as possible.

pms-VALACYCLOVIR can also:

- decrease the number of white blood cells (cells that help you fight infections). This is mainly reported in patients with low resistance to infection.
- alter liver function tests. This is a blood test that lets your healthcare professional know how well your liver is working.

If there are any significant changes due to pms-VALACYCLOVIR, your healthcare professional will decide on the appropriate course of action.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Psychiatric and central nervous system effects: dizziness, confusion, agitation, hallucinations (seeing and hearing things that are not really there), decreased consciousness. This is usually seen in people with kidney problems, or in elderly.			✓
UNKNOWN			
Blood clotting disorder: bruising, bleeding (from gums), fever, fatigue, headache, confusion, numbness, paralysis			✓

Destruction of red blood cells creating anemia: bloody diarrhea, abdominal pain, fatigue, nausea, vomiting, confusion, swelling of hands and feet.			✓
Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect one or more organs): fever, severe rash, peeling skin, swelling of the face, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feel thirsty, urinating less often, less urine.			✓
Kidney pain (pain in the side between ribs and hip or kidney area of your back), kidney failure			✓
Psychiatric and central nervous system symptoms: tremor, loss of coordinated body movements, difficulty in speaking, severe mental health problems in which the person loses contact with reality and is unable to think and judge clearly, fits (seizures), altered brain function, loss of consciousness. This is usually seen in people with kidney problems, or in the elderly.			✓
Rashes including increased sensitivity of the skin to sunlight		✓	
Severe allergic reactions: raised and itchy rashes; swelling, sometimes of the face or mouth, causing difficulty in breathing; collapse or loss of consciousness.			✓
Shortness of breath			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:
Store pms-VALACYCLOVIR tablets between 15° and 30 °C. Protect from light. Keep out of reach and sight of children. Do not take any tablets after the expiry date.

More facts about genital herpes:
What is genital herpes?
Genital herpes, one of the most common sexually transmitted infections, is caused by the herpes simplex virus (HSV), the same family of viruses that causes cold sores or fever blisters. You can get genital herpes by having sex (skin-to-skin contact including genital, anal, and/or oral contact) with a person who has herpes. Genital herpes does not always occur on the genitals. It may occur anywhere in the "boxer short" area for both men and women (from just below the waistline down to the upper thighs, including the buttocks).

Are there any warning signs of a genital herpes outbreak?
Many people have genital herpes and don't even know it. Here are some of the signs and symptoms that may signal a genital herpes outbreak:

- Swelling, pain, itching, or burning in your genital area
- Redness, tiny blisters, or sores
- Burning feeling when urinating
- Genital discharge
- Muscle aches, tiredness, or headaches

There is no cure for genital herpes. Once the herpes virus enters the body, it is present throughout life, alternating between active (outbreak or viral shedding) and inactive states.

Why outbreaks recur is still unknown. Some people know what triggers their genital herpes infection to become active again, while others do not. Some factors that may trigger the virus into activity are lack of sleep, poor diet, stress and menstruation.

Try to notice if these factors cause your infection to return, as you may be able to avoid some of them.

Taking your pms-VALACYCLOVIR as soon as you get the warning signs may actually prevent the blisters from developing.

How did I get genital herpes?

Genital herpes is passed from one person to another through direct intimate contact. It can be transmitted sexually, by direct contact with blisters or sores, which contain many infectious virus particles. It can also be transmitted through skin-to-skin contact with the "boxer short" area even in the absence of blisters, because the virus can be active on the skin without causing symptoms.

Small cuts or scratches in the skin or mucous membranes allow the virus to gain entry into the body more easily. These may not be visible to the naked eye.

Genital herpes cannot be transmitted via handshakes, toilet seats, swimming pools, saunas, hot tubs or blood transfusions.

Can I transmit genital herpes to other people?

Yes. It is important to remember that the herpes virus can be shed from your skin even when you do not have any signs or symptoms. For this reason, you can transmit the infection to your partner through skin-to-skin contact with the "boxer short" area even in the absence of blisters or sores. In 70% of cases, genital herpes is transmitted when there are no signs or symptoms.

How can I reduce the risk of transmitting genital herpes to other parts of my body or to other people?

You do not have to stop having sex if you have genital herpes. However, here are some things you should consider in order to reduce the risk of transmission:

- Avoid sexual contact with your partner when you have an outbreak of genital herpes, or think you are about to have an outbreak.
- Use latex or polyurethane condoms each time you engage in sexual intercourse even when there are no signs of infection.
- Avoid touching or breaking the blisters or sores and do not pick the scabs when they form.
- Always wash your hands if you touch the blisters, sores, or scabs.
- If you or your partner has an active genital herpes infection (or even the warning signs), avoid contact with the blisters or sores.
- When combined with safer sex practices, including condoms, daily therapy with pms-VALACYCLOVIR reduces the risk of transmitting genital herpes to your partner.
- Talk to your healthcare professional about the best options for you and your partner.

What about genital herpes and pregnancy?

There is no evidence that having genital herpes affects fertility in men or women and is unlikely to complicate a pregnancy. The measures described above will also help to reduce the risk of transmitting genital herpes during pregnancy. Special precautions should be taken during pregnancy to avoid transmission to a pregnant woman if her partner has genital herpes. Care is needed at the time of birth if there is an active infection present. Discuss the options available with your healthcare professional.

How can you treat (or manage) your genital herpes?

There are 3 different ways to manage genital herpes with pms-VALACYCLOVIR.

Talk to your healthcare professional if you have questions about treatment with pms-VALACYCLOVIR and if you are concerned about transmitting genital herpes to your partner. Your physician will help you decide which type of therapy is best for you.

If you want more information about pms-VALACYCLOVIR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pharmascience.com, or by calling 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

Last Revised: May 10, 2023