
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HOVILPRI safely and effectively. See full prescribing information for HOVILPRI.

HOVILPRI (pritelivir) tablets, for oral use

Initial U.S. Approval: 2026

INDICATIONS AND USAGE

HOVILPRI is a herpes simplex virus (HSV) helicase-primase inhibitor indicated in immunocompromised adults for the treatment of mucocutaneous lesions caused by herpes simplex virus (HSV) infection that is refractory (with or without documented resistance) to treatment with acyclovir, valacyclovir, or famciclovir. (1)

DOSAGE AND ADMINISTRATION

Recommended dose is 400 mg on the first day, followed by 100 mg once daily with or without food, until HSV lesions have healed. (2.1)

If a dose of HOVILPRI is missed, take it as soon as it is remembered. If it is not taken until the scheduled dosing time on the next day, take two tablets at that time. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg of pritelivir. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Concomitant use of HOVILPRI with certain acid-reducing agents may reduce pritelivir exposure, potentially resulting in reduced therapeutic effect and development of resistance. (2.2, 5.1, 7.2)

ADVERSE REACTIONS

The most common adverse reaction (incidence >5%) was headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Asahi Kasei Therapeutics, Inc. at 1-844-835-6947 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with HOVILPRI. (2.2, 7).
- Avoid concomitant use with esomeprazole or rabeprazole. Avoid concomitant use with omeprazole or lansoprazole at daily doses above 20 mg, or with pantoprazole at daily doses above 40 mg. (2.2, 5.1, 7.2)
- Stagger concomitant use with H2-receptor antagonists or antacids. (2.2, 5.1, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HOVILPRI is indicated in immunocompromised adults for the treatment of mucocutaneous lesions caused by herpes simplex virus (HSV) infection that is refractory (with or without documented resistance) to treatment with acyclovir, valacyclovir, or famciclovir [see *Clinical Studies (14.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Initiate treatment with a loading dose of 400 mg (four 100 mg tablets) on day 1, followed by a maintenance dose of 100 mg (one tablet) daily by mouth with or without food, until HSV lesions have healed [see *Clinical Pharmacology (12.3)*, *Clinical Studies (14.1)*].

2.2 Co-administration with Acid-Reducing Agents

While taking HOVILPRI, avoid concomitant use of the following proton pump inhibitors [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.2)*, *Clinical Pharmacology (12.3)*]:

- Esomeprazole or rabeprazole
- Omeprazole or lansoprazole at daily doses above 20 mg
- Pantoprazole at daily doses above 40 mg

Take HOVILPRI 2 hours before or 12 hours after taking a H₂-receptor antagonist [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.2)*, *Clinical Pharmacology (12.3)*].

Separate any dosing of antacids from HOVILPRI dosing by 2 hours [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.2)*].

2.3 Missed Dosage

If a dose of HOVILPRI is missed, take it as soon as it is remembered. If it is not taken until the scheduled dosing time on the next day, take two tablets at that time.

3 DOSAGE FORMS AND STRENGTHS

HOVILPRI film-coated tablets are white to off-white, round, biconvex and contain 100 mg pritelivir. The tablets are embossed with 'AIC' on one side and with '1' on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions with Acid-Reducing Agents

Concomitant use of HOVILPRI with certain acid-reducing agents may reduce pritelivir exposure, potentially resulting in reduced therapeutic effect and development of resistance. Avoid concomitant use with certain proton pump inhibitors, and stagger concomitant use with H₂-receptor antagonists and antacids [see *Dosage and Administration* (2.2), *Drug Interactions* (7.2), *Clinical Pharmacology* (12.3)].

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

The safety of HOVILPRI was evaluated in 206 adults treated with HOVILPRI and an additional 100 healthy adult participants exposed to HOVILPRI in clinical trials.

Immunocompromised Adults with Mucocutaneous HSV Infection that is Refractory (with or without Documented Resistance) to Treatment with Acyclovir, Valacyclovir, or Famciclovir:

The safety of HOVILPRI was evaluated in a Phase 3, randomized, open-label, comparator-controlled trial, PRIOH-1 (Part C), in immunocompromised participants with mucocutaneous (mucosal and/or cutaneous lesions) HSV infection that was refractory (with or without documented resistance) to treatment with acyclovir, valacyclovir, or famciclovir [see *Clinical Studies* (14)]. Participants received HOVILPRI (400 mg loading dose on Day 1 followed by 100 mg once daily) or Investigator's Choice treatment (IV foscarnet, IV/topical cidofovir, or 5% topical imiquimod) for up to 28 days until all lesions healed, extended up to 42 days if lesions were improving. A total of 101 participants were randomized 1:1 and treated with either HOVILPRI or the Investigator's Choice. Across the 51 participants treated with HOVILPRI, the mean duration of treatment was 27.1 days (range 6–43).

The adverse reaction (all grades) occurring in more than 5% of participants receiving HOVILPRI was headache, which occurred in 6% and 4% of the HOVILPRI and Investigator's choice participants, respectively.

Adverse reactions were reported in 22% of HOVILPRI-treated participants, compared with 54% of participants in the Investigator's Choice treatment arm. Discontinuations due to adverse drug reactions occurred in 2% and 20% of participants, respectively.

Laboratory Abnormalities

Hepatic laboratory abnormalities were observed in both treatment groups in PRIOH-1, Part C. ALT elevations $\geq 2.5 \times$ upper limit of normal (ULN) were reported in 4/51 (8%) participants receiving HOVILPRI and 1/50 (2%) receiving Investigator's Choice, while AST elevations $\geq 2.5 \times$ ULN were reported in 3/51 (6%) and 2/50 (4%) participants, respectively. One participant discontinued HOVILPRI due to elevated liver enzymes.

The safety of HOVILPRI was also evaluated in a non-randomized, open-label, multicenter, single-arm Phase 3 trial, PRIOH-1 (Parts D and F) in immunocompromised adults with acyclovir/foscarnet (ACV/FOS) refractory HSV infection or who were FOS intolerant (N=35). The safety and tolerability profile observed in these

populations was consistent with that observed in Part C, with no new or unexpected adverse drug reactions identified.

7 DRUG INTERACTIONS

7.1 Potential Effects of HOVILPRI on Other Drugs

Pritelivir is a breast cancer resistance protein (BCRP) inhibitor. Co-administration of HOVILPRI with a BCRP substrate may increase the plasma concentrations of the BCRP substrate [see *Clinical Pharmacology* (12.3)], which may increase the risk of adverse reactions. Refer to the prescribing information for co-administered drugs for additional information.

7.2 Potential Effects of Other Drugs on HOVILPRI

Elevation of gastric pH may decrease the systemic bioavailability of HOVILPRI [see *Clinical Pharmacology* (12.3)], which may reduce its effectiveness or cause drug resistance to HOVILPRI [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1)].

Table 1: Clinically Significant Drug Interactions

<i>Proton Pump Inhibitors/ H2-Receptor Antagonists/Antacids</i>		
<i>Prevention or Management</i>	Proton Pump Inhibitors:	Avoid concomitant use of esomeprazole or rabeprazole with HOVILPRI. Avoid concomitant use of omeprazole or lansoprazole at daily doses above 20 mg with HOVILPRI. Avoid concomitant use of pantoprazole at daily doses above 40 mg with HOVILPRI [see <i>Dosage and Administration</i> (2.2)]. Concomitant use of omeprazole, lansoprazole, or pantoprazole below the doses listed above is acceptable, as these lower doses do not reduce pritelivir exposure to a clinically relevant extent.
	H2-Receptor Antagonists:	Take HOVILPRI at least 2 hours before or 12 hours after H2-receptor antagonist intake [see <i>Dosage and Administration</i> (2.2)].
	Antacids:	Take HOVILPRI at least 2 hours before or 2 hours after antacid intake [see <i>Dosage and Administration</i> (2.2)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on HOVILPRI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. In animal reproduction studies, no

adverse developmental effects were observed when pritelivir was administered to rats and rabbits at exposures (AUC) approximately 16- (rats) and 2- (rabbits) times the systemic pritelivir exposure in humans at the therapeutic dose of 100 mg (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Pritelivir was administered orally to pregnant rats at 30, 200 and 1,000 mg/kg/day from gestation days 6 to 17 and to pregnant rabbits at 5, 20, 40, 60 and 80 mg/kg/day from gestation days 6 to 20. In both species, developmental toxicities were only observed at maternally toxic doses, ≥ 200 mg/kg/day in the rat, and ≥ 40 mg/kg/day in the rabbit, resulting in low birth weights in both species, skeletal variations in the rat and fetal loss in rabbits at doses ≥ 60 mg/kg/day. No adverse maternal or embryofetal effects were observed in rats at the low dose (30 mg/kg/day) and rabbits at 20 mg/kg/day resulting in systemic pritelivir exposures (AUC) approximately 5-times for rat, and equal to the human exposure at the therapeutic dose of 100 mg, for rabbits.

In the prenatal and postnatal development study, pritelivir was orally administered to pregnant rats at 25, 75 and 150 mg/kg/day from gestation day 6 to postpartum/lactation day 20. Maternal toxicity occurred at 75 and 150 mg/kg/day resulting in fetal loss, lower birth weights and a delay in sexual maturation but with no influence on physical, functional, or reproductive development. No adverse effects were observed in the offspring at 25 mg/kg/day resulting in maternal systemic pritelivir exposures (AUC) approximately 5-times the human exposure at the therapeutic dose of 100 mg.

8.2 Lactation

Risk Summary

There are no data on the presence of pritelivir or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HOVILPRI and any potential adverse effects on the breastfed infant from HOVILPRI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

There are no data on the effect of pritelivir on human fertility. A fertility study of pritelivir in rats (50, 150 and 500 mg/kg/day) showed adverse effects on male fertility at 500 mg/kg/day. Male rats dosed at 500 mg/kg/day exhibited direct effects on epididymal sperm counts, sperm motility and morphology and a minor increase in severity in lumen detritus in the epididymis. At 150 mg/kg/day, male rats exhibited slight reduction of epididymal sperm counts as well as minor changes in sperm morphology. The effects were confirmed to be reversible after 6 weeks of discontinuing pritelivir with no lasting adverse effects on male reproduction. Male-mediated effects on early embryonic development occurred at 150 and 500 mg/kg/day (i.e., increase in fetal loss in treated and untreated females). No effects on fertility or the offspring occurred at 50 mg/kg/day approximately 6-times the human exposure (AUC) at the therapeutic dose of 100 mg. Sexually mature male monkeys dosed at 1,000 mg/kg/day for 39 weeks had no findings in the reproductive organs or semen [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and efficacy of HOVILPRI have not been established in pediatric patients 18 years of age and younger.

8.5 Geriatric Use

Of the 51 immunocompromised participants treated with HOVILPRI in the Phase 3 PRIOH-1 Part C trial, 20% (10/51) were 65 years and older and 4% (2/51) were 75 years of age and older (range 19-84 years) [see *Clinical Studies* (14)]. No overall differences in safety or effectiveness were observed between patients 65 years of age and older and younger adult patients.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild, moderate, or severe renal impairment. The pharmacokinetics and safety of pritelivir in patients requiring hemodialysis have not been evaluated [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The pharmacokinetics and safety of pritelivir in patients with severe hepatic impairment (Child-Pugh Class C) have not been evaluated [see *Clinical Pharmacology* (12.3)].

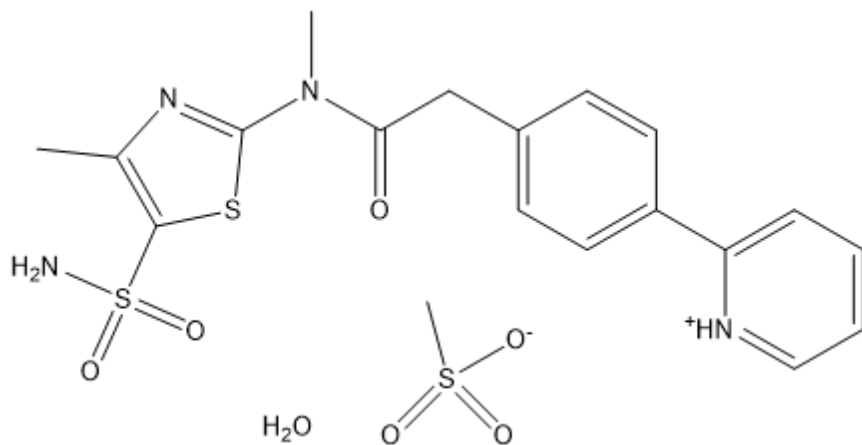
10 OVERDOSAGE

There is no known specific antidote for HOVILPRI. In the event of an overdose, patients should be monitored for adverse reactions and managed with supportive care, as appropriate.

Due to the high plasma protein binding of pritelivir, hemoperfusion or dialysis is unlikely to significantly reduce systemic exposure of pritelivir. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

HOVILPRI (pritelivir), a helicase-primase inhibitor, is developed as a mesylate monohydrate salt. It is chemically described as Benzeneacetamide, N-[5-(aminosulfonyl)-4-methyl-2-thiazolyl]-N-methyl-4-(2-pyridinyl)-, methanesulfonate, hydrate (1:1:1). Its molecular formula $C_{19}H_{22}N_4O_6S_3 \times H_2O$ corresponds to a molecular weight of 516.62 g/mole. Pritelivir mesylate monohydrate salt has the following structural formula:



Each tablet contains 100 mg of pritelivir (equivalent to 123.9 mg of pritelivir mesylate) and is available as immediate release tablets for oral administration.

The tablet core contains standard excipients: colloidal silica dioxide, croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose, as well as the film-coat (hydroxy propyl methyl cellulose and polyethylene glycol) and the colorant/opacifier calcium diphosphate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

HOVILPRI is an antiviral drug against HSV-1 and HSV-2 [see Microbiology (12.4)].

12.2 Pharmacodynamics

Exposure-Response

No exposure-response relationship was identified between steady-state plasma pritelivir exposures at 100 mg once daily and the occurrence of all lesions healed by Day 28.

Cardiac Electrophysiology

At 4 times the recommended maintenance pritelivir dose, clinically significant QTc interval prolongation was not observed.

12.3 Pharmacokinetics

The pharmacokinetic properties of pritelivir following oral administration of HOVILPRI are displayed in Table 2.

Table 2: Pharmacokinetic Properties of Pritelivir

Absorption	
Absolute bioavailability	72%
T _{max} , mean (range) ^a	3 h (2.0–4.5 h)
Food effect ^b	AUC ratio fed/fasted: 1.16 C _{max} ratio fed/fasted: 1.33
Distribution	
Apparent volume of distribution (V _d /F), geometric mean (%CV) ^c	64.1 L (37.3%)
Plasma protein binding	97.3%
Blood-to-plasma ratio, mean ^a	AUC: 1.86
Metabolism	Pritelivir is primarily metabolized by non-enzymatic hydrolysis to its major inactive metabolites, AIC090015 (26.3%) ^d and AIC090105 (14.4%) ^d
Excretion	
% of dose excreted in urine ^c	76.4% (0.6% unchanged)
% of dose excreted in feces ^c	15.5% (6.0% unchanged)

Apparent clearance (CL/F), geometric mean (%CV) ^c	1.08 L/h (33.4%)
Major route of elimination	Non-enzymatic hydrolysis, followed by urinary excretion of the metabolites
Half-life, mean ^a	60 h
Steady-State Exposures^f	
AUC ₀₋₂₄ (μg•h/mL)	91.8 (49.0%)
C _{max} (μg/mL)	4.62 (50.7%)
C _{trough} (μg/mL)	3.14 (50.9%)

^a The values are based on a 100 mg once daily dose.

^b Food effect after high-fat meal: 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat; a total of 1000 calories with ≥50% calories from fat.

^c Derived from population pharmacokinetic model post-hoc estimates for all participants taking 20-280 mg single or multiple doses.

^d Percentages represent the molar ratio of each metabolite to total drug-related material in plasma.

^e Dosing in mass balance study: Healthy participants received pritelivir 500 mg (loading dose, Day 1) and 100 mg once daily (Days 2-8), with a [¹⁴C]-labeled tracer dose co-administered on Day 8. Values represent recovery of total radioactivity as a percentage of administered dose.

^f Pharmacokinetic parameter values based on post-hoc estimates from pritelivir population pharmacokinetic model in immunocompromised participants receiving 100 mg of pritelivir once daily with or without food. Geometric mean (%CV).

Abbreviations: T_{max}, time to maximum plasma concentration; %CV, percent coefficient of variation; C_{max} = maximum concentration; AUC₀₋₂₄ = area under the concentration-time curve over a dosing interval of 24 hours; C_{trough} = concentration at the end of a dosing interval.

C_{max} and AUC were dose-proportional after single dose administration (20–480 mg) and multiple dose administration (5–400 mg once daily). After multiple dosing of 100 mg once daily, steady state was reached within 8 days. When a loading dose of 400 mg pritelivir was administered on Day 1 followed by a maintenance dose of 100 mg once daily, steady-state exposures were reached on Day 2. Plasma concentrations at steady state are approximately 5-fold higher than those after single dose administration.

Specific Populations

There were no clinically significant differences in the pharmacokinetics of pritelivir based on age (19 to 84 years), gender, race (including American Indian/Alaska Native, Asian, Black/African American, White, or other), body weight (48 to 176 kg), or underlying immunocompromised condition (including HIV/AIDS, oncology, transplant, or autoimmune/inflammatory disorder).

Patients with Renal Impairment

In a single-dose pharmacokinetic study, pritelivir exposure (AUC and C_{max}) was comparable between participants with mild (eGFR 60–89 mL/min) or moderate (eGFR 30–59 mL/min) renal impairment and those with normal renal function (eGFR ≥90 mL/min). Pritelivir exposure (AUC and C_{max}) were approximately 1.6-fold higher in participants with severe renal impairment (eGFR 15–29 mL/min, not on hemodialysis) relative to those with normal renal function. Pritelivir pharmacokinetics in patients on hemodialysis is unknown.

Patients with Hepatic Impairment

In a single-dose pharmacokinetic study, pritelivir exposure (AUC and C_{max}) was comparable in participants with moderate hepatic impairment (Child-Pugh Class B) relative to those with normal hepatic function. The effect of severe hepatic impairment (Child-Pugh Class C) on pritelivir pharmacokinetics is unknown.

Drug Interactions

Clinical Drug Interaction Studies

Effect of Other Drugs on the Pharmacokinetics of Pritelivir

Proton pump inhibitors (PPIs): Co-administration of a single oral dose of 100 mg pritelivir (on Day 1) with esomeprazole 40 mg once daily (from Day -3 to Day 1; 4 days total) decreased $C_{\max}$ by approximately 76% and AUC by approximately 59% compared to pritelivir administered alone [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1), *Drug Interactions* (7.2)].

In the Phase 3 trial (PRIOH-1, Parts C-F), pritelivir exposures were evaluated for participants who received concomitant omeprazole or lansoprazole (≤ 20 mg daily), pantoprazole (≤ 40 mg daily), or an H₂-receptor antagonist (with pritelivir administered at least 2 hours before or 12 hours after the H₂-receptor antagonist). Pritelivir exposures in participants receiving these acid-reducing agents were not clinically meaningfully different from those in participants who did not receive any acid-reducing agents [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1), *Drug Interactions* (7.2)].

Table 3: Changes in Pharmacokinetics of Pritelivir in the Presence of Co-administered Drugs

Co-administered Drug and Regimen	Pritelivir Regimen	N	Geometric Mean Ratio (90% CI) of Pritelivir Pharmacokinetics with/without Co-administered Drug (No Effect=1)		
			AUC _{0-inf}	AUC _{0-last}	C _{max}
Esomeprazole 40 mg once daily	100 mg single dose	15	0.41 (0.36, 0.48)	0.41 (0.35, 0.47)	0.24 (0.20-0.30)

Abbreviations: N=number of participants included in the pharmacokinetic analysis, CI= confidence interval, AUC= area under the concentration-time curve, C_{max}= maximum concentration

Effect of Pritelivir on the Pharmacokinetics of Other Drugs

BCRP substrates: Co-administration of multiple pritelivir doses (400 mg on Day 1 followed by 100 mg once daily on Day 2 and Day 3) with a single 20 mg oral dose of rosuvastatin (on Day 3) resulted in a 1.7-fold increase in C_{max} and a 1.4-fold increase in AUC of rosuvastatin compared to rosuvastatin administered alone [see *Drug Interactions* (7.1)].

Table 4: Changes in Pharmacokinetics of Co-administered Drugs in the Presence of Pritelivir

Co-administered Drug and Regimen	Pritelivir Regimen	N	Geometric Mean Ratio (90% CI) of Co-administered Drug Pharmacokinetics with/without Pritelivir (No Effect=1)		
			AUC _{0-inf}	AUC _{0-last}	C _{max}
Rosuvastatin 20 mg single dose	100 mg once daily	16	1.37 (1.27, 1.48)	1.41 (1.28, 1.56)	1.67 (1.45, 1.92)

Abbreviations: N=number of participants included in the pharmacokinetic analysis, CI= confidence interval, AUC= area under the concentration-time curve, C_{max}= maximum concentration

CYP2B6, CYP2C8, CYP2C9, CYP3A4, and OATP2B1 substrates: No clinically significant changes in substrate exposures were observed in clinical drug-drug interaction trials when pritelivir was co-administered with the cytochrome P450 (CYP)2B6 substrate bupropion, the CYP2C8 substrate repaglinide, the CYP2C9

substrate flurbiprofen, the CYP3A4 substrate midazolam, and the organic anion transporting polypeptide (OATP)2B1 substrate celiprolol.

In Vitro Drug Interaction Studies

CYP enzymes: As pritelivir is primarily metabolized by non-enzymatic hydrolysis, leading to the formation of AIC090015 and AIC090105, clinically relevant drug-drug interactions with pritelivir as a CYP enzyme substrate are not expected. Pritelivir does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 at clinically relevant exposures. Pritelivir does not cause clinically relevant induction of CYP1A2, CYP2C9, or CYP2C19. Pritelivir does not cause time-dependent inhibition of any CYP enzymes.

Transporters: Pritelivir is a substrate of both P-glycoprotein (P-gp) and BCRP efflux transporters *in vitro*, but is not a substrate of OATP1B1, OATP1B3, OATP2B1, organic cation transporter (OCT)1, or organic anion transporter (OAT)1. Because pritelivir has a high absolute oral bioavailability of 72%, co-administration of P-gp or BCRP inhibitors is not expected to impact the oral absorption of HOVILPRI to a clinically relevant extent. Pritelivir does not inhibit P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, multidrug and toxin extrusion protein (MATE)1, or MATE2-K at clinically relevant exposures.

Metabolites: The major circulating metabolites of pritelivir, AIC090015 and AIC090105, are not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 to a clinically relevant extent. No clinically significant differences in the pharmacokinetics of OAT substrates are predicted when co-administered with HOVILPRI 100 mg once daily.

12.4 Microbiology

Mechanism of Action

Pritelivir is a HSV helicase-primase inhibitor. It is active against both HSV types, HSV-1 and HSV-2, and prevents *de novo* synthesis of virus deoxyribonucleic acid (DNA) through inhibition of the viral helicase-primase complex. Kinetic analysis of the enzyme complex pUL5-pUL52-6xHis revealed the IC₅₀ value of 30 nM.

Antiviral Activity

Pritelivir exhibits an apparent 50% effective concentration (EC₅₀ value) between 0.01 µM and 0.07 µM in cell culture infected with HSV-1 or HSV-2 (laboratory strains and clinical isolates), depending on cell type, virus strain/isolate, and method used. The median EC₅₀ values of pritelivir were 26 nM (average 26 nM, range 10-45 nM, n=27) and 24 nM (average 30 nM, range 7-70 nM, n=32) against HSV-1 and HSV-2 clinical isolates, respectively.

Viral Resistance

In Cell Culture

Pritelivir-resistant HSV-1 and HSV-2 strains were isolated in cell culture with mutations in the viral helicase (UL5) and primase (UL52) genes. In cell culture the following resistance-associated amino acid substitutions were observed (Table 5).

Table 5: Summary of Pritelivir Resistance-associated Amino Acid Substitutions in Cell Culture

Virus	Protein	Substitutions
HSV-1	pUL5 helicase	N342K, G352R, G352C, G352V, G352N, M355T, K356N, K356T, K356Q, K356R, K356E
HSV-1	pUL52 primase	A899T
HSV-2	pUL5 helicase	N341K, G351R, M354T, K355N, K355T, K355R
HSV-2	pUL52 primase	A906T

In Clinical Trials

In the PRIOH-1 Phase 3 trial (NCT 03073967) in immunocompromised participants, viral sequence analysis was performed on samples obtained from pritelivir-treated participants who did not heal on pritelivir treatment and for whom on-treatment samples were available for analysis. Paired baseline and on-treatment/end-of-treatment sequences were obtained for 8.3% (4/48) of pritelivir-treated participants who experienced treatment failure (lesions not healed by Day 28). The pUL5 K356N (>1,000-fold reduction in susceptibility in cell culture) substitution was detected in 1 participant infected with HSV-1. The pUL5 K355R (50-fold reduction, 2 participants) and pUL5 N341K, pUL5 G351R (distinct viral subpopulations, 33-fold reduction, 1 participant) substitutions were detected in participants infected with HSV-2. In the PRIOH-1 Phase 2 trial (NCT 03073967), the pUL5 K355T (12-fold reduction, 1 participant) substitution was detected in a participant infected with HSV-2.

In another study, the HSV-1 pUL5 N342K (38-fold reduction) + G352C (fold reduction not available) + K356R (fold reduction not available) + pUL52 A899T (100-fold reduction) substitutions were detected in one participant one week after pritelivir discontinuation.

Cross Resistance

Cross resistance is not likely with acyclovir, penciclovir, or foscarnet. Pritelivir retains activity against nucleoside analogue-resistant (e.g., acyclovir) and foscarnet-resistant HSV strains with TK or DNA polymerase substitutions. Substitutions leading to pritelivir resistance do not affect susceptibility to nucleoside analogs and foscarnet.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies with pritelivir are ongoing.

Mutagenesis

Pritelivir free base and pritelivir mesylate monohydrate were not mutagenic in *in vitro* and *in vivo* genotoxicity assays which included bacterial mutation assays in *S. typhimurium*, micronucleus tests with cultured mammalian cells, and in the rodent micronucleus assay.

Impairment of Fertility

In fertility studies in rats, doses of pritelivir at 50, 150, or 500 mg/kg/day were administered to females for 2 weeks before mating, during mating and until day 7 of pregnancy. Males were dosed with 50, 150, or 500

mg/kg/day for 4 weeks before mating and through mating for up to 10 weeks total. Treatment related effects on male fertility including an increase in fetal loss, reduced sperm counts, and morphological and functional deficits in sperm were evident in rats at 500 mg/kg/day because of progressive disturbances to the primary and secondary sex organs. At 150 mg/kg/day, male rats exhibited slight reduction of epididymal sperm counts as well as minor changes in sperm morphology. These effects were no longer apparent after a 6-week recovery, indicating full reversibility. There were no effects on fertility, mating or early embryonic development in females dosed with 150 mg/kg/day and males at 50 mg/kg/day resulting in systemic pritelivir exposures (AUC) approximately 6-times the human exposure at the therapeutic dose of 100 mg. Of note, no effects on the reproductive organs or semen were seen in male sexually mature monkeys over a 39-week treatment period with 1,000 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

Repeat-dose rodent

In a 26-week oral toxicity study in rats at 10, 50, 250 mg/kg/day, early stages of lenticular opacity (cataracts) and vitreous floaters in the eye were observed at 250 mg/kg/day. In a 13-week mouse toxicity study at 100, 500, 1,500 mg/kg/day, lenticular opacity and compound depositions were noted at ≥ 500 mg/kg/day. No ocular findings occurred in the rat and mouse at systemic exposures (AUC) approximately 28- (rats) and 14- (mice) times the human exposure at the therapeutic dose of 100 mg. Further, no ocular findings were apparent in the monkey with up to 39 weeks of treatment at 1,000 mg/kg/day.

14 CLINICAL STUDIES

14.1 Immunocompromised Adults with Mucocutaneous HSV Infection that is Refractory (with or without Documented Resistance) to Treatment with Acyclovir, Valacyclovir, or Famciclovir (PRIOH-1)

The efficacy of HOVILPRI was evaluated in a randomized, open-label, comparator-controlled, superiority trial (PRIOH-1 Phase 3 Trial, Part C; NCT 03073967) in immunocompromised participants with mucocutaneous (mucosal and/or cutaneous lesions) HSV infection that was refractory (with or without documented resistance) to treatment with acyclovir, valacyclovir, or famciclovir. Participants with ocular, CNS, or disseminated HSV disease were not enrolled. Participants received HOVILPRI (400 mg loading dose on Day 1 followed by 100 mg once daily) or Investigator's Choice treatment (IV foscarnet, IV/topical cidofovir, or 5% topical imiquimod) for up to 28 days until all mucocutaneous lesions healed, extended up to 42 days total if lesions were improving but not completely healed after 28 days. Refractory HSV infection (clinical failure) was defined as no clinical improvement after at least 7 days of standard-of-care nucleoside analogue treatment [acyclovir (ACV), valacyclovir (VACV) or famciclovir (FCV)], with or without laboratory confirmed genotypic/phenotypic resistance for the current HSV outbreak.

A total of 101 participants (≥ 18 years) were randomized 1:1 and treated with HOVILPRI (N = 51) or Investigator's Choice (N = 50). The mean age of participants was 53 years (range 19-84 years), 53% were male. Race and ethnicity were as follows: 49% White, 23% Black/African American, 16% American Indian/Alaska native, 10% other, and 3% Asian; 26 % were of Hispanic/Latino ethnicity.

At enrollment, the majority of participants, 71%, had refractory HSV infection and 29% had laboratory confirmed ACV resistance. Participants represented a wide range of immunosuppressive clinical conditions, including one or more of the following underlying conditions: hematologic malignancy/disorder (47%), hematopoietic stem-cell transplantation (40%), HIV infection (38%), autoimmune/inflammatory diseases (29%), non-hematologic malignancies (26%) or solid-organ transplantation (4%). The most common treatment used in

the Investigator's Choice arm was IV foscarnet (70%), followed by topical 5% imiquimod (14%), IV cidofovir (12%), and topical cidofovir (4%).

Efficacy Results

The primary efficacy endpoint was the proportion of participants with all lesions healed with complete epithelization, as assessed by the Investigator, (response rate) during the treatment period up to 28 days. Because HSV establishes lifelong latent infection, treatment is not curative. The primary efficacy result from PRIOH-1 is displayed in Table 8.

Table 6: Primary Efficacy Result in PRIOH-1, Part C

Primary Endpoint	HOVILPRI n/N (%)	Investigator's Choice n/N (%)	Adjusted[†] Treatment Difference (95 % CI)	p-Value
Response rate: proportion of participants with lesions healed up to Day 28*	32/51 (63%)	17/50 (34%)	28.4 (9.6, 47.3)	0.0047

n=number of participants with healed lesions within the respective treatment arm; N=number of participants in the respective arm Full Analysis Set. CI=confidence interval.

*Response rate defined as all mucocutaneous HSV lesions healed by complete epithelization within the treatment period and no appearance of new lesions post-end of treatment, as assessed by the Investigator.

† The stratified Cochran-Mantel-Haenszel test was used to compare treatment groups, adjusting for protocol versions that reflected change in the control arm design.

Confidence Intervals are based on the stratified Sato method and the p-value from the stratified CMH test.

The secondary endpoint was the response rate up to 42 days. The observed response rates were 82% treated with HOVILPRI vs. 42% with Investigator's Choice, with an adjusted treatment difference of 40% (95% CI: 22.7, 57.7). 33 % of participant in the HOVILPRI arm extended treatment up to 42 days, whose lesions were improving by Day 28.

The efficacy of HOVILPRI was further evaluated in Parts D and F of Trial PRIOH-1, which had a non-randomized, open-label, single-arm design to assess the efficacy and safety of HOVILPRI (400 mg loading dose on Day 1 followed by 100 mg once daily). Enrolled participants were immunocompromised and had acyclovir/foscarnet (ACV/FOS) refractory HSV infection or were FOS intolerant (N=35). Underlying immunosuppressive conditions included hematologic malignancy/disorder, hematopoietic stem-cell transplantation, non-hematologic malignancies, HIV infection, autoimmune/inflammatory diseases and solid-organ transplantation. Treatment with HOVILPRI resulted in lesion healing in 40% (95% CI: 23.9, 57.9) of participants during the treatment period up to 28 days and 66% (95% CI: 47.8, 80.9) of participants up to 42 days.

16 HOW SUPPLIED/STORAGE AND HANDLING

How supplied

HOVILPRI 100 mg tablets are white to off-white film-coated tablets. The tablets are round and biconvex with a diameter of about 11 mm, debossed with "1" on one side and "AIC" on the other side and with weight of 513 mg. HOVILPRI is available in cartons of 16 or 32 film-coated tablets.

NDC 68992-100-32- Each carton contains two blister wallets. Each blister wallet contains 16 film-coated tablets, for a total of 32 film-coated tablets per carton.

NDC 68992-100-16- Each carton contains one blister wallet containing 16 film-coated tablets.

Storage

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions

Inform patients that HOVILPRI may interact with some drugs; therefore, advise patients to report the use of any other medications to their healthcare provider [*see Dosage and Administrations (2.2), Warnings and Precautions (5.1), Drug Interactions (7.1, 7.2)*].

Important Administration Instructions

Inform patients that it is important not to miss or skip doses and to take HOVILPRI for the duration that is recommended by the healthcare provider. Instruct patients that if they miss a dose of HOVILPRI, they should take it as soon as they remember. If it is not taken until the scheduled dosing time on the next day, take two tablets at that time [*see Dosage and Administration (2.3)*].

Treatment of Mucocutaneous HSV Infection Lesions

Inform patients that HOVILPRI is indicated to heal lesions caused by HSV but is not a cure for HSV infection.

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PATIENT INFORMATION HOVILPRI (hoe-vil-pree) (pritelivir) tablets, for oral use
What is HOVILPRI? HOVILPRI is a prescription medicine used in adults with weakened immune systems (immunocompromised) to treat lesions caused by herpes simplex virus (HSV) infection that have not improved with the medicines acyclovir, valacyclovir, or famciclovir. HOVILPRI does not cure HSV infection. It is not known if HOVILPRI is safe and effective in children less than 18 years of age.
Before taking HOVILPRI, tell your healthcare provider about all of your medical conditions, including if you: - are pregnant or plan to become pregnant. It is not known if HOVILPRI will harm your unborn baby. - are breastfeeding or plan to breastfeed. It is not known if HOVILPRI passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you take HOVILPRI. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. HOVILPRI may affect the way other medicines work, and other medicines may affect the way HOVILPRI works. Especially tell your healthcare provider if you take medicines used to lower stomach acid, including: - proton pump inhibitors (PPIs) (such as esomeprazole, rabeprazole, omeprazole, lansoprazole, or pantoprazole). - H2-receptor blockers (such as famotidine, ranitidine). - antacids (medicines such as Tums, Mylanta, Maalox). See “How should I take HOVILPRI?” and “What should I avoid while taking HOVILPRI?” if you take any of these medicines. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.
How should I take HOVILPRI? - Take HOVILPRI exactly as your healthcare provider tells you to take it. - The usual dose of HOVILPRI is: - On Day 1 (first day of treatment): take 400 mg by mouth (four 100 mg tablets) at one time. - After Day 1: take 100 mg by mouth (one 100 mg tablet) 1 time a day. - Take HOVILPRI with or without food. - Take HOVILPRI as prescribed by your healthcare provider until your HSV lesions have healed. If you take medicines that reduce stomach acid: - If you take an H2-receptor blocker (such as famotidine, ranitidine), take HOVILPRI at least 2 hours before or 12 hours after taking the H2-receptor blocker. - If you take an antacid (such as Tums, Mylanta, Maalox), take HOVILPRI 2 hours before or 2 hours after taking the antacid. - If you miss a dose of HOVILPRI, take it as soon as you remember. If you don’t remember until the next day’s scheduled dose, take 2 tablets at that time. - If you take too much HOVILPRI, call your healthcare provider, or the Poison Help line (1-800-222-1222), or go to the nearest hospital emergency room right away.
What should I avoid while taking HOVILPRI? Avoid taking the following proton pump inhibitor medicines during treatment with HOVILPRI: - esomeprazole or rabeprazole - omeprazole or lansoprazole (daily dose above 20 mg) - pantoprazole (daily dose above 40 mg) Talk to your healthcare provider before taking any of these medicines.
What are the possible side effects of HOVILPRI? The most common side effect of HOVILPRI is headache. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store HOVILPRI?

- Store HOVILPRI tablets between 68°F to 77°F (20°C to 25°).

Keep HOVILPRI and all medicines out of the reach of children.

General information about the safe and effective use of HOVILPRI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use HOVILPRI for a condition for which it was not prescribed. Do not give HOVILPRI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about HOVILPRI that is written for health professionals.

What are the ingredients in HOVILPRI?

Active ingredient: pritelivir mesylate

Inactive ingredients: colloidal silica dioxide, croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose. The film-coat contains hydroxy propyl methyl cellulose and polyethylene glycol, and calcium diphosphate.

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For more information, go to www.HOVILPRI.com or call 1-844-835-6947

This Patient Information has been approved by the U.S. Food and Drug Administration.

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