TYZEKA™
(telbivudine) Tablets

Rx only

Prescribing Information

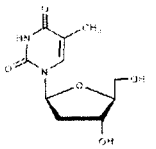
WARNINGS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals.

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including TYZEKA™ (telbivudine). Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, resumption of anti-hepatitis B therapy may be warranted. (See WARNINGS.)

DESCRIPTION

TYZEKA™ is the trade name for telbivudine, a synthetic thymidine nucleoside analogue with activity against hepatitis B virus (HBV). The chemical name for telbivudine is 1-((2S,4R,5S)-4-hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-5-methyl-1H-pyrimidine-2,4-dione, or 1-(2-deoxy-β-L-ribofuranosyl)-5-methyluracil. Telbivudine is the unmodified β-L enantiomer of the naturally occurring nucleoside, thymidine. Its molecular formula is $C_{10}H_{14}N_2O_5$, which corresponds to a molecular weight of 242.23. Telbivudine has the following structural formula:



Telbivudine is a white to slightly yellowish powder. Telbivudine is sparingly soluble in water (>20 mg/mL), and very slightly soluble in absolute ethanol (0.7 mg/mL) and n-octanol (0.1 mg/mL).

TYZEKA™ (telbivudine) film-coated tablets are available for oral administration in 600 mg strength. TYZEKA 600 mg film-coated tablets contain the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet coating contains titanium dioxide, polyethylene glycol, talc and hypromellose.

MICROBIOLOGY

Mechanism of Action

Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase. It is phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours. Telbivudine 5'-triphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5'-triphosphate. Incorporation of telbivudine 5'-triphosphate into viral DNA causes DNA chain termination, resulting in inhibition of HBV replication. Telbivudine is an inhibitor of both HBV first strand (EC_{50} value = 1.3 ± 1.6 μM) and second strand synthesis (EC_{50} value = 0.2 ± 0.2 μM). Telbivudine 5'-triphosphate at concentrations up to 100 μM did not inhibit human cellular DNA polymerases α, β, or γ. No appreciable mitochondrial toxicity was observed in HepG2 cells treated with telbivudine at concentrations up to 10 μM.

Antiviral Activity

The antiviral activity of telbivudine was assessed in the HBV-expressing human hepatoma cell line 2.2.15, as well as in primary duck hepatocytes infected with duck hepatitis B virus. The concentration of telbivudine that effectively inhibited 50% of viral DNA synthesis (EC_{50}) in both systems was approximately 0.2 μM. The anti-HBV activity of telbivudine was additive with adefovir in cell culture, and was not antagonized by the HIV NRTIs didanosine and stavudine. Telbivudine is not active against HIV-1 (EC_{50} value >100 μM) and was not antagonistic to the anti-HIV activity of abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine.

Resistance

In an as-treated analysis of the Phase III global registration trial (007 GLOBE study), 59% (252/430) of treatment-naïve HBeAg-positive and 89% (202/227) of treatment-naïve HBeAg-negative patients receiving telbivudine 600 mg once daily achieved nondetectable serum HBV DNA levels (<300 copies/mL) by Week 52.

At Week 52, 145/430 (34%) and 19/227 (8%) of HBeAg-positive and HBeAg-negative telbivudine recipients, respectively, had evaluable HBV DNA (≥1,000 copies/mL). Genotypic analysis detected one or more amino acid substitutions associated with virologic failure (rtM204I, rtL80I/V, rtA181T, rtL180M, rtL229W/V) in 49 of 103 HBeAg-positive and 12 of 12 HBeAg-negative patients with amplifiable HBV DNA and ≥16 weeks of treatment. The rtM204I substitution was the most frequent mutation and was associated with virologic rebound (≥1 $\log_{10}$ increase above nadir) in 34 of 46 patients with this mutation.

Cross-Resistance

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, lamivudine-resistant HBV strains containing either the rtM204I mutation or the rtL180M/rtM204V double mutation had ≥1,000-fold reduced susceptibility to telbivudine. Telbivudine retained wild-type phenotypic activity (1.2-fold reduction) against the lamivudine resistance-associated substitution rtM204V alone. The efficacy of telbivudine against HBV harboring the rtM204V mutation has not been established in clinical trials. HBV encoding the adefovir resistance-associated substitution rtA181V showed 3- to 5-fold reduced susceptibility to telbivudine in cell culture. HBV encoding the adefovir resistance-associated substitution rtN236T remained susceptible to telbivudine.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

The single- and multiple-dose pharmacokinetics of telbivudine were evaluated in healthy subjects and in patients with chronic hepatitis B. Telbivudine pharmacokinetics are similar between both populations.

Absorption and Bioavailability

Following oral administration of telbivudine 600 mg once-daily in healthy subjects (n=12), steady state peak plasma concentration (C_{max}) was 3.69 ± 1.25 μg/mL (mean ± SD) which occurred between 1 and 4 hours (median 2 hours), AUC was 26.1 ± 7.2 μg-h/mL (mean ± SD), and trough plasma concentrations (C_{trough}) were approximately 0.2-0.3 μg/mL. Steady state was achieved after approximately 5 to 7 days of once-daily administration with ~1.5-fold accumulation, suggesting an effective half-life of ~15 hours.

Effects of Food on Oral Absorption

Telbivudine absorption and exposure were unaffected when a single 600-mg dose was administered with a high-fat (~55 g), high-calorie (~950 kcal) meal. TYZEKA™ (telbivudine) may be taken with or without food.

Distribution

In vitro binding of telbivudine to human plasma proteins is low (3.3%). After oral dosing, the estimated apparent volume of distribution is in excess of total body water, suggesting that telbivudine is widely distributed into tissues. Telbivudine was equally partitioned between plasma and blood cells.

Metabolism and Elimination

No metabolites of telbivudine were detected following administration of [^{14}C]-telbivudine in humans. Telbivudine is not a substrate, or inhibitor of the cytochrome P450 (CYP450) enzyme system (see CLINICAL PHARMACOLOGY, Drug Interactions).

After reaching the peak concentration, plasma concentrations of telbivudine declined in a bi-exponential manner with a terminal elimination half-life ($T_{1/2}$) of 40-49 hours. Telbivudine is eliminated primarily by urinary excretion of unchanged drug. The renal clearance of telbivudine approaches normal glomerular filtration rate suggesting that passive diffusion is the main mechanism of excretion. Approximately 42% of the dose is recovered in the urine over 7 days following a single 600 mg oral dose of telbivudine. Because renal excretion is the predominant route of elimination, patients with moderate to severe renal dysfunction and those undergoing hemodialysis require a dose interval adjustment (see DOSAGE AND ADMINISTRATION).

Cardiac Safety

In an *in vitro* hERG model, telbivudine was negative at concentrations up to 10,000 μM. In a thorough QTc prolongation clinical study in healthy subjects, telbivudine had no effect on QT intervals or other electrocardiographic parameters after multiple daily doses up to 1800 mg.

Special Populations

Gender: There are no significant gender-related differences in telbivudine pharmacokinetics.

Race: There are no significant race-related differences in telbivudine pharmacokinetics.

Pediatrics and Geriatrics: Pharmacokinetic studies have not been conducted in children or elderly subjects.

Renal Impairment

Single-dose pharmacokinetics of telbivudine have been evaluated in patients (without chronic hepatitis B) with various degrees of renal impairment (as assessed by creatinine clearance). Based on the results shown in Table 1, adjustment of the dose interval for TYZEKA is recommended in patients with creatinine clearance of <50 mL/min (see DOSAGE AND ADMINISTRATION).

Table 1. Pharmacokinetic Parameters (mean ± SD) of Telbivudine in Subjects with Various Degrees of Renal Function

	Renal Function (Creatinine Clearance in mL/min)				
	Normal (>80) (n=8) 600 mg	Mild (50-80) (n=8) 600 mg	Moderate (30-49) (n=8) 400 mg	Severe (<30) (n=6) 200 mg	ESRD/ Hemodialysis (n=6) 200 mg
C_{max} (μg/mL)	3.4±0.9	3.2±0.9	2.8±1.3	1.6±0.8	2.1±0.9
AUC_{0-INF} (μg-hr/mL)	28.5±9.6	32.5±10.1	36.0±13.2	32.5±13.2	67.4±36.9
CL_{RENAL} (L/h)	7.6±2.9	5.0±1.2	2.6±1.2	0.7±0.4	

Renally Impaired Patients on Hemodialysis

Hemodialysis (up to 4 hours) reduces systemic telbivudine exposure by approximately 23%. Following dose interval adjustment for creatinine clearance (see DOSAGE AND ADMINISTRATION), no additional dose modification is necessary during routine hemodialysis. TYZEKA should be administered after hemodialysis.

Hepatic Impairment

The pharmacokinetics of telbivudine following a single 600-mg dose have been studied in patients (without chronic hepatitis B) with various degrees of hepatic impairment. There were no changes in telbivudine pharmacokinetics in hepatically impaired subjects compared to unimpaired subjects. Results of these studies indicate that no dosage adjustment is necessary for patients with hepatic impairment.

Drug Interactions

Telbivudine is excreted mainly by passive diffusion so the potential for interactions between telbivudine and other drugs eliminated by renal excretion is low. However, because telbivudine is eliminated primarily by renal excretion, co-administration of telbivudine with drugs that alter renal function may alter plasma concentrations of telbivudine.

Drug-drug interaction studies show that lamivudine, adefovir dipivoxil, cyclosporine and pegylated interferon-alfa 2a do not alter telbivudine pharmacokinetics. In addition, telbivudine does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil, or cyclosporine. No definitive conclusion could be drawn regarding the effects of telbivudine on the pharmacokinetics of pegylated interferon-alfa 2a due to the high inter-individual variability of pegylated interferon-alfa 2a concentrations.

At concentrations up to 12 times that in humans, telbivudine did not inhibit *in vitro* metabolism mediated by any of the following human hepatic microsomal cytochrome P450 (CYP) isoenzymes known to be involved in human medicinal product metabolism: 1A2, 2C9, 2C19, 2D26, 2E1, and 3A4. Based on the above results and the known elimination pathway of telbivudine, the potential for CYP450-mediated interactions involving telbivudine with other medicinal products is low.

INDICATIONS AND USAGE

TYZEKA™ (telbivudine) is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

This indication is based on virologic, serologic, biochemical and histologic responses after one year of treatment in nucleoside-treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease (see Description of Clinical Studies).

Description of Clinical Studies

Adults: The safety and efficacy of telbivudine were evaluated in an international active-controlled, clinical study of 1,367 patients with chronic hepatitis B, called the 007 GLOBE study. All subjects were 16 years of age or older, with chronic hepatitis B, evidence of HBV infection with viral replication (HBsAg-positive, HBeAg-positive or HBeAg-negative, HBV DNA detectable by a PCR assay), and elevated ALT levels ≥1.3 times the upper limit of normal (ULN), and chronic inflammation on liver biopsy compatible with chronic viral hepatitis.

The Week 52 results of the 007 GLOBE study are summarized below.

Clinical Experience in Patients with Compensated Liver Disease: The 007 GLOBE study is a Phase III, randomized, double-blind, multinational study of telbivudine 600 mg PO once daily compared to lamivudine 100 mg once daily for a treatment period of up to 104 weeks in 1,367 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative patients. The primary data analysis was conducted after all subjects had reached Week 52.

HBeAg-positive Subjects: The mean age of subjects was 32 years, 74% were male, 82% were Asian, 12% were Caucasian, and 6% had previously received alfa-interferon therapy. At baseline, subjects had a mean Knodell Necroinflammatory Score ≥7; mean serum HBV DNA as measured by Roche COBAS Amplicor® PCR assay was 9.51 $\log_{10}$ copies/mL; and mean serum ALT was 146 IU/L. Pre- and post-liver biopsy samples were adequate for 86% of subjects.

HBeAg-negative Subjects: The mean age of subjects was 43 years, 77% were male, 65% were Asian, 23% were Caucasian, and 11% had previously received alfa-interferon therapy. At baseline, subjects had a mean Knodell Necroinflammatory Score ≥7; mean serum HBV DNA as measured by Roche COBAS Amplicor® PCR assay was 7.66 $\log_{10}$ copies/mL; and mean serum ALT was 137 IU/L. Pre- and post-liver biopsy samples were adequate for 92% of patients.

Clinical Results (007 GLOBE Study)

Clinical and virologic efficacy endpoints were evaluated separately in the HBeAg-positive and HBeAg-negative subject populations in Study 007.

Table 2. Histological Improvement and Change in Ishak Fibrosis Score at Week 52 (007 GLOBE Study)

	HBeAg-positive (n=797)		HBeAg-negative (n=417)	
	Telbivudine 600 mg (n=399)[1]	Lamivudine 100 mg (n=398)[1]	Telbivudine 600 mg (n=205)[1]	Lamivudine 100 mg (n=212)[1]
Histologic Response[2]				
Improvement	69%	60%	69%	68%
No Improvement	19%	26%	23%	25%
Missing Week 52 Biopsy	12%	15%	8%	7%
Ishak Fibrosis Score[3]				
Improvement	41%	46%	48%	44%
No Change	39%	32%	34%	43%
Worsening	9%	7%	10%	5%
Missing Week 52 Biopsy	12%	15%	8%	7%

[1]Patients with ≥ one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Necroinflammatory Score ≥2

[2]Histologic Response defined as ≥2 point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score

[3]For Ishak Fibrosis Score, improvement defined as a ≥1-point reduction in Ishak Fibrosis Score from Baseline to Week 52

The primary endpoint of Therapeutic Response at Week 52 is a composite serologic endpoint requiring suppression of HBV DNA to <5 $\log_{10}$ copies/mL in conjunction with either loss of serum HBeAg or ALT normalized. Secondary endpoints included Histologic Response, ALT normalization, and various measures of antiviral efficacy.

In HBeAg-positive patients, 75% of the telbivudine subjects and 67% of the lamivudine subjects had a Therapeutic Response. In HBeAg-negative patients, 75% of the telbivudine subjects and 77% of the lamivudine subjects had a Therapeutic Response.

Selected virologic, biochemical, and serologic outcome measures are shown in Table 3.

Table 3. Virological, Biochemical and Serologic Endpoints at Week 52 (007 GLOBE Study)

	HBeAg-positive (n=921)		HBeAg-negative (n=446)	
Response Parameter	**Telbivudine 600 mg (n=458)**	**Lamivudine 100 mg (n=463)**	**Telbivudine 600 mg (n=222)**	**Lamivudine 100 mg (n=224)**
Mean HBV DNA Reduction from Baseline ($\log_{10}$ copies/mL) ± SEM[1,2]	-6.45 (0.11)	-5.54 (0.11)	-5.23 (0.13)	-4.40 (0.13)
% Subjects HBV DNA Negative by PCR	60%	40%	88%	71%
ALT Normalization[3]	77%	75%	74%	79%
HBeAg Seroconversion[4]	23%	22%	NA	NA
HBeAg Loss[4]	26%	23%	NA	NA

[1]Roche COBAS Amplicor® Assay (LLOQ ≤300 copies/mL)

[2]HBeAg-positive: n=443 and 444, HBeAg-negative: n=219 for both telbivudine and lamivudine groups, respectively. Difference in populations due to exclusion of observations after treatment discontinuation due to efficacy and initiation of nonstudy anti-HBV drugs

[3]HBeAg-positive: n=440 and 446, HBeAg-negative: n=203 and 207, for telbivudine and lamivudine groups, respectively. ALT normalization assessed only in subjects with ALT >ULN at baseline

[4]n=432 and 442, for telbivudine and lamivudine groups, respectively. HBeAg seroconversion and loss assessed only in subjects with detectable HBeAg at baseline

Patients who achieved non-detectable HBV DNA levels at 24 weeks were more likely to undergo e-antigen seroconversion, achieve undetectable levels of HBV DNA, normalize ALT, and minimize resistance at one year.

CONTRAINDICATIONS

Telbivudine tablets are contraindicated in patients with previously demonstrated hypersensitivity to any component of the product.

WARNINGS

Exacerbations of Hepatitis After Discontinuation of Treatment

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see ADVERSE REACTIONS, Exacerbations of Hepatitis After Discontinuation of Treatment).

Skeletal Muscle

Cases of myopathy have been reported with telbivudine use several weeks to months after starting therapy. Myopathy has also been reported with some other drugs in this class.

Uncomplicated myalgia has been reported in telbivudine-treated patients (see ADVERSE REACTIONS). Myopathy, defined as persistent unexplained muscle aches and/or muscle weakness in conjunction with increases in creatine kinase (CK) values, should be considered in any patient with diffuse myalgias, muscle tenderness or muscle weakness. Among patients with telbivudine-associated myopathy, there has not been a uniform pattern with regard to the degree or timing of CK elevations. In addition, the predisposing factors for the development of myopathy among telbivudine recipients are unknown. Patients should be advised to report promptly unexplained muscle aches, pain, tenderness or weakness. Telbivudine therapy should be interrupted if myopathy is suspected, and discontinued if myopathy is diagnosed. It is not known if the risk of myopathy during treatment with drugs in this class is increased with concurrent administration of other drugs associated with myopathy, including corticosteroids, chloroquine, hydroxychloroquine, certain HMGCoA reductase inhibitors, fibric acid derivatives, penicillamine, zidovudine, cyclosporine, erythromycin, niacin, and/or azole antifungals. Physicians considering concomitant treatment with these or other agents associated with myopathy should weigh carefully the potential benefits and risks and should monitor patients for any signs or symptoms of unexplained muscle pain, tenderness, or weakness, particularly during periods of upward dosage titration.

PRECAUTIONS

General

Renal Function

Telbivudine is eliminated primarily by renal excretion, therefore dose interval adjustment is recommended in patients with creatinine clearance <50 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). In addition, co-administration of TYZEKA™ (telbivudine) with drugs that affect renal function may alter plasma concentrations of telbivudine and/or the co-administered drug (see DOSAGE AND ADMINISTRATION).

Patients Resistant to Antiviral Drugs for Hepatitis B

There are no adequate and well-controlled studies for telbivudine treatment of patients with established lamivudine-resistant hepatitis B virus infection. In cell culture, telbivudine is not active against HBV encoding amino acid substitutions M204I or M204V/L180M. Telbivudine retains wild-type phenotypic activity against the lamivudine resistance-associated substitution rtM204V alone; however, the efficacy of telbivudine against HBV harboring the rtM204V mutation has not been established in clinical trials.

There are no adequate and well-controlled studies for telbivudine treatment of patients with established adefovir-resistant hepatitis B virus infection. HBV encoding the adefovir resistance-associated substitution rtN236T remains susceptible to telbivudine, while HBV encoding an A181V amino acid substitution showed 3- to 5-fold reduced susceptibility to telbivudine in cell culture.

Liver Transplant Recipients

The safety and efficacy of telbivudine in liver transplant recipients are unknown. The steady-state pharmacokinetics of telbivudine was not altered following multiple dose administration in combination with cyclosporine. If telbivudine treatment is determined to be necessary for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus, renal function should be monitored both before and during treatment with TYZEKA (see CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

Information for Patients

A patient package insert (PPI) for TYZEKA is available for patient information.

Patients should remain under the care of a physician while taking TYZEKA. They should discuss any new symptoms or concurrent medications with their physician.

Patients should be advised to report promptly unexplained muscle weakness, tenderness or pain.

Patients should be advised that TYZEKA is not a cure for hepatitis B, that the long-term treatment benefits of telbivudine are unknown at this time and in particular, that the relationship of initial treatment response to outcomes such as hepatocellular carcinoma and decompensated cirrhosis is unknown.

Patients should be informed that deterioration of liver disease may occur in some cases if treatment is discontinued, and that they should discuss any change in regimen with their physician.

Patients should be advised that treatment with TYZEKA has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination (see PRECAUTIONS, Labor and Delivery).

Drug Interactions

Telbivudine is excreted mainly by passive diffusion so the potential for interactions between telbivudine and other drugs eliminated by renal excretion is low. However, because telbivudine is eliminated primarily by renal excretion, co-administration of telbivudine with drugs that alter renal function may alter plasma concentrations of telbivudine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Telbivudine has shown no carcinogenic potential. Long term oral carcinogenicity studies with telbivudine were negative in mice and rats at exposures up to 14 times those observed in humans at the therapeutic dose of 600 mg/day.

There was no evidence of genotoxicity based on *in vitro* or *in vivo* tests. Telbivudine was not mutagenic in the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli* strains with or without metabolic activation. Telbivudine was not clastogenic in mammalian-cell gene mutation assays, including human lymphocyte cultures and an assay with Chinese hamster ovary cells with or without metabolic activation. Furthermore, telbivudine showed no effect in an *in vivo* micronucleus study in mice.

In reproductive toxicology studies, no evidence of impaired fertility was seen in male or female rats at systemic exposures approximately 14 times that achieved in humans at the therapeutic dose.

Pregnancy Category B

Telbivudine is not teratogenic and has shown no adverse effects in developing embryos and fetuses in preclinical studies. Studies in pregnant rats and rabbits showed that telbivudine crosses the placenta. Developmental toxicity studies revealed no evidence of harm to the fetus in rats and rabbits at doses up to 1000 mg/kg/day, providing exposure levels 6- and 37-times higher, respectively, than those observed with the 600 mg/day dose in humans.

There are no adequate and well-controlled studies of telbivudine in pregnant women. Because animal reproductive toxicity studies are not always predictive of human response, telbivudine should be used during pregnancy only if potential benefits outweigh the risks.

Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to telbivudine, healthcare providers are encouraged to register such patients in the AntiRetroviral Pregnancy Registry by calling 1-800-258-4263.

Labor and Delivery

There are no studies in pregnant women and no data on the effect of telbivudine on transmission of HBV from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV infection.

Nursing Mothers

Telbivudine is excreted in the milk of rats. It is not known whether telbivudine is excreted in human milk. Mothers should be instructed not to breast-feed if they are receiving TYZEKA.

Pediatric Use

Safety and effectiveness of telbivudine in pediatric patients have not been established.

Geriatric Use

Clinical studies of telbivudine did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger subjects. In general, caution should be exercised when prescribing TYZEKA to elderly patients, considering the greater frequency of decreased renal function due to concomitant disease or other drug therapy. Renal function should be monitored in elderly patients, and dosage adjustments should be made accordingly. (See PRECAUTIONS, Renal Function and DOSAGE AND ADMINISTRATION.)

Special Populations

Telbivudine has not been investigated in co-infected hepatitis B patients (e.g., patients co-infected with HIV, HCV or HDV).

ADVERSE REACTIONS

Approximately 760 subjects have been treated with telbivudine in clinical studies at a dose of 600 mg once daily. Assessment of adverse reactions is primarily based on the pivotal 007 GLOBE study in which 1,367 patients with chronic hepatitis B received double-blind treatment with telbivudine 600 mg/day (n=680 patients) or lamivudine (n=687 patients) for up to 104 weeks. Median duration of treatment in the 007 GLOBE study was 60 weeks for telbivudine- and lamivudine-treated patients. The safety profiles of telbivudine and lamivudine were generally comparable in this study.

Clinical Adverse Events

In clinical studies telbivudine was generally well tolerated, with most adverse experiences classified as mild or moderate in severity and not attributed to telbivudine. In the 007 GLOBE study patient discontinuations for adverse events, clinical disease progression or lack of efficacy were 0.6% for telbivudine and 2.0% for lamivudine. Frequently occurring adverse events regardless of attributability to telbivudine were upper respiratory tract infection (14%), fatigue and malaise (12%), abdominal pain (12%), nasopharyngitis (11%), headache (11%), blood CPK increased (9%), cough (7%), nausea and vomiting (7%), influenza and influenza-like symptoms (7%), post-procedural pain (7%), diarrhea and loose stools (7%), pharyngolaryngeal pain (5%), pyrexia (4%), arthralgia (4%), rash (4%), back pain (4%), dizziness (4%), myalgia (3%), insomnia (3%), and dyspepsia (3%).

Frequently occurring adverse events regardless of attributability to lamivudine were headache (14%), upper respiratory tract infection (13%), abdominal pain (13%), fatigue and malaise (11%), nasopharyngitis (10%), influenza and influenza-like symptoms (8%), blood CPK increased (7%), cough (6%), post-procedural pain (6%), nausea and vomiting (6%), dyspepsia (5%), diarrhea and loose stools (5%), dizziness (5%), pharyngolaryngeal pain (4%), rash (4%), hepatic/RUQ pain (4%), arthralgia (4%), back pain (4%), pyrexia (3%), rhinorrhea (3%), ALT increased (3%), and pruritus (3%).

Selected, treatment-emergent, clinical adverse events of moderate to severe intensity, without consideration of study drug causality, during the pivotal 007 GLOBE study clinical trial are presented in Table 4.

Table 4. Selected Treatment-Emergent Clinical Adverse Events[a] (Grade 2-4) of Moderate to Severe Intensity Reported in the 007 GLOBE Study

Body System/Adverse Event	Telbivudine 600 mg (n=680)	Lamivudine 100 mg (n=687)
All subjects with any Grade 2-4 AE	22%	22%
General		
Fatigue/Malaise[b]	1%	1%
Pyrexia	1%	<1%
Musculoskeletal & Connective Tissue		
Arthralgia	<1%	1.0%
Muscle-Related Symptoms[c]	2%	2%
Gastrointestinal		
Abdominal Pain[d]	<1%	<1%
Diarrhea/Loose Stools[e]	<1%	<1%
Gastritis	<1%	0
Respiratory, Thoracic, & Mediastinal		
Cough[f]	<1%	<1%
Nervous System		
Headache[g]	1%	2%

[a]Includes adverse events categorized as possibly/reasonably or not possibly/reasonably related to the treatment regimen by the Investigator. Excludes upper respiratory infection, pharyngitis/nasopharyngitis, post-procedural pain, influenza and influenza-like symptoms and laboratory abnormalities that were considered adverse events. Also excludes adverse events with a frequency of less than 0.7% in the LdT arm

[b]Includes preferred terms: fatigue and malaise

[c]Includes preferred terms: back pain, fibromyalgia, muscle cramp, musculoskeletal chest pain, myalgia, myopathy, pain, pain in extremity, and tenderness

[d]Includes preferred terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and gastrointestinal pain. Adverse events under preferred term "abdominal pain upper" with an event or lower level term descriptions of right upper quadrant pain were excluded from the abdominal pain category and coded under hepatic pain/RUQ pain

[e]Includes preferred terms: diarrhea, loose stools, and frequent bowel movements

[f]Includes preferred terms: cough and productive cough

[g]Includes preferred terms: headache, migraine, sinus headache, and tension headache

Frequencies of selected treatment-emergent laboratory abnormalities in the 007 GLOBE study are listed in Table 5.

Table 5. Selected Treatment-Emergent Grade 3-4 Laboratory Abnormalities[1] in Patients with Chronic Hepatitis B in the 007 GLOBE Study

Test	Telbivudine 600 mg (n=680)	Lamivudine 100 mg (n=687)
Creatine Kinase (CK) ≥7.0 x ULN	9%	3%
ALT >10.0 x ULN and 2.0 x baseline[2]	3%	5%
ALT (SGPT) >3.0 x baseline	4%	8%
AST (SGOT) >3.0 x baseline	3%	6%
Lipase >2.5 x ULN	2%	4%
Amylase >3.0 x ULN	<1%	<1%
Total Bilirubin >5.0 x ULN	<1%	<1%
Neutropenia (ANC ≤749/mm^3)	2%	2%
Thrombocytopenia (Platelets ≤49,999/mm^3)	<1%	<1%

[1]On-treatment value worsened from baseline to Grade 3 or Grade 4 during therapy

[2]American Association for the Study of Liver Diseases (AASLD) definition of acute hepatitis flare

Creatine kinase (CK) elevations were more frequent among subjects on telbivudine treatment, as shown above in Table 5. CK elevations occurred in both treatment arms; however median CK levels were higher in telbivudine-treated patients by Week 52. Grade 1-4 CK elevations occurred in 72% of telbivudine-treated patients and 42% of lamivudine-treated patients, whereas Grade 3/4 CK elevations occurred in 9% of telbivudine-treated patients and 3% of lamivudine-treated patients. Most CK elevations were asymptomatic but the mean recovery time was longer for subjects on telbivudine than subjects on lamivudine. While there was not a uniform pattern with regard to the type of adverse event and timing with respect to the CK elevation, 8% of telbivudine-treated patients with Grade 1-4 CK elevations experienced a CK-related adverse event[1] (within a 30-day window) compared to 6% of lamivudine-treated patients. In this subgroup of patients with CK-related adverse events, 9% of telbivudine-treated patients subsequently interrupted or discontinued study drug. These patients recovered after study drug discontinuation or interruption. Less than 1% of telbivudine subjects overall (n=3/680) were diagnosed with myopathy with muscular weakness; these patients also recovered after study drug discontinuation (see WARNINGS, Skeletal Muscle).

[1]Includes preferred terms: back pain, chest wall pain, non-cardiac chest pain, chest discomfort, flank pain, muscle cramp, muscular weakness, MSK pain, MSK chest pain, MSK discomfort, MSK stiffness, myalgia, myofascial pain syndrome, myopathy, myositis, neck pain, non-cardiac chest pain, and pain in extremity.

As shown in Table 5, on-treatment ALT elevations were more frequent on lamivudine treatment. Additionally, the overall incidence of on-treatment ALT flares, using AASLD criteria (ALT >10 x ULN and >2.0 x baseline), was slightly higher in the lamivudine arm (5.1%) than the telbivudine arm (3.2%). The incidence of ALT flares was similar in the two treatment arms in the first six months. ALT flares occurred less frequently in both arms after Week 24, with a lower incidence in the telbivudine arm (0.4%) compared to the lamivudine arm (2.2%). For both lamivudine and telbivudine subjects, the occurrence of ALT flares was more common in HBeAg positive subjects than in HBeAg negative subjects. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations of Hepatitis After Discontinuation of Treatment (See WARNINGS)

There are insufficient data on post-treatment exacerbations of hepatitis after discontinuation of telbivudine treatment.

DRUG ABUSE AND DEPENDENCE

Telbivudine is not a controlled substance and no potential for dependence has been observed.

OVERDOSAGE

There is no information on intentional overdose of telbivudine, but one subject experienced an unintentional and asymptomatic overdose. Healthy subjects who received telbivudine doses up to 1800 mg/day for 4 days had no increase in or unexpected adverse events. A maximum tolerated dose for telbivudine has not been determined. In the event of an overdose, telbivudine should be discontinued, the patient must be monitored for evidence of toxicity, and appropriate general supportive treatment applied as necessary.

In case of overdosage, hemodialysis may be considered. Within 2 hours, following a single 200-mg dose of telbivudine, a 4-hour hemodialysis session removed approximately 23% of the telbivudine dose.

DOSAGE AND ADMINISTRATION

Adults and Adolescents (≥16 years of age)

The recommended dose of telbivudine for the treatment of chronic hepatitis B is 600 mg once daily, taken orally, with or without food. The optimal treatment duration has not been established.

Renally Impaired Subjects

Telbivudine may be used for the treatment of chronic hepatitis B in patients with impaired renal function. No adjustment to the recommended dose of telbivudine is necessary in patients whose creatinine clearance is ≥50 mL/min. Adjustment of dose interval is required in patients with creatinine clearance <50 mL/min including those with ESRD on hemodialysis (Table 6). For patients with ESRD, telbivudine should be administered after hemodialysis.

Table 6. Dose Interval Adjustment of TYZEKA™ in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Dose of Telbivudine
≥50	600 mg once daily
30-49	600 mg once every 48 hours
<30 (not requiring dialysis)	600 mg once every 72 hours
ESRD	600 mg once every 96 hours

No adjustment to the recommended dose of telbivudine is necessary in patients with hepatic impairment.

HOW SUPPLIED

TYZEKA™ (telbivudine) 600-mg tablets are white to slightly yellowish film-coated, ovaloid-shaped tablets, imprinted with "LDT" on one side.

Bottle of 30 tablets (NDC 24108-101-01) with child-resistant closure.

Storage

Store TYZEKA tablets in original container at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

For all medical inquiries call: 1-877-8-TYZEKA (1-877-889-9352).

Keep this and all drugs out of the reach of children.

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Idenix NOVARTIS

Manufactured by:
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Marketed by:
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Cambridge, MA 02139

Novartis Pharmaceuticals Corporation
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VEREGEN™

(Kunecatechins)

Ointment, 15%

Rx Only

For Topical Dermatologic Use Only

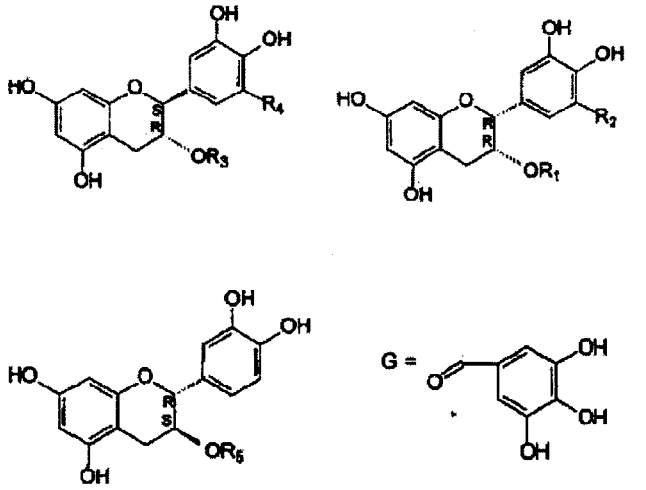
Not for Ophthalmic, Oral, Intravaginal, or Intra-anal Use

DESCRIPTION

Veregen™ is a botanical drug product for topical use. The drug substance in Veregen is Kunecatechins, which is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis (L.) O Kuntze*, and is a mixture of catechins and other green tea components. Catechins constitute 85 to 95% (by weight) of the total drug substance which includes more than 55% of Epigallocatechin gallate (EGCg), other catechin derivatives such as Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECg) and some additional minor catechin derivatives i.e. Gallocatechin gallate (GCg), Gallocatechin (GC), Catechin gallate (Cg), and Catechin (C). In addition to the known catechin components, it also contains gallic acid, caffeine, and theobromine which together constitute about 2.5% of the drug substance. The remaining amount of the drug substance contains undefined botanical constituents derived from green tea leaves.

The structural formulae of catechins are shown below.

General Structure of Catechins



Component	Abbrev.	R1	R2	R3	R4	R5
(–)-Epigallocatechin Gallate	(–)-EGCg	G	OH		–	–
(–)-Epicatechin Gallate	(–)-ECg	G	H		–	–
(–)-Epigallocatechin	(–)-EGC	H	OH	–		–
(–)-Epicatechin	(–)-EC	H	H	–	–	
(+)-Gallocatechin Gallate	(+)-GCg	–	–	G	OH	–
(–)-Gallocatechin	(–)-GC	–	–	H	OH	–
(–)-Catechin Gallate	(–)-Cg	–	–	G	H	–
(+)-Catechin	(+)-C	–		–	–	H

Each gram of the ointment contains 150 mg of Kunecatechins in a water free ointment base consisting of isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mode of action of Veregen™ Ointment, 15% involved in the clearance of genital and perianal warts is unknown. In vitro, Kunecatechins had anti-oxidative activity; the clinical significance of this finding is unknown.

Pharmacokinetics

The pharmacokinetics of topically applied Veregen Ointment has not been sufficiently characterized at this time. However, data suggest that systemic exposure to catechins after repeated topical application of Veregen Ointment 15% is likely to be less than observed after a single oral intake of 400ml green tea.

CLINICAL STUDIES

Two Phase 3 randomized, double-blind, vehicle-controlled studies were performed to investigate the safety and efficacy of Veregen™ Ointment in the treatment of immunocompetent patients 18 years of age and older with external genital and perianal warts. The subjects applied the ointment 3 times daily for up to 16 weeks or until complete clearance of all warts (baseline and new warts occurring during treatment).

Over both studies the median baseline wart area was 51 mm^2 (range 12 to 585 mm^2), and the median baseline number of warts was 6 (range 2 to 30).

The primary efficacy outcome measure was the response rate defined as the proportion of patients with complete clinical (visual) clearance of all external genital and perianal warts (baseline and new) by week 16, presented in Tables 1 and 2 for all randomized subjects dispensed medication.

Table 1: Efficacy by Region

	Complete Clearance
All Countries (includes the United States)	
Veregen™ 15% (*N* = 397)	213 (53.6%)
Vehicle (*N* = 207)	73 (35.3%)
United States	
Veregen™ 15% (*N* = 21)	5 (23.8%)
Vehicle (*N* = 9)	0 (0.0%)

Table 2. Efficacy by Gender

	Complete Clearance
Males	
Veregen™ 15% (*N* = 205)	97 (47.3%)
Vehicle (*N* = 118)	34 (28.8%)
Females	
Veregen™ 15% (*N* = 192)	116 (60.4%)
Vehicle (*N* = 89)	39 (43.8%)

Median time to complete wart clearance was 16 weeks and 10 weeks, respectively, in the two phase 3 clinical trials.

The incidence rate of recurrence of external genital and perianal warts after treatment in patients with complete clearance is unknown.

INDICATION AND USAGE

Veregen™ is indicated for the topical treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older.

CONTRAINDICATIONS

Veregen™ is contraindicated in individuals with a history of sensitivity reactions to any of the components of the ointment. In case of hypersensitivity, treatment should be discontinued.

WARNINGS

Veregen™ has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and should not be used for the treatment of these conditions.

PRECAUTIONS

General

Use of Veregen™ on open wounds should be avoided.
The safety and efficacy of Veregen™ in immunosuppressed patients have not been established.
Safety and efficacy have not been established for Veregen™ in the treatment of external genital and perianal warts beyond 16-weeks or for multiple treatment courses.
Patients should be advised to avoid exposure of the genital and perianal area to sun/UV-light as Veregen™ has not been tested under these circumstances.

Information for Patients

General Information

Patients using Veregen™ should receive the following information and instructions:

1. This medication is only to be used as directed by a physician. It is for external use only. Eye contact should be avoided as well as application into the vagina or anus.
2. It is not necessary to wash off Veregen™ prior to the next application. When the treatment area is washed or a bath is taken, the ointment should be applied afterwards.
3. It is common for patients to experience local skin reactions such as erythema, erosion, edema, itching, and burning at the site of application. Severe skin reactions can occur and should be promptly reported to the healthcare provider. Should severe local skin reaction occur, the ointment should be removed by washing the treatment area with mild soap and water and further doses held.
4. Sexual (genital, anal or oral) contact should be avoided while the ointment is on the skin, or the ointment should be washed off prior to these activities. Veregen™ may weaken condoms and vaginal diaphragms. Therefore the use in combination with Veregen™ is not recommended.
5. Female patients using tampons should insert the tampon before applying the ointment. If the tampon is changed while the ointment is on the skin, accidental application of the ointment into the vagina must be avoided.
6. Veregen™ may stain clothing and bedding.
7. Veregen™ is not a cure and new warts might develop during or after a course of therapy. If new warts develop during the 16 –week treatment period, these should also be treated with Veregen™.
8. The effect of Veregen™ on the transmission of genital/perianal warts is unknown.
9. Patients should be advised to avoid exposure of the genital and perianal area to sun/UV light as Veregen™ has not been tested under these circumstances.
10. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
11. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The Maximum Recommended Human Dose (MRHD) of Veregen™ Ointment, 15% was set at three times daily topical administration of 250 mg, 750 mg total, containing 112.5 mg Kunecatechins for the animal multiple of human exposure calculations presented in this labeling. Dose multiples were calculated based on the human equivalent dose (HED).

In an oral (gavage) carcinogenicity study, Kunecatechins was administered daily for 26 weeks to p53 transgenic mice at doses up to 500 mg/kg/day (22-fold MRHD). Treatment with Kunecatechins was not associated with an increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined. Veregen™ Ointment, 15% has not been evaluated in a dermal carcinogenicity study.

Kunecatechins was negative in the Ames test, in vivo rat micronucleus assay, UDS test, and transgenic mouse mutation assay, but positive in the mouse lymphoma mutation assay.

Daily vaginal administration of Veregen™ Ointment, 15% to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not cause adverse effects on mating performance and fertility at doses up to 0.15 mL/rat/day. This dose corresponds to approximately 150 mg/rat/day (8-fold MRHD).

Pregnancy Category: C
Embryo-fetal development studies were conducted in rats and rabbits using intravaginal and systemic routes of administration, respectively. Oral administration of Kunecatechins during the period of organogenesis (gestational Days 6 to 15 in rats or 6 to 18 in rabbits) did not cause treatment related effects on embryo-fetal development or teratogenicity at doses of up to 1,000 mg/kg/day (86-fold MRHD in rats; 173-fold MRHD in rabbits).

In the presence of maternal toxicity (characterized by marked local irritation at the administration sites and decreased body weight and food consumption) in pregnant female rabbits, subcutaneous doses of 12 and 36 mg/kg/day of Kunecatechins during the period of organogenesis (gestational Days 6 to 19) resulted in corresponding influences on fetal development including reduced fetal body weights and delays in skeletal ossification. No treatment related effects on embryo-fetal development were noted at 4 mg/kg/day (0.7-fold MRHD). There was no evidence of teratogenic effects at any of the doses evaluated in this study.

A combined fertility / embryo-fetal development study using daily vaginal administration of Veregen™ Ointment, 15% to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not show treatment-related effects on embryo-fetal development or teratogenicity at doses up to 0.15 mL/rat/day (8-fold MRHD).

A pre- and post-natal development study was conducted in rats using vaginal administration of Veregen™ Ointment, 15% at doses of 0.05, 0.10 and 0.15 mL/rat/day from Day 6 of gestation through parturition and lactation. The high and intermediate dose levels of 0.15 (8-fold MRHD) and 0.10 mL/rat/day resulted in an increased mortality of the F_0 dams, associated with indications of parturition complications. The high dose level of 0.15 mL/rat/day also resulted in an increased incidence of stillbirths. There were no other treatment-related effects on pre- and post-natal development, growth, reproduction and fertility at any dose tested.

There are no adequate and well-controlled studies in pregnant women. Veregen™ Ointment, 15% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether topically applied Veregen™ is excreted in breast milk.

Pediatric Use
Safety and efficacy in pediatric patients have not been established.

Geriatric Use
Seven patients (1.4%), older than 65 years of age were treated with Veregen™ in clinical studies. This, however, is an insufficient number of subjects to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

ADVERSE EVENTS / LOCAL SKIN REACTIONS
In Phase 3 clinical trials, a total of 397 subjects received Veregen™ Ointment, 15% three times per day topical application for the treatment of external genital and perianal warts for up to 16 weeks.

Serious local adverse events of pain and inflammation were reported in two subjects (0.5%), both women.

In clinical trials, the incidence of local adverse events leading to discontinuation or dose interruption (reduction) was 5% (19/397). These included the following events: application site reactions (local pain, erythema, vesicles, skin erosion/ulceration), phimosis, inguinal lymphadenitis, urethral meatal stenosis, dysuria, genital herpes simples, vulvitis, hypersensitivity, pruritus, pyodermitis, skin ulcer, erosions in the urethral meatus, and superinfection of warts and ulcers.

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 rates observed in practice.

Local and regional reactions (includes adenophathy) occurring at >1% in the treated group are presented in Table 3.