

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Tyzeka (telbivudine) tablets
Tyzeka (telbivudine) oral solution

Initial U.S. Approval: 2006

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS & SEVERE ACUTE EXACERBATIONS OF HEPATITIS B
See full prescribing information for complete boxed warning.
• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues (5.1).
• Severe acute exacerbations of hepatitis B have been reported in patients who discontinued anti-hepatitis B therapy, including Tyzeka. Hepatic function should be monitored closely in patients who discontinue therapy. Resumption of anti-hepatitis B therapy may be warranted (5.2).

RECENT MAJOR CHANGES

- Indications and Usage, Chronic Hepatitis B (1.1) 3/2011
- Dosage and Administration, Adults and Adolescents (16 years of age and older) (2.1) 3/2011
- Dosage and Administration, Renal Impairment (2.2) 9/2010
- Dosage and Administration, Duration of Therapy (2.4) 3/2011

INDICATIONS AND USAGE

Tyzeka is an HBV nucleoside analogue reverse transcriptase inhibitor 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 (1.1).

DOSAGE AND ADMINISTRATION

- Adults and Adolescents (16 years of age and older): 600 mg once daily, taken orally, with or without food (2.1).
- Renal Impairment: Dose adjustment required in patients with creatinine clearance less than 50 mL/min, (2.2) as follows:

Creatinine Clearance (mL/min)	Tyzeka Dose	
	Oral Solution (100 mg/5 mL)	Tablet (600 mg)
greater than or equal to 50	30 mL once daily	1 tab every 24 hrs
30 – 49	20 mL once daily	1 tab every 48 hrs
less than 30 (not requiring dialysis)	10 mL once daily	1 tab every 72 hrs
End stage renal disease (ESRD)	6 mL once daily	1 tab every 96 hrs ¹

¹When administered on hemodialysis days, administer Tyzeka after hemodialysis (2.2).

DOSAGE FORMS AND STRENGTHS

- Tablet: 600-mg tablets supplied in 30-count bottles (3.1).
- Oral Solution: 100 mg/5 mL solution supplied in 300 mL bottle (3.2).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Lactic acidosis and severe hepatomegaly with steatosis: If suspected, treatment should be suspended (5.1).
- Severe acute exacerbations of hepatitis B after discontinuation: Monitor hepatic function closely for at least several months (5.2, 6.1).
- Myopathy: Tyzeka should be interrupted if myopathy is suspected; and discontinued if confirmed. It is unknown whether risk of myopathy is increased with concomitant use of other medications associated with myopathy (5.3).
- Peripheral Neuropathy: Tyzeka should be interrupted if peripheral neuropathy is suspected; and discontinued if confirmed. Risk increased when used in combination with pegylated interferon alfa-2a. Avoid concomitant use of pegylated interferon alfa-2a or other interferons (5.4, 7).

ADVERSE REACTIONS

In clinical trials, the most common adverse reactions (greater than or equal to 3%), of any severity, were: fatigue, increased creatine kinase (CK), headache, cough, diarrhea, abdominal pain, nausea, pharyngolaryngeal pain, arthralgia, pyrexia, rash, back pain, dizziness, myalgia, ALT increased, dyspepsia, insomnia, and abdominal distension (6.1). The most common adverse events resulting in Tyzeka discontinuation included increased CK, nausea, diarrhea, fatigue, myalgia, and myopathy (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Co-administration of Tyzeka with drugs that affect renal function may alter plasma concentrations of Tyzeka and/or coadministered drug (7).
- Co-administration of Tyzeka with pegylated interferon alfa-2a or other interferons may increase the risk and severity of peripheral neuropathy (7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised:03/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS & SEVERE ACUTE EXACERBATIONS OF HEPATITIS B

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis B

2 DOSAGE AND ADMINISTRATION

- 2.1 Adults and Adolescents (16 years of age and older)
- 2.2 Renal Impairment
- 2.3 Hepatic Impairment
- 2.4 Duration of Therapy

3 DOSAGE FORMS AND STRENGTHS

- 3.1 Tablets
- 3.2 Oral Solution

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Lactic Acidosis
- 5.2 Exacerbations of Hepatitis B after Discontinuation of Treatment
- 5.3 Myopathy
- 5.4 Peripheral Neuropathy

6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers

- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Liver Transplant Recipients
- 8.8 Co-Infected Patients
- 8.9 Racial/Ethnic Minorities

9 DRUG ABUSE AND DEPENDENCE

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics in Adults
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Clinical Experience in Nucleoside-Naïve Adults

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS & SEVERE ACUTE EXACERBATIONS OF HEPATITIS B

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 [see *Warnings and Precautions (5.1)*].

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including Tyzeka. 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 and Precautions (5.2)*].

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis B

Tyzeka 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.

The following points should be considered when initiating therapy with Tyzeka:

- This indication is based on virologic, serologic, biochemical and histologic responses in nucleoside-treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease [see *Clinical Studies (14)*].
- For HBeAg-positive patients, Tyzeka should only be initiated in patients with HBV DNA less than 9 log₁₀ copies/mL and ALT greater than or equal to 2x Upper Limit of Normal (ULN) prior to treatment.
- For HBeAg-negative patients, Tyzeka should only be initiated in patients with HBV DNA less than 7 log₁₀ copies/mL prior to treatment.
- On-treatment response should guide continued therapy [see *Dosage and Administration (2.1)* and *Microbiology (12.4)*].
- Tyzeka has not been evaluated in patients co-infected with HIV, HCV or HDV.
- Tyzeka has not been evaluated in liver transplant recipients or in patients with decompensated liver disease.
- Tyzeka has not been studied in well-controlled trials for the treatment of patients with established nucleoside analog reverse transcriptase inhibitor-resistant hepatitis B virus infection, but is expected to be cross-resistant to lamivudine [see *Microbiology (12.4)*].
- The safety and efficacy of Tyzeka have not been evaluated in Black/African American or Hispanic patients [see *Use in Specific Populations (8.9)*].

2 DOSAGE AND ADMINISTRATION

2.1 Adults and Adolescents (16 years of age and older)

Due to higher rates of resistance that may develop with longer term treatment among patients with incomplete viral suppression, treatment should only be initiated, if pre-treatment HBV DNA and ALT measurements are known, in the following patient populations:

For HBeAg-positive patients, HBV DNA should be less than 9 log₁₀ copies/mL and ALT should be greater than or equal to 2x ULN prior to treatment with Tyzeka.

For HBeAg-negative patients, HBV DNA should be less than 7 log₁₀ copies/mL prior to treatment with Tyzeka.

HBV DNA levels should be monitored at 24 weeks of treatment to assure complete viral suppression (HBV DNA less than 300 copies/mL). Alternate therapy should be initiated for patients who have detectable HBV DNA after 24 weeks of treatment. Optimal therapy should be guided by further resistance testing.

The recommended dose of Tyzeka for the treatment of chronic hepatitis B is 600 mg once daily, taken orally, with or without food.

Tyzeka oral solution (30 mL) may be considered for patients who have difficulty with swallowing tablets.

2.2 Renal Impairment

Tyzeka may be used for the treatment of chronic hepatitis B in patients with impaired renal function. No adjustment to the recommended dose of Tyzeka is necessary in patients whose creatinine clearance is greater than or equal to 50 mL/min. Adjustment of the total daily dose of Tyzeka oral solution or of the interval for administration of Tyzeka tablets is required in patients with creatinine clearance less than 50 mL/min including those with ESRD on hemodialysis (Table 1).

Table 1 Dose Adjustment of Tyzeka in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Tyzeka Oral Solution Dose (5 mL = 100 mg)	Tyzeka Tablet Dose (1 tablet = 600 mg)
greater than or equal to 50	30 mL once daily	1 tablet every 24 hrs
30–49	20 mL once daily	1 tablet every 48 hrs
less than 30 (not requiring dialysis)	10 mL once daily	1 tablet every 72 hrs
ESRD	6 mL once daily	1 tablet every 96 hrs ¹

¹When administered on hemodialysis days, Tyzeka should be administered after hemodialysis.

2.3 Hepatic Impairment

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

2.4 Duration of Therapy

For patients with incomplete viral suppression (HBV DNA greater than or equal to 300 copies/mL) after 24 weeks of treatment, alternate therapy should be instituted. HBV DNA should be monitored every 6 months to assure continued response. If patients test positive for HBV DNA at any time after their initial response, alternate treatment should be instituted. Optimal therapy should be guided by resistance testing.

The optimal duration of therapy with Tyzeka for patients with chronic hepatitis B is unknown.

3 DOSAGE FORMS AND STRENGTHS

3.1 Tablets

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 0078-0538-15) with child-resistant closure.

3.2 Oral Solution

Tyzeka (telbivudine) oral solution is a clear, colorless to pale yellow, passion fruit flavored liquid. Tyzeka oral solution contains 100 mg of telbivudine per 5 milliliters. Therefore, 30 mL of the oral solution provides a 600 mg dose of telbivudine.

Bottle containing 300 mL oral solution (NDC 0078-0539-85) with child-resistant closure and embossed dosing cup. The dosing cup is intended for measurement of Tyzeka oral solution only.

4 CONTRAINDICATIONS

None

Reference ID: 2924807

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

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. Female gender, obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering HBV nucleoside analogue reverse transcriptase inhibitors to patients with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Tyzeka should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.2 Exacerbations of Hepatitis B after Discontinuation of Treatment

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including Tyzeka. 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 Adverse Reactions (6.1)*].

5.3 Myopathy

Cases of myopathy/myositis have been reported with Tyzeka use several weeks to months after starting therapy. Myopathy has also been reported with some other drugs in this class. Rhabdomyolysis has been reported during postmarketing use of Tyzeka [*see Adverse Reactions (6.2)*].

Uncomplicated myalgia has been reported in Tyzeka-treated patients [*see Adverse Reactions (6.1)*]. 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 Tyzeka-associated myopathy, no pattern with regard to the degree or timing of CK elevations has been observed. In addition, the predisposing factors for the development of myopathy among Tyzeka recipients are unknown. Patients should be advised to report promptly unexplained muscle aches, pain, tenderness or weakness. Tyzeka therapy should be interrupted if myopathy is suspected, and discontinued if myopathy is confirmed. It is unknown whether the risk of myopathy during treatment with drugs in this class is increased with concurrent administration of other drugs associated with myopathy, including but not limited to: corticosteroids, chloroquine, hydroxychloroquine, certain HMGCoA reductase inhibitors, fibric acid derivatives, penicillamine, zidovudine, cyclosporine, erythromycin, niacin, and certain azole antifungals. Physicians initiating concomitant treatment with any drug associated with myopathy should monitor patients closely for any signs or symptoms of unexplained muscle pain, tenderness, or weakness.

5.4 Peripheral Neuropathy

Peripheral neuropathy has been reported with Tyzeka alone or in combination with pegylated interferon alfa-2a and other interferons. In one clinical trial, an increased risk and severity of peripheral neuropathy was observed with the combination use of Tyzeka and pegylated interferon alfa-2a compared to Tyzeka alone [*see Drug Interactions (7)*]. The safety and efficacy of Tyzeka in combination with pegylated interferons or other interferons for the treatment of chronic hepatitis B has not been demonstrated. Patients should be advised to report any numbness, tingling, and/or burning sensations in the arms and/or legs, with or without gait disturbance. Tyzeka therapy should be interrupted if peripheral neuropathy is suspected, and discontinued if peripheral neuropathy is confirmed [*see Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Lactic acidosis and severe hepatomegaly with steatosis [*See Boxed Warning, Warnings and Precautions (5.1)*]

- Severe acute exacerbations of hepatitis after discontinuation of treatment [See *Boxed Warning, Warnings and Precautions (5.2)*]
- Myopathy [See *Warnings and Precautions (5.3)*]
- Peripheral Neuropathy [See *Warnings and Precautions (5.4)*]

6.1 Clinical Trial Experience

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

Assessment of adverse reactions is primarily based on two studies (007 GLOBE and NV-02B-015) in which 1,699 subjects with chronic hepatitis B received double-blind treatment with Tyzeka 600 mg/day (n=847 subjects) or lamivudine (n=852 subjects) for 104 weeks. The median duration of therapy was 104 weeks for both treatment groups.

In the 104 week clinical studies, most adverse experiences reported with Tyzeka were classified as mild or moderate in severity and were not attributed to Tyzeka. Selected adverse events of any severity which were reported in greater than or equal to 3% of Tyzeka and lamivudine recipients are shown in Table 2. With the exception of increased creatine kinase (CK), which was reported more frequently among Tyzeka recipients, the adverse event profile was similar for the two drugs.

Table 2 Selected Common Adverse Events^a in Pooled Studies 007 GLOBE and NV-02B-015

Adverse Event (Preferred Term)	Tyzeka N=847 n (%)^b	Lamivudine N=852 n (%)^b
Fatigue	106 (13)	95 (11)
CK increased	90 (11)	52 (6)
Headache	83 (10)	95 (11)
Cough	52 (6)	45 (5)
Diarrhea	50 (6)	46 (5)
Abdominal pain, upper	49 (6)	52 (6)
Nausea	45 (5)	40 (5)
Pharyngolaryngeal pain	38 (5)	31 (4)
Arthralgia	37 (4)	38 (5)
Pyrexia	34 (4)	27 (3)
Rash	33 (4)	21 (3)
Back pain	33 (4)	32 (4)
Dizziness	32 (4)	43 (5)
Abdominal pain	29 (3)	31 (4)
Myalgia	27 (3)	17 (2)
ALT increased	27 (3)	31 (4)
Dyspepsia	24 (3)	39 (5)
Insomnia	24 (3)	22 (3)
Abdominal distension	22 (3)	19 (2)
Pruritus	18 (2)	23 (3)
Hepatitis B exacerbation	17 (2)	36 (4)

^a Adverse events reported in greater than or equal to 3% subjects in either treatment group

^b n (%) = the number and proportion of subjects in whom adverse event was reported

Moderate to severe (Grade 2-4) adverse events were reported in 239/847 (28%) of Tyzeka recipients and 229/852 (27%) of lamivudine recipients. The profile of adverse events of moderate to severe intensity was

similar in both treatment groups and no individual adverse event was reported in greater than 2% of subjects in either treatment group.

Discontinuations due to adverse events were reported in 4% of Tyzeka recipients and 4% of lamivudine recipients. The most common adverse events resulting in Tyzeka discontinuation included increased CK, nausea, diarrhea, fatigue, myalgia, and myopathy.

Peripheral neuropathy was reported as an adverse event in less than 1% (2/847) of subjects receiving Tyzeka monotherapy [see *Warnings and Precautions* (5.4)]. Of Tyzeka-treated subjects less than 1% (5/847) were diagnosed with myopathy/myositis (presenting with muscular weakness) [see *Warnings and Precautions* (5.3)].

Laboratory Abnormalities

Frequencies of selected treatment-emergent laboratory abnormalities in the 007 GLOBE and NV-02B-015 studies are listed in Table 3.

Table 3 Selected Treatment-Emergent Grade 3-4 Laboratory Abnormalities^a in Patients with Chronic Hepatitis B in the 104-Week Pooled 007 GLOBE and NV-02B-015 Studies

Test	Tyzeka 600 mg (n=847)	Lamivudine 100 mg (n=852)
Creatine Kinase (CK) greater than 7.0 x ULN	13%	4%
ALT greater than 10.0 x ULN and 2.0 x baseline ^b	5%	8%
ALT greater than 3 x baseline	7%	13%
AST (SGOT) greater than 3.0 x baseline	6%	10%
Lipase greater than 2.5 x ULN	2%	4%
Amylase greater than 3.0 x ULN	less than 1%	less than 1%
Total Bilirubin greater than 5.0 x ULN	less than 1%	less than 1%
Neutropenia (ANC less than or equal to 749/mm ³)	2%	2%
Thrombocytopenia (Platelets less than or equal to 49,999/mm ³)	less than 1%	less than 1%

^a On-treatment value worsened from baseline to Grade 3 or Grade 4 during therapy

^b American Association for the Study of Liver Diseases (AASLD) definition of acute hepatitis flare

Creatine Kinase (CK) Elevations

Creatine kinase (CK) elevations were more frequent among subjects on Tyzeka treatment. By 104 weeks of treatment, Grade 1-4 CK elevations occurred in 79% of Tyzeka-treated subjects and 47% of lamivudine-treated subjects. Grade 3 or 4 CK elevations occurred in 13% of Tyzeka-treated subjects and 4% of lamivudine-treated subjects. Most CK elevations were asymptomatic, but the mean recovery time was longer for subjects on Tyzeka than subjects on lamivudine.

Among Tyzeka-treated subjects with Grade 1-4 CK elevations, 10% developed a musculoskeletal adverse event compared to 5% of lamivudine-treated subjects. A total of 2% (13/847) Tyzeka-treated subjects interrupted or discontinued study drug due to CK elevation or musculoskeletal adverse events¹.

¹ Includes the Preferred Terms: back pain, chest wall pain, non-cardiac chest pain, chest discomfort, flank pain, muscle cramp, muscular weakness, musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, myofascial pain syndrome, myopathy, myositis, neck pain, and pain in extremity.

ALT Flares during Treatment

The incidence of ALT flares, defined as ALT greater than 10 x ULN and greater than 2 x baseline, was similar in the two treatment arms (3%) in the first six months. After week 24, ALT flares were reported less frequently

in the Tyzeka arm (2%) compared to the lamivudine arm (5%). Periodic monitoring of hepatic function is recommended during chronic hepatitis B treatment.

Exacerbations of Hepatitis after Discontinuation of Treatment

In the subset of subjects who discontinued treatment prematurely for reasons other than efficacy, or who elected not to continue Tyzeka in another clinical trial, 9/154 (6%) Tyzeka-treated and 10/180 (6%) lamivudine-treated subjects experienced an exacerbation of hepatitis (ALT elevation greater than 2 x baseline and greater than 10 x ULN) in the 4-month post-treatment period.

6.2 Postmarketing Experience

The following adverse reactions have been reported during postmarketing use of Tyzeka. Because these reactions were reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to Tyzeka exposure.

Musculoskeletal and Connective Tissue Disorders

Rhabdomyolysis

Nervous System Disorders

Paraesthesia, hypoaesthesia

Metabolism and Nutrition Disorders

Lactic acidosis

7 DRUG INTERACTIONS

Tyzeka is excreted mainly by passive diffusion so the potential for interactions between Tyzeka and other drugs eliminated by renal excretion is low. However, because Tyzeka is eliminated primarily by renal excretion, coadministration of Tyzeka with drugs that alter renal function may alter plasma concentrations of Tyzeka [*see Clinical Pharmacology (12.3)*].

A clinical trial investigating the combination of Tyzeka, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination may be associated with an increased risk of peripheral neuropathy occurrence and severity, in comparison to Tyzeka alone [*see Warnings and Precautions (5.4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 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 Tyzeka in pregnant women. Because animal reproductive toxicity studies are not always predictive of human response, Tyzeka should be used during pregnancy only if potential benefits outweigh the risks.

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of Tyzeka did not include sufficient numbers of subjects aged 65 and older 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 Clinical Pharmacology (12.3) and Dosage and Administration (2.2)*].

8.6 Renal Impairment

Tyzeka is eliminated primarily by renal excretion, therefore dose regimen adjustment is recommended in patients with creatinine clearance less than 50 mL/min, including patients with ESRD requiring hemodialysis [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

8.7 Liver Transplant Recipients

The safety and efficacy of Tyzeka in liver transplant recipients has not been evaluated. The steady-state pharmacokinetics of Tyzeka was not altered following multiple dose administration in combination with cyclosporine. If Tyzeka 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 (12.3) and Dosage and Administration (2.2)*].

8.8 Co-Infected Patients

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

8.9 Racial/Ethnic Minorities

The safety and efficacy of Tyzeka have not been evaluated in Black/African American or Hispanic patients. It is not known if safety and efficacy can be extrapolated from studied populations.

9 DRUG ABUSE AND DEPENDENCE

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

10 OVERDOSAGE

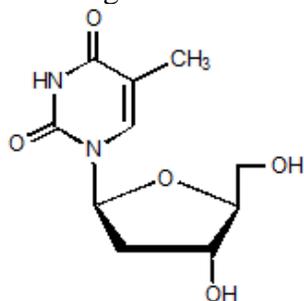
There is no information on intentional overdose of Tyzeka, but one subject experienced an unintentional and asymptomatic overdose. Healthy subjects who received Tyzeka doses up to 1800 mg/day for 4 days had no increase in or unexpected adverse events. A maximum tolerated dose for Tyzeka has not been determined. In the event of an overdose, Tyzeka 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.

11 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-
Reference ID: 2924807

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 (greater than 20 mg/mL), and very slightly soluble in absolute ethanol (0.7 mg/mL) and n-octanol (0.1 mg/mL).

Tyzeka 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.

Tyzeka oral solution is available for oral administration in 100 mg/5 mL strength. Tyzeka oral solution contains the following inactive ingredients: citric acid anhydrous, benzoic acid, passion fruit flavor, sodium saccharin, sodium hydroxide, and purified water. A 600 mg dose (30 mL) of Tyzeka oral solution contains approximately 47 mg of sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tyzeka is an antiviral drug [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

In a randomized, partially single-blinded, placebo and active-controlled, four-period crossover study, 53 healthy subjects were administered Tyzeka 600 mg, a suprathreshold Tyzeka 1800 mg dose, placebo, and moxifloxacin 400 mg. After 7 days of dosing, Tyzeka did not prolong the QT interval. The maximum placebo-adjusted mean (upper 1-side 95% CI) change from baseline in QTcF on day 7 were 3.4 msec (5.9 msec) for the 600 mg and 4.4 msec (6.9 msec) for the 1800 mg dosing regimens.

12.3 Pharmacokinetics in Adults

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

Absorption and Bioavailability

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

Effects of Food on Oral Absorption

Tyzeka absorption and exposure were unaffected when a single 600-mg dose was administered with a high-fat (\sim 55 g), high-calorie (\sim 950 kcal) meal. Tyzeka 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 [¹⁴C]-telbivudine in humans. Telbivudine is not a substrate, or inhibitor of the cytochrome P450 (CYP450) enzyme system.

After reaching the peak concentration, plasma concentrations of Tyzeka declined in a biexponential manner with a terminal elimination half-life ($T_{1/2}$) of 40-49 hours. Tyzeka is eliminated primarily by urinary excretion of unchanged drug. The renal clearance of Tyzeka 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 Tyzeka. Because renal excretion is the predominant route of elimination, patients with moderate to severe renal dysfunction and those undergoing hemodialysis require a dose regimen adjustment [see *Dosage and Administration* (2.2)].

Special Populations

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

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

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

Renal Impairment: Single-dose pharmacokinetics of Tyzeka have been evaluated in subjects (without chronic hepatitis B) with various degrees of renal impairment (as assessed by creatinine clearance). Based on the results shown in Table 4, adjustment of the dose regimen for Tyzeka is recommended in patients with creatinine clearance of <50 mL/min [see *Dosage and Administration* (2.2)].

Table 4 Pharmacokinetic Parameters (mean ± SD) of Tyzeka in Subjects with Various Degrees of Renal Function

	Renal Function (Creatinine Clearance in mL/min)				
	Normal (greater than 80) (n=8) 600 mg	Mild (50-80) (n=8) 600 mg	Moderate (30-49) (n=8) 400 mg	Severe (less than 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-∞} (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 Subjects on Hemodialysis: Hemodialysis (up to 4 hours) reduces systemic Tyzeka exposure by approximately 23%. Following dose regimen adjustment for creatinine clearance [see *Dosage and Administration* (2.2)], no additional dose modification is necessary during routine hemodialysis. When administered on hemodialysis days, Tyzeka should be administered after hemodialysis.

Hepatic Impairment: The pharmacokinetics of Tyzeka following a single 600-mg dose have been studied in subjects (without chronic hepatitis B) with various degrees of hepatic impairment. There were no changes in Tyzeka 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

Drug-drug interaction studies show that lamivudine, adefovir dipivoxil, cyclosporine, pegylated interferon alfa-2a and tenofovir disoproxil fumarate do not alter Tyzeka pharmacokinetics. In addition, Tyzeka does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil, cyclosporine, or tenofovir disoproxil fumarate. No definitive conclusion could be drawn regarding the effects of Tyzeka 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.

12.4 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. Telbivudine is an inhibitor of both HBV first strand (EC_{50} value = $1.3 \pm 1.6 \mu\text{M}$) and second strand synthesis (EC_{50} value = $0.2 \pm 0.2 \mu\text{M}$). Telbivudine 5'-triphosphate at concentrations up to $100 \mu\text{M}$ 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 $10 \mu\text{M}$.

Antiviral Activity in Cell Culture

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 $0.2 \mu\text{M}$. 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 greater than $100 \mu\text{M}$) and was not antagonistic to the anti-HIV activity of abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine. The absence of activity of telbivudine against HIV has not been evaluated in clinical trials.

Resistance

In an as-treated analysis of the Phase III global registration trial (NV-02B-007 GLOBE study), 59% (252/430) of treatment-naïve HBeAg-positive and 89% (202/227) of treatment-naïve HBeAg-negative subjects receiving Tyzeka 600 mg once daily achieved non-detectable serum HBV DNA levels (less than 300 copies/mL) by Week 52. Of those who continued treatment beyond Week 52, 58% (243/418) and 85% (190/224) of HBeAg-positive and HBeAg-negative Tyzeka recipients, respectively, had undetectable HBV DNA at Week 104 (or at the end of dosing in treatment Year 2).

The cumulative frequency of genotypic resistance (emergence of the rtM204I/V substitution) to Tyzeka based on an as-treated analysis of HBeAg-positive and HBeAg-negative subjects at Weeks 52 and 104 was 7% and 22%, respectively. Genotypic analysis of paired baseline and Tyzeka-treatment failure isolates from 182 evaluable subjects with amplifiable HBV DNA and greater than or equal to 16 weeks of treatment showed that the rtM204I/V substitution was associated with virologic failure (HBV DNA greater than or equal to 1,000 copies/mL) and virologic rebound (greater than or equal to 1 \log_{10} increase above nadir). The rtM204I substitution was the most frequent substitution, detectable in isolates from 143/182 (79%) of evaluable subjects, and was frequently found with substitutions rtL80I/V and rtL180M. The rtM204I substitution was found infrequently with rtV27A, rtL82M, rtV173L, rtT184I/S, rtA200V, rtL229F/V/W, and rtR289K substitutions. The HBV of 16 subjects developed rtA181S/T amino acid substitutions while receiving Tyzeka. Eight of these 16 subjects had outgrowth of HBV expressing an rtM204I/V substitution without the rtA181 substitution and 1 subject's HBV had both the rtM204I and rtA181T substitutions.

Subjects with higher baseline viral load had higher rates of genotypic resistance to Tyzeka, while subjects who achieved HBV DNA levels less than 300 copies/mL at Week 24 had lower rates of genotypic resistance to Tyzeka. By Week 104, 32% (95/293) of HBeAg-positive subjects with baseline viral DNA levels greater than or equal to 9 \log_{10} copies/mL developed genotypic resistance to Tyzeka, compared to 15% (20/136) of the subjects with viral DNA levels less than 9 \log_{10} copies/mL. In HBeAg-negative subjects, 17% (22/132) of the subjects with baseline viral DNA levels greater than or equal to 7 \log_{10} copies/mL developed genotypic resistance to Tyzeka, compared to 5% (5/95) of the subjects with viral DNA levels less than 7 \log_{10} copies/mL.

By Week 104, 41% (97/239) of HBeAg-positive subjects who failed to achieve viral DNA levels less than 300 copies/mL at Week 24 developed genotypic resistance to Tyzeka, compared to 9% (18/190) of the subjects with non-detectable serum HBV DNA levels (less than 300 copies/mL) at Week 24. In HBeAg-negative subjects, 35% (15/43) of the subjects who failed to achieve viral DNA levels less than 300 copies/mL at Week 24 developed genotypic resistance to Tyzeka, compared to 7% (12/184) of the subjects with non-detectable serum HBV DNA levels (less than 300 copies/mL) at Week 24.

Cross-Resistance

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, lamivudine-resistant HBV strains expressing either the rtM204I substitution or the rtL180M/rtM204V double substitution had greater than or equal to 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 substitution 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. The rtA181S and rtA181T substitutions conferred 2.7- and 3.5-fold reductions in susceptibility to telbivudine, respectively. The rtA181T substitution is associated with decreased clinical response in patients with HBV treated with adefovir and entecavir. HBV encoding the adefovir resistance-associated substitution rtN236T remained susceptible to telbivudine.

13 NONCLINICAL TOXICOLOGY

13.1 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.

Effects on fertility were studied in rats administered telbivudine as juveniles or adults. Juvenile rats were treated with telbivudine at doses of 0, 250, 1000, and 2000 mg/kg/day from post natal days 14 to 70. These rats were mated following a 5 week drug-free recovery period. Up to 50% reduction of fertility was associated with doses 1000 mg/kg/day and higher, which was equivalent to a systemic exposure approximately 7.5 times that achieved in humans at the therapeutic dose. The no observed adverse effect level (NOAEL) for effects on fertility or mating parameters was 250 mg/kg/day, which was equivalent to systemic exposure levels 2.5 to 2.8 times that achieved in humans at the therapeutic dose. In contrast, such reduction of fertility was absent in adult rats treated with telbivudine at doses up to 2000 mg/kg/day, equivalent to a systemic exposure approximately 14 times that achieved in humans at the therapeutic dose.

14 CLINICAL STUDIES

14.1 Clinical Experience in Nucleoside-Naïve Adults

The safety and efficacy of long-term (104-week) Tyzeka treatment were evaluated in one active-controlled, clinical study (NV-02B-007 GLOBE Study) that included 1,367 subjects with chronic hepatitis B and a smaller supportive study (NV-02B-015) that included 332 subjects. 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 greater than or equal to 1.3 x ULN, no evidence of hepatic decompensation, and chronic inflammation on liver biopsy compatible with chronic viral hepatitis.

Reference ID: 2924807

NV-02B-007 GLOBE Study

The Week 52 and Week 104 results of the 007 GLOBE study are summarized below.

The 007 GLOBE study was a Phase III, randomized, double-blind, multinational study of Tyzeka 600 mg once daily compared to lamivudine 100 mg once daily for a treatment period of 104 weeks in 1,367 (n= 680 Tyzeka; n=687 lamivudine) nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative subjects. The primary data analysis was conducted after all subjects had reached Week 52.

HBeAg-positive Subjects: (n= 458 Tyzeka; n= 463 lamivudine) 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 greater than or equal to 7; mean serum HBV DNA as measured by Roche COBAS Amplicor[®] PCR assay was 9.52 log₁₀ copies/mL; and mean serum ALT was 153 IU/L. Pre- and post-liver biopsy samples were adequate for 86% of subjects.

HBeAg-negative Subjects: (n=222 Tyzeka; n= 224 lamivudine) 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 greater than or equal to 7; mean serum HBV DNA as measured by Roche COBAS Amplicor[®] PCR assay was 7.54 log₁₀ copies/mL; and mean serum ALT was 140 IU/L. Pre- and post-liver biopsy samples were adequate for 92% of subjects.

Clinical Results

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

The primary endpoint of Therapeutic Response at Week 52 was a composite endpoint requiring suppression of HBV DNA to less than 5 log₁₀ copies/mL in conjunction with either loss of serum HBeAg or ALT normalization. Key secondary endpoints included histologic response, ALT normalization, and measures of virologic response.

At Week 52, in HBeAg-positive patients, 75% of Tyzeka subjects and 67% of lamivudine subjects had a Therapeutic Response; in HBeAg-negative patients 75% of Tyzeka subjects and 77% of lamivudine subjects had a Therapeutic Response.

Analysis of the histological response at Week 52 is shown in Table 5.

Table 5 Histological Improvement and Change in Ishak Fibrosis Score at Week 52 (007 GLOBE Study)

	HBeAg-positive (n=797)		HBeAg-negative (n=417)	
	Tyzeka 600 mg (n=399) ¹	Lamivudine 100 mg (n=398) ¹	Tyzeka 600 mg (n=205) ¹	Lamivudine 100 mg (n=212) ¹
Histologic Response²				
Improvement	69%	60%	69%	68%
No Improvement	19%	26%	23%	25%
Missing Week 52 Biopsy	12%	15%	8%	7%
Ishak Fibrosis Score³				
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 greater than or equal to one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Necroinflammatory Score greater than or equal to 2

² Histologic Response defined as greater than or equal to 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 greater than or equal to a 1-point reduction in Ishak Fibrosis Score from baseline to Week 52

Subjects were eligible to continue blinded treatment to Week 104. In the ITT population, 624/680 (92%) Tyzeka recipients and 599/687 (87%) lamivudine recipients completed study treatment to Week 104. At Week 104, in HBeAg-positive patients, 63% of Tyzeka subjects and 48% of lamivudine subjects had a Therapeutic Response, while in HBeAg-negative patients 78% of Tyzeka subjects and 66% of lamivudine subjects had a Therapeutic Response.

Selected virologic, biochemical, and serologic outcome measures at Weeks 52 and 104 are shown in Table 6.

Table 6 Virological, Biochemical and Serologic Endpoints at Weeks 52 and 104 (007 GLOBE Study)

Response Parameter	HBeAg-positive (n=921)				HBeAg-negative (n=446)			
	Tyzeka 600 mg (n=458)		Lamivudine 100 mg (n=463)		Tyzeka 600 mg (n=222)		Lamivudine 100 mg (n=224)	
	Week 52	Week 104	Week 52	Week 104	Week 52	Week 104	Week 52	Week 104
Mean HBV DNA Reduction from Baseline (log ₁₀ copies/mL) ± SEM ¹	-6.45 (0.11)	-5.74 (0.15)	-5.54 (0.11)	-4.42 (0.15)	-5.23 (0.13)	-5.00 (0.15)	-4.40 (0.13)	-4.17 (0.16)
% Subjects HBV DNA Negative by PCR	60%	56%	40%	39%	88%	82%	71%	57%
ALT Normalization ²	77%	70%	75%	62%	74%	78%	79%	70%
HBeAg Seroconversion ³	23%	30%	22%	25%	NA	NA	NA	NA
HBeAg Loss ³	26%	35%	23%	29%	NA	NA	NA	NA

¹ Roche COBAS AmpliCor® Assay (LLOQ less than or equal to 300 copies/mL).

²ALT normalization assessed only in subjects with ALT greater than ULN at baseline.

³ 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 were less likely to develop resistance at one and two years.

Study NV-02B-015

The efficacy results of the 007 GLOBE study were supported by results of study NV-02B-015. This was a Phase III, randomized, double-blind, study of Tyzeka 600 mg once daily compared to lamivudine 100 mg once daily for a treatment period of 104 weeks in 332 (n=167 Tyzeka; n=165 lamivudine) nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative Chinese subjects. The primary efficacy endpoint was serum HBV DNA reduction from baseline. In this study the composite endpoint Therapeutic Response was a key secondary endpoint. Histological response was not assessed as an outcome measure in this study.

Clinical Results

Among HBeAg-positive subjects (n=147 Tyzeka; n=143 lamivudine) results for key endpoints at Week 104 included Therapeutic Response (66% vs. 41%), mean HBV DNA reduction (-5.47 vs. -3.97 log₁₀ copies/mL), HBV DNA PCR negativity (58% vs. 34%), ALT normalization (73% vs. 59%), HBeAg loss (40% vs. 28%) and HBeAg seroconversion (29% vs. 20%), for Tyzeka and lamivudine, respectively. Because the number of HBeAg-negative subjects in this study was small (n=42), definitive conclusions could not be drawn regarding efficacy outcomes in this subpopulation.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets

Tyzeka 600 mg tablets are white to slightly yellowish film-coated, ovaloid-shaped tablets, imprinted with “LDT” on one side.

Bottle of 30 tablets (NDC 0078-0538-15) with child-resistant closure.

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].

Oral Solution

Tyzeka (telbivudine) oral solution is a clear, colorless to pale yellow, passion fruit flavored liquid. Tyzeka oral solution contains 100 mg of telbivudine per 5 milliliters.

Bottle containing 300 mL oral solution (NDC 0078-0539-85) with child-resistant closure and embossed dosing cup. The dosing cup is intended for measurement of Tyzeka oral solution only.

Store Tyzeka oral solution in original container at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Use within two months after opening the bottle. Do not freeze.

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

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

17 PATIENT COUNSELING INFORMATION

- See FDA-approved patient labeling (Medication Guide)

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 to report promptly any numbness, tingling, and/or burning sensations in the arms and/or legs, with or without difficulty walking.

Patients should be advised that Tyzeka is not a cure for hepatitis B, that the long-term treatment benefits of Tyzeka are unknown at this time. In particular, 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. HBV prevention strategies should be discussed with patients, including safe sexual practices, and avoidance of needle sharing or sharing any personal items which may contain residual blood or body fluids, such as razor blades or toothbrushes. Additionally, a vaccine is available for prevention of hepatitis B infection in susceptible individuals.

Patients on a low sodium diet should be advised that Tyzeka oral solution contains approximately 47 mg of sodium per 600 mg dose (30 mL).

Patients should be advised to dispose of unused or expired Tyzeka by using a community pharmaceutical take-back disposal program, or by placing unused Tyzeka in a closed container, such as a sealed bag, into household trash. All identifying information should be removed from the original Tyzeka container prior to disposal.