PRODUCT MONOGRAPH

Pr SEBIVO®

telbivudine

Tablets (film-coated) 600 mg

Antiviral Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Film-coated tablet 600 mg	None. For a complete listing, please see the DOSAGE FORMS COMPOSITION AND PACKAGING section of this Product Monograph

INDICATIONS AND CLINICAL USE

SEBIVO® is indicated for the treatment of chronic hepatitis B in adults of 16 years and older with compensated liver disease with evidence of viral replication and active liver inflammation.

This indication is based on a single Phase 3 intent-to-treat trial for 104 weeks in nucleoside-naive patients with HB e Ag positive or HB e Ag negative chronic HBV infection with compensated liver disease. The primary endpoint was based on virological, serological and biochemical data. There are no available data on telbivudine in patients harbouring lamivudine resistant virus nor in patients with decompensated chronic hepatitis B, co-infected patients (co-infected with HIV or Hepatitis C or D) or in patients in the liver transplant setting.

The following points should be considered when initiating therapy with SEBIVO.

- For HBeAg positive patients, SEBIVO treatment **should only** be initiated in patients with baseline HBV DNA < 9 log 10 copies/mL and baseline ALT≥ 2x ULN.
- For HBeAg negative patients, SEBIVO treatment **should only** be initiated in patients with baseline HBV DNA < 7 log 10 copies/mL
- On treatment response should guide continued therapy

Geriatrics (> 65 years of age):
Available data are insufficient to support a specific dose recommendation for patients over the age of 65 years (see WARNINGS AND PRECAUTIONS).

Pediatrics (< 16 years of age):
No studies have been performed in children under the age of 16 years.

CONTRAINDICATIONS

SEBIVO is contraindicated in patients with previously demonstrated hypersensitivity to telbivudine or any component of the product. **For a complete listing, see the DOSAGE FORMS, COMPOSITION and PACKAGING section of the Product Monograph.**

The concomitant use of telbivudine with pegylated interferon alfa-2a is contraindicated (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy. Hepatic function must 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, re-initiation of anti-hepatitis B therapy may be warranted.

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.

Metabolism and Nutrition disorders

Post-marketing cases of lactic acidosis have also been reported with telbivudine. Cases were more often secondary to other serious conditions (e.g. rhabdomyolysis) and/or associated with muscle related events (e.g., myopathy, myositis). In some cases, fatal outcomes were reported when lactic acidosis was secondary to rhabdomyolysis. Treatment with SEBIVO should be discontinued if clinical or laboratory findings suggestive of lactic acidosis occur.

Musculoskeletal

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. Isolated cases of rhabdomyolysis have been reported during post-marketing use of telbivudine (see POST-MARKET ADVERSE DRUG REACTIONS).

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 co-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.

Neurologic

An increased risk of developing serious peripheral neuropathy has been observed in one study with the combined use of telbivudine 600 mg daily, and pegylated interferon alfa-2a, compared to telbivudine or pegylated interferon alfa-2a alone (see CONTRAINDICATIONS and DRUG INTERACTIONS). Such risk cannot be excluded for other alfa-interferons (pegylated or standard).

In a pilot trial of telbivudine and pegylated interferon alfa – 2a used in combination, peripheral neuropathy has been a serious event in 10% of patients. Additionally, non-serious peripheral neuropathy cases were also reported. Symptoms of these cases included weakness and paresthesias and pain in the legs, with the time to onset in most cases being 3 months. An increased risk cannot be ruled out for combination treatment with other interferon products (pegylated or standard). The benefit of the combination of telbivudine with interferon alfa (pegylated or standard) is not currently established.

Peripheral neuropathy has also occurred uncommonly in clinical trial patients receiving telbivudine monotherapy (0.3%; 5/2000) and in post marketing reports. If peripheral neuropathy is suspected in a patient receiving telbivudine, treatment with telbivudine should be reconsidered.

Use of Telbivudine in Lamivudine Resistant Patients:

Available evidence does not support the use of telbivudine in patients with established lamivudine resistant Hepatitis B virus infection. In vitro, telbivudine was not active against the single mutant M204V hepatitis B virus (HBV) strains containing double mutant rtM204V/rtL180M or single mutant rtM204I (See ACTION AND CLINICAL PHARMACOLOGY: Pharmacodynamics and ACTION AND CLINICAL PHARMACOLOGY: Resistance: *In Vitro*). There have been no clinical studies in these patients.

Use of Telbivudine in Adefovir Resistant Patients:

There are no adequate and well controlled clinical studies of telbivudine treatment in patients with established adefovir - resistant Hepatitis B virus infection. *In vitro,* HBV encoding the adefovir resistance-associated substitution rtA181V showed a 4.1-fold reduced susceptibility to telbivudine. The rtA181S and rtA181T substitutions conferred 2.7- and 3.5-fold reductions in susceptibility to telbivudine, respectively. The rtA181T substitution is associated with a decreased clinical response in subjects with HBV treated with adefovir and entecavir. HBV encoding the adefovir resistance-associated substitution rtN236T remained susceptible to telbivudine (see ACTION AND CLINICAL PHARMACOLOGY: Resistance: *In Vitro*).

Patients with Renal Impairment

Telbivudine is eliminated primarily by renal excretion, therefore dose interval adjustment is recommended in patients with creatinine clearance <50 mL/min (<0.835 mL/s), including patients on hemodialysis (see DOSAGE AND ADMINISTRATION). In addition, co-administration of SEBIVO with substances that affect renal function may alter plasma concentrations of telbivudine and/or the co-administered substance (see DRUG INTERACTIONS).

Telbivudine has not been studied in patients on CAPD (continuous ambulatory peritoneal dialysis).

Liver transplant recipients

The safety and efficacy of telbivudine in liver transplant recipients are unknown. The steady state pharmacokinetics of telbivudine were not altered following multiple dose administration in combination with cyclosporine (4 mg/kg/day, given in two divided doses). There is no information at higher doses of cyclosporine. If telbivudine treatment is considered necessary in a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus, renal function must be monitored both before and during treatment with SEBIVO (see DRUG INTERACTIONS).

Cardiovascular

There is no evidence of cardiotoxicity for telbivudine. 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 was not observed to have an effect on QT intervals or other electrocardiographic parameters after multiple daily doses up to 1800 mg.

Special Populations

Co-infected Patients

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

Pregnant Women

There are no adequate and well-controlled studies of telbivudine in pregnant women. Data (from the Antiretroviral Pregnancy Registry, literature, and spontaneous post-marketing reports) on exposure to telbivudine during pregnancy are available from 1696 women (173 in first trimester and 1523 in second and/or third trimester). There was no increase in the rate of live birth defects, spontaneous abortion or elective termination during telbivudine treatment and no foetal/neonatal toxicity was reported. The population exposed and monitored to date is only sufficient to detect major teratogenicity, and cannot detect an increase in the risk of relatively rare defects; however, no pattern of birth defects suggestive of a common etiology was seen.

Telbivudine is not teratogenic and has shown no adverse effects in developing embryos and foetuses 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 foetus in rats and rabbits at doses up to 1,000 mg/kg/day, providing exposure levels 6- to 37-times higher, respectively, than those observed with the therapeutic dose (600 mg/day) in humans. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see TOXICOLOGY: Reproductive Toxicity).

SEBIVO may be considered for use during pregnancy if the benefit to the mother outweighs the potential risk to the foetus. Alternatively, SEBIVO may be considered for use in pregnancy when there is potential benefit to the foetus by reducing the risk of HBV transmission from mother to infant. Appropriate interventions based on current guidelines should be used to prevent neonatal acquisition of HBV infection.

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.

Nursing Women

Telbivudine is excreted in the milk of rats. It is not known whether telbivudine is excreted in human milk. Women should not breast-feed if they are taking SEBIVO.

Pediatrics (< 16 years of age)

The safety and effectiveness of SEBIVO in pediatric patients below the age of 16 have not been established.

Geriatrics (> 65 years of age)

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 must be exercised when prescribing SEBIVO to elderly patients in view of the greater frequency of decreased renal function due to concurrent disease or concomitant use of other medicinal products (see ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Renal Impairment). It may be useful to monitor renal function in this population.

Sexual Function/Reproduction

There are no clinical data on the effects of telbivudine on male or female fertility. In reproductive toxicology studies, no evidence of impaired fertility was seen when either male or female rats were treated with telbivudine at doses up to 2000 mg/kg/day (systemic exposures approximately 14 times those achieved in humans at the therapeutic dose) and mated with untreated rats (see TOXICOLOGY: Reproductive Toxicology).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Assessment of adverse reactions is primarily based on 2 studies (007 GLOBE and NV-02B-015) in which 1699 patients received either double-blind treatment with telbivudine 600mg /day (n= 847) or with lamivudine 100mg /day (n=852) for104 weeks. The most common telbivudine related adverse event was CK elevation

Clinical Trial Adverse Drug Reactions

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

Approximately 1,500 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 two studies (007 GLOBE and NV-02B-015) in which 1,699 patients with chronic hepatitis B received double-blind treatment with telbivudine 600 mg/day (n=847) or lamivudine (n=852) for 104 weeks.The safety profiles of telbivudine and lamivudine were generally comparable in these studies.

In the 104 week clinical studies telbivudine was generally well tolerated, with most adverse experiences classified as mild or moderate in severity. In the 007 GLOBE and NV-02B-015 studies patient discontinuations for adverse events, clinical disease progression or lack of efficacy were 1.5% for telbivudine and 4.1% for lamivudine.

SEBIVO was not associated with renal toxicity. Seventy two percent (185/256) of patients who entered the 007 GLOBE trial with mild renal impairment at baseline (estimated mean glomerular filtration rate (eGFR) 60 - 90 mL per min) had normal renal function (eGFR >90 mL per min)

after 104 weeks of SEBIVO treatment. None worsened to moderate impairment (eGFR < 60 ml per min). The eGFR, assessed by MDRD, increased by 11.3 mL/min after 104 weeks of SEBIVO therapy. After 208 weeks, SEBIVO-treated patients who participated in trial CLDT600A2303 had a mean eGFR increase of 14.9 mL/min from baseline.

Clinical adverse reactions attributed to study drug in the 104 Week Pooled 007 GLOBE and NV-02B-015 Studies are presented in Table 1.

Table 1: Clinical Adverse Reactions Attributed to Study Drug in ≥ 1% of Patients in the 104 Week Pooled 007 GLOBE and NV-02B-015 Studies.

	Telbivudine 600 mg n= 847 (%)	**Lamivudine 100 mg n= 852 (%)**
General		
Fatigue	4.4	2.6
Gastrointestinal		
Nausea	2.6	2.0
Diarrhoea	1.3	0.7
Abdominal Pain	0.7	1.3
Nervous system		
Headache	3.0	2.9
Dizziness	1.4	0.8
Dermatological		
Rash	1.2	0.7

Less common (<1%) Clinical Trial Adverse Drug Reactions

Peripheral neuropathy

Abnormal Hematologic and Clinical Chemistry Findings

Creatine kinase elevation

Creatine kinase (CK) elevations occurred in both treatment arms. However, median CK levels were higher in telbivudine-treated patients. In the pooled analysis from 007 GLOBE and NV-02B-015, by 104 weeks of treatment, Grade 3/4 CK elevations occurred in 12.6% of telbivudine-treated patients (n=847) and 4.0% of lamivudine-treated patients (n=852). Most CK elevations were asymptomatic and CK values typically decreased by the next visit on continued treatment. Analysis of clinical adverse events in patients with CK elevations indicated no significant difference between telbivudine-treated and lamivudine-treated patients.

Treatment-emergent CK abnormalities in the 104-week pooled 007 (GLOBE) and NV-02B-015 studies are presented in Table 2.

Table 2: Treatment-Emergent CK Abnormalities[1] in the 104-week pooled 007 (GLOBE) and NV-02B-015 Studies

CK Toxicity Grade[¥ 2]	Telbivudine 600 mg n= 847(%)	Lamivudine 100 mg n= 852 (%)
Grade 1 (1 to 3.0 x ULN)	38.8	35.0
Grade 2 (>3.0 to 7.0 x ULN)	28.0	7.9
Grade 3 (>7.0 to 10.0 x ULN)	5.3	1.2
Grade 4 (> 10 x ULN)	7.3	2.8
Total of Grades 1-4 (≥1 x ULN)	79.5	46.8
Discontinuation/Interruption due to CK[3]	0.7 *	0.1

[1] On-treatment value worsened from baseline to Grade 1 to 4 during therapy up to Week 104
[2] 22% of patients had pre-treatment Grade 1-4 CK elevations.
[3] Discontinuation/interruption due to adverse events with preferred terms "BlOOD CREATINE PHOSPHOKINASE INCREASED" up to week 104
* One patient discontinued in each treatment group and 5 patients in the telbivudine group had study drug interrupted
¥ CK toxicity grade corresponds to the 1992 version of the DAIDS AE grading table,

In an open-label single arm, Phase IV study in 2,206 Chinese patients (CLDT600ACN03), grade 3/4 CK elevations were reported in 3.1% of telbivudine-treated patients by week 52.

Treatment-emergent Grade 3-4 laboratory abnormalities in the 104-Week Pooled 007 GLOBE and NV-02B-015 studies are presented in Table 3.

Table 3: Treatment-Emergent Grade 3-4 Laboratory Abnormalities[1] in the 104-Week Pooled 007 GLOBE and NV-02B-015 Studies

Test	Telbivudine 600 mg n=847 (%)	Lamivudine 100 mg n=852 (%)
Creatine Kinase (CK) ≥7.0 x ULN	13	4
ALT greater than 10.0 x ULN and 2.0 x baseline [2]	5	8
ALT (SGPT) > 3.0 x baseline	7	13
AST (SGOT) > 3.0 x baseline	6	10
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

ALT flares

In the pooled study results, the incidence of ALT flares, defined as ALT greater than 10x ULN and greater than 2x baseline, was similar in the two treatment arms (3% in telbivudine arm, 2.9% in lamivudine arm) in the first six months. ALT flares occurred less frequently in both arms after

Week 24, with a lower incidence in the telbivudine arm (2.0%) compared to the lamivudine arm (5.3%) as presented in Table 4. Periodic monitoring of hepatic function is recommended during treatment.

Table 4

Summary of ALT flares[1] by 6-month intervals in the pooled 007 GLOBE and NV-02B-015 studies

	Telbivudine 600 mg (n = 847)	Lamivudine 100 mg (n = 852)
Overall	4.8 %	7.9 %
Baseline to week 24	3.0 %	2.9 %
Week 24 to week 52	0.4 %	1.7 %
Week 52 to week 76	0.7 %	2.0 %
Week 76 to week 104	1.3 %	2.0 %
Week 24 to end of treatment	2.0 %	5.3%

[1] intermittent elevations of aminotransferase activity to >10x upper limit of normal and >2x baseline value.

Results at 208 weeks

After 104 weeks of telbivudine therapy, 78% of patients (530/680) from study 007 GLOBE and 82% (137/167) of patients from study NV-02B-015 enrolled into the extension study CLDT600A2303 to continue telbivudine treatment for up to 208 weeks. The long-term safety population in study CLDT600A2303 consisted of 655 patients, including 518 patients from study 007 GLOBE and 137 patients from study NV-02B-015.

The overall safety profile from the pooled analysis up to 104 and 208 weeks was similar. The most frequent Grade 3 /4 laboratory abnormality was elevated CK which occurred in 15.9% (104/655) of patients treated with telbivudine for 208 weeks. Most grade 3 or 4 CK elevations were asymptomatic and transient. Of the patients with grade 3 /4 CK elevation, 8.7% (9/104) experienced an on-treatment AE possibly related to myopathic/muscle injury within 30 days of the grade 3 /4 CK elevation. Myalgia (5 patients) was the most common AE of this type.

Exacerbations of hepatitis after discontinuation of treatment

There are insufficient data in patients who have discontinued telbivudine treatment to determine the effects on post-treatment exacerbations of hepatitis after discontinuation of telbivudine treatment (see WARNINGS AND PRECAUTIONS). However severe acute exacerbations of hepatitis B may occur in patients who have discontinued anti - hepatitis B therapy and hepatic

function must therefore be closely monitored in those patients, with both clinical and laboratory follow-up for at least several months.

In study 2303, off-treatment ALT flares were reported for 5 (7.6%) patients in the telbivudine treatment arm (n=66) and 4 (7.0%) patients in the lamivudine treatment arm (n=57). All ALT flares reported occurred during the first 52 weeks of the off-treatment follow-up in study CLDT600A2303. No other events of off-treatment exacerbation of hepatitis B upon telbivudine withdrawal were reported.

Drug abuse and dependence

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

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been identified based on post-marketing spontaneous reports and are organized by system organ classes. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Metabolism and Nutrition disorders

Lactic acidosis.

Musculoskeletal, connective tissue and bone disorders

Rhabdomyolysis.

DRUG INTERACTIONS

Overview

Since telbivudine is eliminated primarily by renal excretion (see ACTION AND CLINICAL PHARMACOLOGY: Excretion), co-administration of SEBIVO with substances that affect renal function may affect clinical plasma concentrations of telbivudine and/or the co-administered substance. Drug-drug interaction studies were performed with the coadministration of telbivudine with lamivudine, adefovir dipivoxil, pegylated interferon alfa 2a and cyclosporine A.

Telbivudine and peginterferon alfa -2a:

A clinical trial investigating the combination of telbivudine 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk for developing serious peripheral neuropathy at the rate of 10% (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS). An increased risk cannot be ruled out for combination treatment with other dose regimens of alfa interferons (pegylated or standard). The benefit of the combination of telbivudine with other alfa interferons (pegylated or standard) is not currently established.

There appeared to be no statistically significant effect of a single 180 subcutaneous dose of peginterferon (180 micrograms) on the steady state pharmacokinetics of telbivudine. In the presence of high inter-individual variability, the mean Cmax and AUC 0 to 168 h of peginterferon were increased by approximately 64% and 40% respectively, when co-administered with multiple doses of telbivudine (600 mg) in healthy subjects.

Telbivudine and lamivudine: The steady-state pharmacokinetics of telbivudine and lamivudine were not clinically significantly altered following multiple dose administration of a subtherapeutic dose of telbivudine (200mg) in combination with lamivudine (100mg) in healthy subjects. There is no information at a clinical dose of telbivudine.

Telbivudine and adefovir dipivoxil: The steady - state pharmacokinetics of telbivudine and adefovir dipivoxil appeared to be unaltered following multiple dose administration of telbivudine (600mg) in combination with multiple dose adefovir dipivoxil (10mg) in healthy subjects.

Telbivudine and cyclosporine A: The steady - state pharmacokinetics of telbivudine and cyclosporine A appeared to be unaltered following multiple dose administration of telbivudine in combination with multiple doses of cyclosporine A (4 mg/kg/day given in two divided doses) in healthy subjects. There is no information at higher doses of cyclosporine A.

Telbivudine and tenofovir disoproxil fumarate: The steady - state pharmacokinetics of telbivudine were unaltered following multiple dose administration in combination with tenofovir disoproxil fumarate.

Telbivudine effect on the pharmacokinetics of other drugs**:** Telbivudine does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil, cyclosporine A or tenofovir disoproxil fumarate. 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 (see section on Drug Interaction between Telbivudine and Pegylated interferon - 2a).

The effects of coadministration of SEBIVO with other drugs that are renally eliminated or are known to affect renal function have not been evaluated and patients should be monitored closely for adverse events when SEBIVO is coadministered with such drugs.

At concentrations up to 12 times that used 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 drug metabolism: 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. Telbivudine does not induce cytochrome P450 isoenzymes in animals. Based on the above results and the known elimination pathway of telbivudine, the potential for CYP450-mediated interactions involving SEBIVO with other medicinal products is low.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dose interval adjustment is recommended in patients with moderate to severe renal impairment (creatinine clearance < 50 ml/min) (see Renal impairment below).

Due to higher rates of resistance that may develop with longer term treatment among patients with incomplete viral suppression, treatment should only be initiated after baseline HBV DNA criteria are met. (see INDICATIONS AND CLINICAL USE)

Recommended Dose and Dosage Adjustment

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

Monitoring and duration of treatment

On-treatment response at week 24 has been shown to be predictive of longer term response. HBV DNA levels should be monitored at 24 weeks of treatment to ensure complete viral suppression (HBV DNA less than 300 copies/mL). Treatment modification should be initiated for patients who have detectable HBV DNA after 24 weeks of treatment.

HBV DNA should be monitored every 6 months to ensure continued response. If patients test positive for HBV DNA at any time after their initial response, treatment modification should be instituted. Optimal therapy should be guided by resistance testing.

The optimal treatment duration has not been established.

Renal impairment: (See WARNINGS AND PRECAUTIONS: Special Population and ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Renal Impairment)

SEBIVO may be used for the treatment of chronic hepatitis B in patients with impaired renal function. No adjustment of the recommended dose of telbivudine is necessary in patients whose creatinine clearance is ≥50 mL/min (≥0.835 mL/s). Adjustment of the dose interval is required in

patients with creatinine clearance <50 mL/min (<0.835 mL/s) including those with end stage renal disease (ESRD) on haemodialysis, as shown in Table 5 below:

Table 5: Dose interval adjustment of SEBIVO in patients with renal impairment

Creatinine clearance (mL/min)	Dose of SEBIVO
≥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

* End stage renal disease

End stage renal disease (ESRD) patients

For patients with ESRD, SEBIVO should be administered after haemodialysis (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renally Impaired Patients on haemodialysis). Telbivudine has not been studied in CAPD patients.

Hepatic impairment

No adjustment of the recommended dose of SEBIVO is necessary in patients with hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment).

Pediatric patients (age below 16 years)

No studies have been performed in children under the age of 16 years (see WARNINGS AND PRECAUTIONS).

Elderly patients (age above 65 years)

Available data are insufficient to support a specific dose recommendation for patients over the age of 65 years (see WARNINGS AND PRECAUTIONS).

OVERDOSAGE

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

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

Tested doses of up to 1,800 mg/day for four days (three times greater than the recommended daily dose) have been well tolerated. A maximum tolerated dose of telbivudine has not been determined.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase.

Pharmacodynamics

Telbivudine is efficiently 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} = 0.4-1.3 µM) and second-strand (EC_{50} = 0.12-0.24 µM) synthesis, and shows a distinct preference for inhibiting second-strand production. By contrast, telbivudine-5'-triphosphate at concentrations up to 100 µM did not inhibit human cellular DNA polymerases alpha, beta, or gamma. In assays relating to human mitochondrial structure, function and DNA content, telbivudine lacked an appreciable toxic effect at concentrations up to 10 µM and did not increase lactic acid production *in vitro*.

Pharmacokinetics

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: Following oral administration of a 600 mg single dose of telbivudine to healthy subjects (n = 12), steady state peak plasma concentration (C_{max}) of telbivudine was 3.69 ± 1.25 µg/mL (Mean ± SD) which occurred between 1 and 4 hours (median 2.0 hours). The telbivudine area under the plasma concentration-time curve ($AUC_{0\text{-}INF}$) 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 approximately 1.5-fold accumulation, suggesting an effective half-life of approximately 15 hours. The pharmacokinetics of telbivudine are dose-related in the 25 to 1800 mg dose range.

Effect of food on oral absorption

Telbivudine absorption and exposure were unaffected when a single 600 mg dose was administered with food. SEBIVO 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.

Metabolism: No metabolites of telbivudine were detected following administration of ^{14}C-telbivudine in humans. Telbivudine is not a substrate, inhibitor or inducer of the cytochrome P450 (CYP450) enzyme system (see DRUG INTERACTIONS).

Excretion: After reaching peak concentration, plasma disposition of telbivudine declined in a bi-exponential manner with a terminal elimination half-life ($t_{1/2}$) of 41.8 ± 11.8 hours. Telbivudine is eliminated primarily by urinary excretion of unchanged substance. 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 haemodialysis require a dose interval adjustment (see DOSAGE AND ADMINISTRATION).

Resistance

In Vitro

The activity of telbivudine was assessed in cell-based assays against a number of HBV genomic variants associated with lamivudine and adefovir resistance in HBV-infected patients. The M204V mutant is a key intermediate leading to the emergence of the L180M/M204V lamivudine resistant strain. Telbivudine failed to exhibit antiviral activity against the M204I and L180M / M204V mutants as indicated by the fold changes to wild type of > 1360 + / 262, and demonstrated only marginal activity against the L180M / M204I double mutant (fold change of > 1049 + / 226).

In cell culture, telbivudine showed a 2-fold enhanced activity against HBV containing the N236T mutation and a 3.5-fold shift reduced susceptibility to HBV containing the A181T mutation, which are the most common form of adefovir-resistance mutations seen in HBV-infected patients. HBV encoding an A181V amino acid substitution showed a 4.1- fold reduced susceptibility to telbivudine in cell culture. HBV encoding an A181S amino acid substitution showed a 2.7-fold reduction in susceptibility to telbivudine *in vitro.*

In HIV-1 infected patients, nucleoside analogues such as lamivudine and entecavir can induce YMDD-based (M184V) HIV drug resistant strains. Telbivudine does not demonstrate activity against HIV-1 in cell culture. The presence or absence of telbivudine activity against HIV has not been evaluated in clinical trials.

Clinical Resistance

The safety and efficacy of long term (104 week) telbivudine treatment SEBIVO were evaluated in two established international active-controlled clinical studies that included 1,699 patients with chronic hepatitis B (007 GLOBE and NV-02B-015).

Week 52:

In an as-treated analysis of the Phase 3 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 600mg 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 (≥1000 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. The clinical resistance data indicate negligible selection of YMDD mutant HBV by the M204V pathway. No L180M/M204V double mutant was seen in patients treated with telbivudine in the 007 GLOBE study. No novel or telbivudine-specific resistance mutations were identified.

Genotypic resistance rates

One year data from 007 GLOBE – Intent to treat population

At week 48, 5% (23/458) of HBeAg-positive and 2% (5/222) of HBeAg-negative telbivudine treated patients in 007 GLOBE, had virological breakthrough with confirmed genotypic resistance.

One- and two-year resistance data from 007 GLOBE – Subpopulation considering baseline characteristics and week 24 HBV DNA, and excluding patients with detectable HBV DNA at beginning of year two.

Cumulative genotypic resistance rates were assessed in patients from study 007 GLOBE (n = 680) by baseline factors (HBV DNA < 9 log10 copies/ml and ALT ≥ 2x ULN for HBeAg positive; HBV DNA < 7 log10 copies/ml for HBeAg negative) where only patients with undetectable HBV DNA at week 24 and at the beginning of year two were included. At week 52, resistance rates were 0% for both HBeAg-positive and HBeAg-negative patients; at week 104, the resistance rates were 1.8% for HBeAg-positive and 2.3% for HBeAg-negative patients (Table 6).

Table 6 Resistance rates for overall and subgroups of patients at Week 52 and Week 104 – study 007 GLOBE

	HBeAg-positive			HBeAg-negative		
Cumulative genotypic resistance, %	**Overall (N=458)**	**Baseline HBV DNA <9 log_{10} and ALT≥2xULN (N=80)**	**Baseline HBV DNA <9 log_{10}, ALT≥2xULN and undetectable HBV DNA at Week 24 (N=57)**	**Overall (N=222)**	**Baseline HBV DNA < 7 log_{10} (N=91)**	**Baseline HBV DNA < 7log_{10} and undetectable HBV DNA at Week 24 (N=86)**
Week 52	5.0 % (23 / 458)	0% (0 / 80)	0% (0 / 57)	2.3 % (5 / 222)	0% (0 / 91)	0% (0 / 86)
Week 104	25.1% (115 / 458)	11.3% (9 / 80)	1.8% (1 / 57)	10.8% (24 / 222)	3.3 % (3 / 91)	2.3 % (2 / 86)

Four-year data from CLDT600A2303 - Subpopulation excluding patients with detectable HBV DNA at the beginning of years 2, 3 and 4

Cumulative genotypic resistance rates up to 208 weeks were calculated for study CLDT600A2303, excluding patients with detectable HBV DNA at the beginning of years 2, 3 and 4. The overall cumulative resistance rate at 4 year was 20.0% in the overall population (n = 310); 22.3% in HBeAg-positive and 16.0% in HBeAg-negative patients.

Genotypic mutation pattern

In the 007 GLOBE study, 55.7% (255/458) of treatment-naïve, HBeAg-positive patients and 82.0% (182/222) of treatment-naïve, HBeAg-negative patients receiving telbivudine 600 mg once daily achieved non-detectable serum HBV DNA levels (<300 copies/mL) by week 104 Genotypic analysis of 203 evaluable sample pairs with HBV DNA ≥1000 copies/mL demonstrated that the primary mutation associated with telbivudine resistance was rtM204I often associated with mutations rtL180M and rtL80I/V and infrequently with rtV27A, rtL82M, rtV173L, rtT184I, and rtA200V. Baseline factors associated with development of genotypic drug resistance included: lamivudine treatment, higher baseline HBV DNA, lower baseline serum ALT, and increased body weight/BMI (Body Mass Index). On treatment response parameters at week 24 that predicted emergence of drug resistant virus by week 104 were HBV DNA >300 copies/ml and elevation of serum ALT.

Genotypic analysis from telbivudine-treated patients at week 208 (CLDT600A2303) showed no novel 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. HBV encoding the adefovir resistance-associated substitutions rtN236T remains fully susceptible to telbivudine, with 0.5- fold change in susceptibility to telbivudine in cell culture. *In vitro*, HBV encoding the adefovir resistance-associated substitution rtA181V showed a 4.1-fold reduced susceptibility to telbivudine. The rtA181S and rtA181T substitutions conferred 2.7- and 3.5-fold reductions in susceptibility to telbivudine, respectively. Substitution at rtA194T had 0.99-fold shift in susceptibility to telbivudine in cell culture.

In cell culture testing, telbivudine retains full activity against an M204V single mutant strain that is an intermediate in the lamivudine resistance pathway. However, telbivudine showed reduced activity against recombinant HBV variants containing the YMDD mutations associated with lamivudine resistance (L180M/M204V or M204I). Based on the very similar IC_{50} values for telbivudine and lamivudine against these mutants in in vitro studies, efficacy in patients with established lamivudine resistance is not expected. The use of telbivudine in these patients should therefore only be considered in well controlled clinical trials until availability of further clinical data. Clinical data indicate that telbivudine-resistant HBV strains are likely to carry the M204I mutation which is known to be resistant to lamivudine but remains sensitive to PMEA the active component of adefovir. HBV encoding the adefovir resistance-associated substitutions rtN236T or rtA181 remained susceptible to telbivudine.

Special Populations and Conditions

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

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

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

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 (see DOSAGE AND ADMINISTRATION).

Renal Impairment: The 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 7, adjustment of the dose interval for telbivudine is recommended in patients with creatinine clearance of <50 mL/min (<0.835 mL/s) (see DOSAGE AND ADMINISTRATION).

Table 7: Pharmacokinetic parameters (Mean ± SD) of telbivudine in subjects with various degrees of renal function after a single dose

	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/ Post-Haemodialysis (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
$AUC_{0\text{-}INF}$ (µg•h/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 haemodialysis: Haemodialysis (up to 4 hours) reduces systemic telbivudine exposure by approximately 23%. Following dose interval adjustment for creatinine clearance, no additional dose modification is necessary during routine haemodialysis (see DOSAGE AND ADMINISTRATION). SEBIVO should be administered after haemodialysis.

STORAGE AND STABILITY

SEBIVO film-coated tablets should be stored at a temperature between 15- 30°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SEBIVO (telbivudine) 600 mg film-coated tablets are white to slightly yellowish film-coated, ovaloid-shaped tablets, imprinted with "LDT" on one side. Available in PVC/aluminum blisters. Pack size: 28 film-coated tablets.

Each SEBIVO film-coated tablet contains 600 mg of telbivudine, and the following non-medicinal ingredients (in alphabetical order): colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet coating contains hypromellose, polyethylene glycol, talc and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

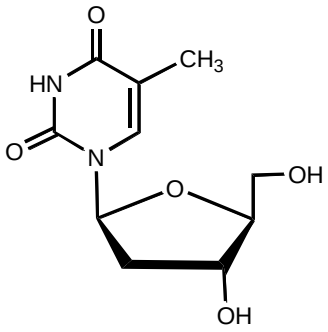
Drug Substance

Proper name: telbivudine

Chemical name: 1-(2-deoxy-β-L-ribofuranosyl)-5-methyluracil

Molecular formula and molecular mass: $C_{10}H_{14}N_2O_5$ (242.23)

Structural formula:



Physicochemical properties:

Telbivudine is the unmodified β-L enantiomer of the naturally occurring nucleoside, thymidine. Telbivudine is a white to slightly yellowish powder with a pKa of 9.61, and a melting point of 189ºC. It is sparingly soluble (1 g/30 mL - 1 g/100 mL) in water, sodium chloride 0.9 % in water and 5% glucose solution.

CLINICAL TRIALS

Study demographics and trial design

The safety and efficacy of SEBIVO® were established in an international active-controlled clinical study of 1,367 patients with chronic hepatitis B and compensated liver disease called the 007 "GLOBE" study. All patients 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 PCR assay), elevated ALT levels ≥ 1.3 times the upper limit of normal (ULN), and chronic inflammation on liver biopsy compatible with chronic viral hepatitis.

Study 007 "GLOBE"

The 007 "GLOBE" study is a Phase 3, randomised, double-blind, multinational study of telbivudine 600 mg once daily compared to lamivudine 100 mg once daily in 1,367 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative patients with compensated liver disease. The primary data analysis was conducted after all patients had reached week 52.HBeAg-positive patients: The mean age of patients was 32 years, 74% were male, 82% were Asian, 12% were Caucasian, and 6% had previously received alpha-interferon therapy. At baseline, patients had a mean Knodell necroinflammatory score ≥7, mean serum HBV DNA as measured by Roche COBAS Amplicor® PCR assay was 9.52 $\log_{10}$ copies/mL and mean serum ALT was approximately 153 IU/litre. Pre- and post-liver biopsy samples were adequate for 86% of patients.

HBeAg-negative patients: The mean age of patients was 43 years, 79% were male, 65% were Asian, 23% were Caucasian, and 11% had previously received alpha-interferon therapy. At baseline, patients had a mean Knodell necroinflammatory score ≥7, mean serum HBV DNA as measured by Roche COBAS Amplicor® PCR assay was 7.54 $\log_{10}$ copies/mL and mean serum ALT was approximately 140 IU/litre. Pre- and post-liver biopsy samples were adequate for 92% of patients.

The week 52 and week 104 results of the 007 GLOBE trial are summarized below.

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 $\log_{10}$ copies per 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 SEBIVO patients and 67% of lamivudine patients had a therapeutic response; in HBeAg-negative patients, 75% of SEBIVO patients and 77% of lamivudine patients had a therapeutic Rresponse.

Patients were eligible to continue blinded treatment to week 104. In the ITT population, 624/680 (92%) SEBIVO recipients and 599/687 (87%) lamivudine recipients completed trial treatment to week 104. At week 104, in HBeAg-positive patients, 63% of SEBIVO patients and 48% of lamivudine patients had a therapeutic response, while in HBeAg-negative patients 78% of SEBIVO patients and 66% of lamivudine patients had a therapeutic response.

Selected virologic, biochemical, and serologic outcome measures at weeks 52 and 104 are shown in Table 8.

Table 8 Virological, Biochemical and Serologic Endpoints at Weeks 52 and 104 (007 GLOBE Trial)

Response Parameter	HBeAg-positive (n=921)				HBeAg-negative (n=446)			
	SEBIVO 600 mg (n=458)		Lamivudine 100 mg (n=463)		SEBIVO 600 mg (n=222)		Lamivudine 100 mg (n=224)	
Time point	**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 per 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 undetectable 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
Therapeutic response	75%	63%	67%	48%	75%	78%	77%	66%

[1] Roche COBAS Amplicor® Assay (LLOQ less than or equal to 300 copies per mL).

[2]ALT 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 minimize resistance at one year.

Telbivudine was superior to lamivudine in HBeAg-positive patients for the key secondary endpoint of histological response, as shown in Table 9. In HBeAg-negative patients, telbivudine was statistically non-inferior to lamivudine for histological response.

Table 9: Histological improvement and change in Ishak fibrosis score at week 52 (007 GLOBE study)

	HBeAg-positive (n = 921)		HBeAg-negative (n = 446)	
	Telbivudine 600 mg (n = 384)[1]	**Lamivudine 100 mg (n = 386)[1]**	**Telbivudine 600 mg (n = 199)[1]**	**Lamivudine 100 mg (n = 207)[1]**
Histological response[2]				
Improvement	71%*	61%	71%	70%
No Improvement	17%	24%	21%	24%
Ishak fibrosis score[3]				
Improvement	42%	47%	49%	45%
No change	39%	32%	34%	43%
Worsening	8%	7%	9%	5%
Missing week 52 biopsy	12%	15%	9%	7%

[1] Patients with ≥ one dose of study drug with evaluable baseline liver biopsies and baseline Knodell histological activity index (HAI) score >3

[2] Histological 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

*p = 0.0024

Predictability analysis

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

Prespecified analyses were performed to assess relationships between early antiviral responses and efficacy. Patients were categorized at week 24 according to PCR analysis. HBeAg-positive patients who achieved the lowest viral load at week 24 (below the level of quantitation of the assay, <300 copies/mL) had the highest rates of therapeutic response (94% and 85%), PCR-negativity (95% and 82%), and HBeAg seroconversion (39% and 46%), and the lowest rates of Virologic Breakthrough (2% and 11%) after both one and two years of treatment, respectively.

007 GLOBE – Subpopulation considering baseline characteristics and week 24 HBV DNA, and excluding patients with detectable HBV DNA at beginning of year 2

Efficacy was assessed in patients from study 007 GLOBE (n = 680) by baseline factors (HBV DNA < 9 $\log_{10}$ copies/ml and ALT ≥ 2x ULN for HBeAg positive; HBV DNA < 7 $\log_{10}$ copies/ml for HBeAg negative) where only patients with undetectable HBV DNA at week 24 and at the beginning of year 2 were included. At week 52, undetectable serum HBV DNA rates

were 96.5% or 97.7% for HBeAg-positive and HBeAg-negative patients; at week 104, were 90.9% for HBeAg-positive and 92.9% for HBeAg-negative patients (Table10).

Table 10: Efficacy responses at weeks 52 and 104 by baseline factors and on-treatment response at week 24 (007 GLOBE)

	HBeAg-positive[1]	**HBeAg-negative[2]**
Year 1/week 52	n = 57	N = 86
Undetectable serum HBV DNA	96.5%	97.7%
HBeAg seroconversion	39.6%	-
Year 2/week 104[3]	n = 55	n = 84
Undetectable serum HBV DNA	90.9%	92.9%
HBeAg seroconversion	53.2%	-

[1] HBeAg-positive patients with baseline HBV DNA < 9 $\log_{10}$ copies/ml, baseline ALT ≥ 2xULN, and undetectable HBV DNA at treatment week 24.
[2] HBeAg-negative patients with baseline HBV DNA < 7 $\log_{10}$ copies/ml and undetectable HBV DNA at week 24.
[3] Includes patients with undetectable HBV DNA at the beginning of year 2.

Study NV-02B-015

NV-02B-015 is a Phase III, randomized, double-blind, study of telbivudine 600 mg once daily compared to lamivudine 100 mg once daily for a treatment period of 104 weeks in 332 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative Chinese patients with compensated liver disease. The primary efficacy endpoint was serum HBV DNA reduction at Week 52, defined as the reduction (in $\log_{10}$ copies/mL) in serum HBV DNA levels from baseline values. Therapeutic response was a key secondary endpoint.

Study NV-02B-015 - Outcomes at Week 52 and Week 104

Selected virological, biochemical and serological outcome measures are shown in Table 11. Efficacy results from study NV-02B-015 are consistent with the 007 GLOBE study results at week 52 and week 104 respectively.

Table 11 Virological, Biochemical and Serologic Endpoints and Therapeutic Response at weeks 52 and 104 (NV-02B-015)

Response Parameter	HBeAg-positive (n=147)				HBeAg-negative (n=42)			
	Telbivudine 600 mg (n=147)		Lamivudine 100 mg (n=142)		Telbivudine 600 mg (n=20)		Lamivudine 100 mg (n=22)	
Time point	**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 per mL) ± SEM[1]	-6.33 (0.18)	-5.47* (0.26)	-5.49 (0.18)	-3.97 (0.27)	-5.49 (0.40)	-5.59 (0.51)	-4.81 (0.38)	-4.20 (0.49)
% Subjects HBV DNA undetectable by PCR	67%*	58%*	38%	34%	85%	90%	77%	68%
ALT normalization[2]	87%	73%	75%	59%	100%	95%	78%	78%
HBeAg seroconversion[3]	25%	29%	18%	20%	NA	NA	NA	NA
HBeAg loss[3]	31%	40%	20%	28%	NA	NA	NA	NA
Therapeutic response	85%*	66%*	62%	41%	100%	90%	82%	68%

[1] Roche COBAS Amplicor® Assay (LLOQ less than or equal to 300 copies per mL).

[2] n=142/18 and 135/18, for telbivudine and lamivudine treated HBeAg positive / negative groups, respectively. ALT normalization assessed only in subjects with ALT > ULN at baseline.

[3] n = 138 for both telbivudine and lamivudine groups. HBeAg seroconversion and loss assessed only in subjects with detectable HBeAg at baseline.

* $p \leq 0.0001$

Study CLDT600A2303 - Clinical results up to week 208

Study CLDT600A2303 is an open-label 104-week extension study of up to 208 -weeks of continuous telbivudine treatment in chronic hepatitis B patients with compensated liver disease who were previously treated in studies 007 GLOBE and NV-02B-015. A subset of 502 patients (293 HBeAg-positive and 209 HBeAg-negative, excluding those with virological breakthrough and confirmed genotypic resistance at entry into study CLDT600A2303) were analyzed. At week 208, the majority of patients (76% for HBeAg-positive and 86% for HBeAg-negative patients) maintained undetectable HBV DNA levels (< 300 copies/ml) and normalized ALT (86% for HBeAg-positive and 90% for HBeAg-negative patients). HBeAg-positive patients with undetectable HBV DNA at week 24 had better outcomes at 208 weeks ((88% of patients with undetectable HBV DNA at Week 24 maintained undetectable HBV DNA at Week 208).

The cumulative HBeAg seroconversion rate increased with the duration of treatment: 27.6% at week 52, 41.6% at week 104, 48.5% at week 156 and 53.2% at week 208. Higher rates of seroconversion were observed in HBeAg-positive patients who achieved undetectable HBV DNA at week 24 (40.1% at week 52, 52.5% at week 108, 59.3% at week 156 and 65.4% at week 208)

Study CLDT600ACN04E1- Impact of treatment on Liver histology

In study CLDT600ACN04E1, 57 chronic hepatitis B patients (38 HBeAg-positive and 19 HBeAg-negative) compensated liver disease and with with paired liver biopsies at baseline and after 3-5 years of telbivudine treatment were evaluated for changes in liver histology. The Knodell necroinflammation and Ishak fibrosis scores showed a statistical significant improvement versus baseline (Table 12). After treatment 98.2% of patients had no or minimal liver necroinflammation (Knodell necroinflammatory score ≤ 3), and 84.2% of patients had no or minimal liver fibrosis (Ishak fibrosis score ≤ 1). Changes in Knodell necroinflammatory and Ishak scores were similar for HBeAg-positive and HBeAg-negative patients.

Table 12 Histological improvement in patients after 3-5 years of telbivudine treatment

N=57	Baseline Mean(SD)	Post treatment Mean (SD)	Reduction from Baseline to post treatment Mean(SD)	P
Knodell necroinflammatory score	7.6 (2.9)	1.4 (0.9)	6.3 (2.8)	< 0.0001
Ishak fibrosis score	2.2 (1.1)	0.9 (1.0)	1.3 (1.3)	< 0.0001

Study NV-02B-018

NV-02B-018 is a Phase IIIb, randomized, open-label, multi-center study of treatment with telbivudine 600 mg once daily compared to adefovir dipivoxil 10 mg once daily for a treatment period of 52 weeks in 135 adult subjects with chronic hepatitis B HBeAg-positive patients with compensated chronic liver disease. The primary endpoint was serum HBV DNA reduction from baseline at Week 24 with a secondary comparison at Week 52.

In study NV-02B-018, the mean age of subjects was 32 years, 76% were male, 92% were Asian, 4% were Caucasian, and 1% had previously received alfa-interferon therapy. At baseline, 95 % of subjects were diagnosed with Chronic hepatitis B ≥ 9 years ago, mean serum HBV DNA as measured by Roche COBAS Amplicor® PCR assay was 9.67 $\log_{10}$ copies/mL, and mean serum ALT was 173 IU/L.

At Week 24, the mean reduction of serum HBV DNA from baseline was -6.29 vs -4.92 $\log_{10}$ copies/mL for telbivudine (n= 45) and adefovir dipivoxil (n=90), respectively.

DETAILED PHARMACOLOGY

See **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics.**

Effect of food on oral absorption

Telbivudine absorption and exposure were unaffected when a single 600 mg dose was administered with food (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). Studies conducted using the clinical study formulation demonstrated no food effect on the pharmacokinetics of telbivudine. No food effect studies were conducted using the commercial formulation of telbivudine. The clinical and the commercial formulations are equivalent (i.e., same rate and extent of absorption) under fasted conditions).

MICROBIOLOGY

Mechanism of Action

Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase.

Antiviral Activity

The *in vitro* antiviral activity of telbivudine was assessed in HBV-expressing human hepatoma cell line 2.2.15, as well as in primary duck hepatocytes infected with duck hepatitis B virus (DHBV). The concentration of telbivudine that effectively inhibited 50% of viral synthesis (EC_{50}) in both systems was approximately 0.2 μM. The antiviral activity of telbivudine is specific to hepatitis B virus and related hepadnaviruses. No activity was noted against multiple other RNA and DNA viruses including human immunodeficiency virus (HIV) type 1 (EC_{50} value

>200 µM). The absence of activity of telbivudine against HIV has not been evaluated in clinical trials.

In 4- and 12-week studies of hepadnavirus-infected woodchucks, a relevant animal model for HBV, telbivudine significantly reduced viral DNA levels. Within 28 days, at oral doses of 10 mg/kg/day, serum viral DNA levels decreased by as much as 8 $\log_{10}$ to undetectable levels (<300 copies/mL by PCR). Following drug withdrawal, viral rebound occurred within four weeks. When telbivudine was given orally to woodchucks at lower doses (1 mg/kg/day) for 12 weeks, viral load reductions of at least 6 $\log_{10}$ were seen in all telbivudine-treated animals.

Resistance and Cross-Resistance
See ACTION AND CLINICAL PHARMACOLOGY.

TOXICOLOGY

Acute Toxicity

Single dose toxicity studies in the Sprague-Dawley rat and the cynomolgus monkey confirmed no toxicity at oral (gavage) doses up to 2000 mg/kg.

Repeat-dose Toxicity

Preclinical toxicity studies produced a variety of findings (see Table 13: Sub-Chronic and Chronic Toxicology). Chronic oral dosing up to 1000 mg/kg/day in rats and monkeys demonstrated no adverse effects at significant multiples of human exposure (6- to 8-fold).

Carcinogenicity

Telbivudine has shown no carcinogenic potential (See Table 14: Genetic Toxicology and Carcinogenicity). Long-term oral carcinogenicity studies with telbivudine were negative in mice and rats at exposures up to 14-times higher than observed in humans at a therapeutic dose of 600 mg/day.

Genotoxicity

There was no evidence of genotoxicity based on *in vitro* or *in vivo* tests (See Table 14: Genetic Toxicology and Carcinogenicity). 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 a transformation assay with Chinese hamster ovary cells with or without metabolic activation. Furthermore, telbivudine was negative in an *in vivo* micronucleus study in mice.

Reproductive toxicity

In reproductive toxicology studies, no evidence of impaired fertility was seen when either male or female rats were treated with telbivudine at doses up to 2000 mg/kg/day (systemic exposures approximately 14-times those observed in humans at the therapeutic dose) and mated with untreated rats (see TOXICOLOGY: Reproductive Toxicology).

A separate study indicated reduced fertility when both male and female rats were treated with telbivudine doses of 500 or 1000 mg/kg/day. A lower fertility index was noted in pairs given 500 (76%) or 1000 (72%) mg/kg/day when compared to concurrent controls (92%). There were no abnormalities in sperm morphology or function, and the testes and ovaries were histologically unremarkable.

Fertility was assessed as part of a juvenile toxicology study in which rats treated from day 14 to day 70 were mated with rats from other litters receiving the same treatment. The mean number of days to mating was slightly higher at 1000 and 2000 mg/kg/day. The fertility indices were reduced at 1000 mg/kg (40%) and 2000 mg/kg/day (50%) compared to the 80% value in the control group. In this study, the mating index and conception rate were slightly reduced, however the ovarian and uterine parameters of those females mating successfully were unaffected by administration of telbivudine. There was no effect on fertility or mating parameters at 250 mg/kg/day where the exposure was 2.5 to 2.8 times higher than exposure achieved in humans at the therapeutic dose.

No evidence of embryo or fetal toxicity due to telbivudine was seen in standard tests of reproductive toxicology. In rabbits doses of telbivudine providing exposure levels of 37 times those observed in humans at the therapeutic dose (600mg) were associated with an increased incidence of abortion and early delivery. These events were accompanied by other signs of telbivudine toxicity including reduced feed consumption and gastrointestinal effects and were considered to be secondary to maternal toxicity. (see Table 15: Reproductive Toxicology).

Table 13: Sub-Chronic and Chronic Toxicology

Study Type	Species	Route	Doses [Mg/kg/day)	Findings
4-week	CB6F1 mice	PO	0, 500, 1000, 2000	No drug-related clinical signs or mortalities. Increases in certain white and red blood cell parameters in mice given 2000 mg/kg of telbivudine were considered possibly but not conclusively related to telbivudine exposure. NOAEL: 2000 mg/kg/day
13-week	CD-1 mice	PO	0, 500, 1000, 3000	No evidence for systemic toxicity from telbivudine at any dose studied. Mean body weights were occasionally higher in all three female dose groups and the top two male treatment groups, but there was no statistical correlate in body weight or food consumption. The mean absolute liver weight for the 1000 mg/kg dose group females was higher than in controls, but mean weights relative to body or brain weight were not different from controls. NOEL: 3000 mg/kg/day
28-day	SD rat	PO	0, 500, 1000, 2000	A decrease in neutrophil count occurred in males given 2000 mg/kg/day, but the relevance of this finding for telbivudine is unclear. Increased food consumption in males given 1000 and 2000 mg/kg/day was observed but not judged to represent toxic effects. NOAEL: 2000 mg/kg/day.
3/6-month	SD rat	PO	0, 250, 500, 1000	There were no clinical signs or adverse effect on body weight or food consumption attributed to telbivudine administration. In addition, no telbivudine-related macroscopic or microscopic morphologic changes were noted and therefore the NOEL was 1000 mg/kg/day after 3- or 6-months of treatment. NOEL: 1000 mg/kg/day
14-day	SD rat	i.v.	0, 5, 15, 45	15 mg/kg: mild decrease in white blood cell count, lymphocyte counts (females) 45 mg/kg: mild decrease in white blood cell count, lymphocyte counts [Males); equivocal histological changes in pancreas (apoptosis, inflammation, atrophy); kidney (tubular dilation, interstitial nephritis, pyelonephritis); cystitis; ureteritis; heart inflammatory focus NOAEL: 15 mg/kg/day
28-day	Cynomolgus monkey	PO	0, 500, 1000, 2000	Emesis was noted in 8 monkeys at 16 instances, mostly in telbivudine-treated monkeys. There was a high incidence of soft feces across all dose groups including controls and was more pronounced in the 2000 mg/kg/day dose group. NOAEL: 2000 mg/kg/day

Study Type	Species	Route	Doses [Mg/kg/day)	Findings
3/9-month	Cynomolgus monkey	PO	0, 250, 500, 1000	Soft stools and emesis were observed in a dose-related manner in females treated with telbivudine compared to controls, however, similar findings in males failed to indicate a role for telbivudine, as controls were equally affected. Axonopathy in all groups including controls noted in both spinal cord and sciatic nerve sections. The sciatic nerve findings had a higher incidence in 1000 mg/kg/day group females (3 out of 4) compared to the control group (2 out of 4), but there was no clear difference between the males in all dose groups. In the spinal cord, axonopathic changes were most frequent in 1000 mg/kg/day dose group males with no evidence of a test-article effect in females. Such distribution of nerve and cord lesions is not typical for treatment-related effects. These findings were considered equivocal and the role of telbivudine in the pathogenesis of the axonal injury noted in these tissues could not be determined. NOAEL: 1000 mg/kg/day
1 & 5 day [MTD)	Cynomolgus monkey	IV	2, 10, 40	No evidence for systemic toxicity from telbivudine at any dose studied. No telbivudine-related deaths or clinical signs were observed. NOAEL: 40 mg/kg/day
14-day	Cynomolgus monkey	IV	0, 2, 10, 40	No evidence for systemic toxicity from telbivudine at any dose studied. No telbivudine-related deaths or clinical signs were observed. NOEL: 40 mg/kg/day

Table 14: Genetic Toxicology and Carcinogenicity

Study Type	Species	Route	Doses	Findings
Ames test	Salmonella typhimurium strains TA98, TA100, TA1535, TA1537. E. coli strain WP2uvrA	*In vitro*	0, 5 to 5000 µg/plate (in the presence and absence of S9)	The plate incorporation mutation (Ames) assay was negative in all five bacterial strains tested, when compared with control, at doses up to 5000 micrograms per plate. Therefore, telbivudine was considered to be non-mutagenic under the conditions of this assay.
Chromosome aberration assay	Chinese Hamster Ovary cells	*In vitro*	0, 1 to 5000 µg/mL (in the presence and absence of S9)	Telbivudine did not increase chromosomal aberrations assay any of the concentrations tested, compared with controls, in the presence or absence of S9. Therefore, telbivudine was non-clastogenic under the conditions of this assay.
Chromosome aberration assay	Human peripheral blood lymphocytes	*In vitro*	0, 5 to 2422 µg/mL (in the presence and absence of S9)	Telbivudine was negative in chromosomal aberration assay at all concentrations tested and was considered non-clastogenic in cultured human lymphocytes. All study criteria were met for a valid assay.
Micronucleus test	CD-1 mice	PO	500, 1000, and 2000 mg/kg, vehicle control and positive control (cyclophosphamide)	There was no evidence of chromosome damage in the mouse micronucleus test after a single oral dose of up to 2000 mg/kg of telbivudine, when compared with controls. All study criteria were met for a valid assay. Telbivudine was not clastogenic in this assay.
Rat carcinogenicity study (2 yr)	SD rats	PO	0, 500, 1000, and 2000 mg/kg/day	Study dosing ended at wk 85 in 2000 mg/kg/day group due to excessive mortality rate; study terminated after wk 95 (m) or 96 (f), also due to excessive mortality. Mortality due largely to spontaneous rat chronic progressive nephropathy. Telbivudine was not carcinogenic in rats, even at a dose of 2000 mg/kg/day which exceeded the MTD (1000 mg/kg/day).

Study Type	Species	Route	Doses	Findings
Transgenic mouse carcinogenicity study (6 mo)	CB6F1-TgrasH2 mice	PO	0, 500, 1000, 2000 mg/kg/.day; positive control N-methyl-N-Nitrosourea (MNU), at 75 mg/kg once intraperitoneally on study day 1	Telbivudine was not carcinogenic in CB6F1-TgrasH2 mice. Tumors were observed in the control group, confirming the model.

Table 15: Reproductive Toxicology

Study Type	Species	Route	Doses [Mg/kg/day)	Findings
Fertility, reproduction and embryo-fetal development	SD rat	PO	0, 100, 500, 1000	There was no significant maternal toxicity or treatment-related effects on embryo-fetal development or other litter parameters. Therefore, the NOAEL for embryo-fetal development and maternal toxicity was 1000 mg/kg/day, the highest dose tested. The only possible treatment-related reproductive finding was lower mean fertility rates at 500 and 1000 mg/kg/day when given to both male and female rats prior to and during mating. Potential telbivudine-related effects on rat fertility were investigated in two subsequent studies (below).
Fertility of Males	SD rat	PO	0, 1000, 2000 [Males treated)	There were no adverse telbivudine-related effects on mating, fertility or litter parameters in rats. Therefore, the no-observed effect level for reproductive performance and fertility was 2000 mg/kg/day in male rats. At a dose of 2000 mg/kg/day, male rats had increased food consumption before cohabitation, when compared with controls. The NOAEL for paternal toxicity was 2000 mg/kg/day.
Fertility of Females	SD rat	PO	0, 2000 (females treated)	There were no adverse drug-related effects on mating, fertility or litter parameters in rats. Therefore, the NOAEL for reproductive toxicity was 2000 mg/kg/day in female rats. At a dose of 2000 mg/kg/day, female rats had increased food consumption and body weights before cohabitation, when compared with controls. The NOAEL for maternal toxicity was 2000 mg/kg/day.

Study Type	Species	Route	Doses [Mg/kg/day)	Findings
Peri-postnatal development, reproduction and fertility	SD rat	PO	100, 250, and 1000 and vehicle control (time-mated F0 dams were treated during gestation and lactation).	Telbivudine administration was not associated with mortality, clinical observations or trouble maintaining pregnancy (F0). Maternal administration of telbivudine had no effect on growth, development, learning, memory or reproductive performance of offspring (F1) at doses as high as 1000 mg/kg/day. The reproductive NOEL for the dams and the viability and growth of offspring (F1) was 1000 mg/kg/day, the highest dose tested. There were no reproductive effects, maternal toxicity, or behavioral changes in any F1 offspring that were exposed to telbivudine in utero and during nursing from a dam that received up to 1000 mg/kg/day of telbivudine. In addition, there were no gross fetal observations in 2nd generation fetuses from F0 dams treated with telbivudine. The maternal and fetal NOEL was 1000 mg/kg over both generations.
Embryo-fetal development	HRa (NZW) SPF Rabbits	PO	50, 250, and 1000 and vehicle control	Maternal toxicity, as indicated by abnormal feces and decreased food consumption, was observed at the highest dose tested. The NOAEL was 250 mg/kg/day, due to lower body weight gains. A slight increase in the number of abortions and early litter deliveries at 1000 mg/kg/day was attributed to material toxicity. Administration of telbivudine did not cause any gross, soft tissue or skeletal alterations at any dose level,. The developmental NOAEL is 1000 mg/kg/day in rabbits, the highest dose tested.

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[*] *references available upon request*

PART III: CONSUMER INFORMATION

Pr SEBIVO®
telbivudine

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

Please read all of this leaflet carefully before you start taking this medicine. Keep this leaflet. You may need to read it again. If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:

- SEBIVO is a prescription medicine used for chronic infection with hepatitis B virus (HBV) in adults of 16 years and older, who also have active liver inflammation. SEBIVO has not been studied in children and is not recommended for anyone less than 16 years old.

What it does:
SEBIVO belongs to a group of medicines called antiviral medicines, which are used to treat infection with viruses.

Hepatitis B is caused by infection with the hepatitis B virus (HBV), which multiplies in the liver and causes liver damage.

SEBIVO may lower the amount of HBV in the body

SEBIVO may lower the ability of HBV to multiply and infect new liver cells

SEBIVO may reduce the damage to the liver by HBV

SEBIVO will not cure HBV infection

It is important to stay under your healthcare provider's care while taking SEBIVO. Your healthcare provider will test the level of the hepatitis B virus in your blood regularly.

When it should not be used:
Do not take SEBIVO if you are allergic (hypersensitive) to telbivudine or any of the other ingredients of SEBIVO (see "What the important nonmedicinal ingredients are" for a complete list of ingredients in SEBIVO).

Tell your healthcare provider if you think you have had an allergic reaction to any of these ingredients. If you think you may be allergic, ask your doctor for advice.

Do not take SEBIVO if you are being treated with pegylated interferon alfa-2a (see "BEFORE you use SEBIVO" and "INTERACTIONS WITH THIS MEDICATION")

What the medicinal ingredient is:
telbivudine

What the important nonmedicinal ingredients are:
SEBIVO contains the following nonmedicinal ingredients (in alphabetical order): colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet coating contains hypromellose, polyethylene glycol, talc and titanium dioxide.

What dosage form it comes in:
SEBIVO is available in 600 mg film-coated tablets.
These are white to slightly yellowish, ovaloid-shaped, film-coated tablets with "LDT" imprinted on one side.

Does SEBIVO lower the risk of passing HBV to others?
SEBIVO does not stop you from spreading HBV to others by sex, sharing needles, or being exposed to your blood. Talk to your healthcare provider about safe sexual practices that protect your partner. Never share needles. Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades. A shot (vaccine) is available to protect people at risk from becoming infected with HBV.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Severe worsening of hepatitis (liver inflammation) has occurred in patients who have stopped taking anti-hepatitis B therapy. Your doctor will monitor your condition in this case and may resume therapy.
- Lactic acidosis (increase in lactic acid level in blood) which may or may not be associated with severe hepatomegaly with steatosis (enlarged fatty liver), including fatal cases have been reported in patients using SEBIVO, either alone or in combination. Lactic acidosis is a medical emergency and must be treated in the hospital. Call your healthcare provider right away if you get any of the signs of lactic acidosis (see below)

1. Some people who have taken medicines like SEBIVO (a nucleoside analogue) have developed a serious condition called lactic acidosis (build up of an acid in the blood). Lactic acidosis is a medical emergency and must be treated in the hospital. Call your healthcare provider right away if you get any of the following signs of lactic acidosis:

- you feel very weak or tired
- you have unusual muscle pain
- you have trouble breathing
- you have stomach pain with nausea and vomiting
- you feel cold, especially in your arms and legs
- you feel dizzy or light-headed

- you have a fast or irregular heartbeat
- you have abdominal swelling or discomfort

2. Some people who have taken medicines like SEBIVO have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Call your healthcare provider right away if you get any of the following signs of liver problems:
- your skin or the white of your eyes turn yellow (jaundice)
- your urine turns dark
- your bowel movements (stools) turn light in colour
- you don't feel like eating food for several days or longer
- you feel sick to your stomach (nausea)
- you have lower stomach pain

3. Your hepatitis B infection may get worse or become very serious if you stop SEBIVO
- take SEBIVO exactly as prescribed
- do not run out of SEBIVO
- do not stop SEBIVO without talking to your healthcare provider

4. Like other medication in this drug class, SEBIVO may cause some people to experience generalized muscle pain, muscle weakness or muscle tenderness as a side effect. Rarely this may lead to a serious muscle problem including muscle breakdown (rhabdomyolysis) which can result in kidney damage. Tell your doctor right away if you get any of the following signs of muscle effects from SEBIVO:
- muscle pain
- muscle weakness
- muscle tenderness

Your healthcare provider will need to monitor your health and do regular blood tests to check your liver if you stop SEBIVO. Tell your healthcare provider right away about any new or unusual symptoms that you notice after you stop taking SEBIVO.

BEFORE you use SEBIVO talk to your healthcare provider if:

- you are treated with any type of alpha interferons **or** if you are treated with pegylated interferon alfa-2a (see also "When it should not be used" and "Interactions With This Medication").

- you have any kidney problems. Your doctor may change the way you take SEBIVO.
- You are taking any other medicines. Your doctor is concerned with those that affect the kidney.
- you have had a liver transplant.
- you are pregnant or planning to become pregnant. Your doctor will advise you whether you should take SEBIVO while you are pregnant. If you take SEBIVO while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry. Do not stop treatment with SEBIVO without your doctor's advice.
- You are breast-feeding or planning to breast-feed. It is not known if SEBIVO can pass into your breast milk or if it can harm your baby. You should not breast-feed during treatment with SEBIVO.

Be sure to also tell your doctor if you are infected with HIV, hepatitis C or D, or have been treated with any antiviral medicines.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, herbal and vitamin supplements.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist.

INTERACTIONS WITH THIS MEDICATION

SEBIVO is eliminated primarily by the kidney. Co-administration of SEBIVO with medicine that affects kidney function may affect blood levels of SEBIVO and/or the co-administered medicine.

Do not take SEBIVO if you are being treated with pegylated interferon alfa-2a. This combination may increase your risk of developing peripheral neuropathy (numbness, tingling, and/or burning sensations in the arms and/or legs). Tell your doctor or pharmacist if you are being treated with other types of alfa interferon for chronic hepatitis B or C (see also "ABOUT THIS MEDICATION" and "BEFORE you use SEBIVO").

PROPER USE OF THIS MEDICATION

SEBIVO should only be started in patients with certain hepatitis B virus levels because of the risk of developing resistance. Your healthcare professional will need to do blood tests to determine this.

Take SEBIVO exactly as prescribed. Your healthcare provider will tell you how frequent and how much SEBIVO to take. You should check with your healthcare provider if you are not sure. You can take SEBIVO with or without food.

Usual adult dose (16 years and over):

The usual dose is one 600 mg tablet once a day, at about the same time each day.

The tablet may be taken with or without food. Swallow the tablet whole with some water. Do not chew, split or crush the tablet.

Your doctor may prescribe a different dosing schedule if you have kidney problems. Tell your doctor if you have, or ever have had, any kidney problems.

Do not change your dose or the way you take SEBIVO, or stop taking SEBIVO without talking to your healthcare provider. Your hepatitis B symptoms may get worse or become serious if you stop taking SEBIVO. Once it has been decided with your healthcare provider to stop taking SEBIVO,

it is important to stay under your healthcare provider's care. Your healthcare provider will need to do regular blood tests to check your liver.

When your supply of SEBIVO starts to run low, get more from your healthcare provider or pharmacy. Do not run out of SEBIVO.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take SEBIVO, take it as soon as you remember and then take your next dose at its regular time. However, if it is almost time for your next dose, skip the dose you missed and take the next one at the usual time.

Do not take a double dose to make up for a forgotten tablet. This may increase the chance of you getting an unwanted side effect. Ask your doctor or pharmacist if you are not sure what to do.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

The most common side effects of SEBIVO are tiredness, headache, nausea, dizziness, diarrhea, and rash. A very common lab abnormality is the increase in a blood marker which may be produced by the muscle.

SEBIVO may cause the following serious side effects (see WARNINGS and PRECAUTIONS)

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency/Symptom /Effect	Talk with your doctor or pharmacist immediately		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency/Symptom /Effect		Talk with your doctor or pharmacist immediately		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	**Effect:** Lactic acidosis **Symptoms:** Difficulty breathing		✓	
	Tiredness		✓	
	Drowsiness		✓	
	Unusual muscle pain		✓	
	Headache/ Dizziness		✓	
	Stomach pain with nausea and vomiting		✓	
	Fast/irregular heartbeat		✓	
Very rare	**Effect:** Flare-ups of hepatitis B virus infection following treatment discontinuation **Symptoms:** Skin/white of eyes turn yellow		✓	
	Stool turn light in colour		✓	
	Dark urine		✓	
	Loss of appetite for several days or longer		✓	
	Nausea		✓	
	Lower stomach pain		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency/Symptom /Effect		Talk with your doctor or pharmacist immediately		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Unknown (post-marketing experience)	**Effect:** Muscle breakdown (rhabdomyolysis) **Symptoms:** Muscle pain Muscle weakness Muscle tenderness		 ✓ ✓ ✓	

These are not all the side effects of SEBIVO. The list of side effects is not complete at this time because SEBIVO is still under study. Report any new or continuing symptoms to your healthcare provider. If you have any questions about side effects, ask your health care provider. Your healthcare provider may be able to help you manage these side effects.

HOW TO STORE IT

Store SEBIVO film-coated tablets at room temperature (15-30ºC).

As with all medicines, keep SEBIVO out of the reach and sight of children.

Do not use SEBIVO after the expiry date shown on the carton.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Post Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the product monograph, prepared for health professionals can be found at: www.novartis.ca or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at: 1-800-363-8883

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