NOVARTIS

Sebivo™

Antiviral for systemic use

DESCRIPTION AND COMPOSITION

Pharmaceutical form

White to slightly yellowish, ovaloid, slightly curved film-coated tablet with beveled edges; imprinted (debossed) with "LDT" on one side; in a blister pack of 28 tablets.

Active substance

Telbivudine
Each film-coated tablet contains 600 mg telbivudine.

Excipients

Tablet core: cellulose microcrystalline; povidone; sodium starch glycolate; magnesium stearate; silica, colloidal anhydrous.
Tablet film coat: titanium dioxide (E171); macrogol; talc; hypromellose.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Sebivo is indicated for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in patients who have compensated liver disease, evidence of viral replication and active liver inflammation and who are nucleoside analogue naïve.

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 $\geq$ 2x ULN.
- For HBeAg-negative patients, Sebivo treatment should only be initiated in patients with baseline HBV DNA $< 7 \log_{10}$ copies/mL.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

Adults

The recommended dose of Sebivo is 600 mg once daily.

Due to risk of 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 section INDICATIONS).

Monitoring and duration of treatment

On-treatment response at week 24 has been shown to be predictive of longer-term response (see section CLINICAL STUDIES). HBV DNA levels should be monitored at 24 weeks of treatment to ensure complete viral suppression (HBV DNA less than 300 copies/mL). For patients with detectable HBV DNA after 24 weeks of therapy, treatment modifications should be considered.

HBV DNA should be monitored every 6 months to ensure continued response. If patients are tested positive for HBV DNA at any time after their initial response, treatment modification should be considered. Optimal therapy should be guided by resistance testing.
The optimal treatment duration has not been established.

Special populations

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. Dose adjustment is required in patients with creatinine clearance <50 mL/min including those with end stage renal disease (ESRD) on hemodialysis. Dose adjustment may be achieved by changing the interval of the tablet dose, as shown below in Table 1.

Table 1 Dose adjustment of Sebivo in patients with renal impairment

Creatinine clearance (mL/min)	Tablet Dose (1 tablet = 600 mg)
≥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

ESRD patients

For patients with ESRD, Sebivo should be administered after hemodialysis (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

No adjustment of the recommended dose of Sebivo is necessary in patients with hepatic impairment (see section CLINICAL PHARMACOLOGY).

Pediatric patients (below 16 years)

No studies have been performed in children under the age of 16 years. Therefore, until more information is available, Sebivo is not recommended for use in children.

Geriatrics (65 years age and above)

No data are available to support a specific dose recommendation for patients over the age of 65 years (see section WARNINGS AND PRECAUTIONS).

Method of administration

Sebivo is to be taken orally, with or without food.

CONTRAINDICATIONS

Telbivudine tablets are contraindicated in patients with previous demonstrated hypersensitivity to the active substance or to any of the excipients.

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

WARNINGS AND PRECAUTIONS

Exacerbations of Hepatitis

Severe acute exacerbations of chronic hepatitis B are relatively frequent, and are characterized by transient elevation of serum ALT. Following initiation of antiviral treatment, serum ALT may rise in some patients while serum levels of HBV DNA fall. On average, 4-5 weeks elapsed prior to the occurrence of an exacerbation in patients treated with telbivudine. Overall, ALT flares occurred more frequently in HBeAg-positive patients than in HBeAg-negative patients. In patients with compensated liver disease, this elevation of serum ALT is generally not accompanied by elevated levels of serum bilirubin or by other signs of hepatic decompensation. The risk of hepatic decompensation – and of a subsequent exacerbation of hepatitis – may be elevated in patients with cirrhosis. Such patients should therefore be closely monitored.

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, resumption of anti-hepatitis B therapy may be warranted.

Lactic acidosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside/nucleotide analogues alone or in combination with antiretrovirals. Treatment with nucleoside analogues should be discontinued when rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology occur. Benign digestive symptoms, such as nausea, vomiting and abdominal pain, may be indicative of lactic acidosis development. Severe cases, sometimes with fatal outcome, were associated with pancreatitis, liver failure/hepatic steatosis, renal failure and higher levels of serum lactate. Caution should be exercised when prescribing nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease. These patients should be followed closely.

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.

Skeletal muscle

Cases of myopathy have been reported with telbivudine use several weeks to months after starting therapy. Myopathy has also been reported with some other drugs in this class. Isolated cases of rhabdomyolysis have been reported during post-marketing use of telbivudine (see section ADVERSE DRUG REACTIONS).

Uncomplicated myalgia has been reported in telbivudine-treated patients (see section ADVERSE DRUG 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 patients with diffuse myalgia's, 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, pencillamine, 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.

Peripheral neuropathy

Peripheral neuropathy has been uncommonly reported in telbivudine-treated patients. If peripheral neuropathy is suspected, treatment with telbivudine should be reconsidered (see section ADVERSE DRUG REACTIONS).

In one study, an increased risk of developing peripheral neuropathy has been observed with the combined use of telbivudine, 600 mg daily, and pegylated interferon alfa-2a 180 micrograms once weekly compared to telbivudine or pegylated interferon alfa-2a, 180 micrograms once weekly alone (see section CONTRAINDICATIONS and INTERACTIONS). Such risk cannot be excluded for other dose regimens of pegylated interferon alfa-2a, or other alfa interferons (pegylated or standard). The benefit of the combination of telbivudine with interferon alfa (pegylated or standard) is not currently established.

Renal function

Telbivudine is eliminated primarily by renal excretion, therefore dose adjustment is recommended in patients with creatinine clearance <50 mL/min, including patients on hemodialysis (see section DOSAGE REGIMEN 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 section INTERACTIONS).

Patients resistant to antiviral drugs for hepatitis B

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 hepatitis B virus (HBV) strain containing rtM204V/rtL180M or rtM204I mutations (see section CLINICAL STUDIES).

There are no adequate and well controlled studies of telbivudine treatment in patients with established adefovir-resistant hepatitis B virus infection. Results from cell-based assays showed that the adefovir resistance-associated substitution A181V had 1.5- to approximately 4-fold reduced susceptibility to telbivudine.

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. 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 section INTERACTIONS). Cyclosporin concentrations in blood should be monitored if cyclosporin is administered concurrently with telbivudine. (See section INTERACTIONS).

Special populations

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

Use in elderly patients

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.

Use in Children (age below 16 years)

No studies have been performed in children under the age of 16 years. Therefore, until more information is available, Sebivo is not recommended for use in children.

Information for Patients

Patients should be advised that treatment with Sebivo has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination.

ADVERSE DRUG REACTIONS

Summary of the safety profile

Approximately 1,500 subjects have been treated with telbivudine in clinical studies at a dose of 600mg 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. The most common adverse reactions were grade 3 or 4 blood creatine kinase elevations (6.8%), fatigue (4.4%), headache (3.0%) and nausea (2.6%). In the 007 GLOBE and NV-02B-015 studies, patient discontinuation 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.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions recorded in the pooled 104 week 007 GLOBE and NV-02B-015 studies are listed by MedDRA system organ class in Table 2. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2 Clinical adverse reactions in patients with chronic hepatitis B, treated with telbivudine 600mg, reported in the pooled 104 week 007 GLOBE and NV-02B-015 studies

Nervous System Disorders	
Common	Dizziness, headache
Uncommon	Peripheral neuropathy, dysgeusia, hypoaesthesia, paresthesia, sciatica
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Gastrointestinal Disorders	
Common	Diarrhoea, blood lipase increased, nausea, abdominal pain
Uncommon	Gastritis
Skin and subcutaneous tissue disorders	
Common	Rash
Musculoskeletal, connective tissue and bone disorders	
Uncommon	Arthralgia, myalgia, myopathy/myositis, pain in the extremities, back pain, muscle spasm, neck pain, flank pain
General disorders and administration site conditions	
Common	Fatigue, malaise, pyrexia
Investigations	
Common	Blood creatine phosphokinase increased, alanine aminotransferase increased,

	blood amylase increased,
Uncommon	Aspartate aminotransferase increased

Description of selected adverse reactions

Creatine kinase elevation

Creatinine 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% 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.

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.

ALT flares

The incidence of alanine aminotransferase (ALT) flares was similar in the two treatment arms in the first six months. ALT flares occurred less frequently in both arms after Week 24, with a lower incidence in the telbivudine arm (2.0%) compared to the lamivudine arm (5.3%) as shown in Table 3. Periodic monitoring of hepatic function is recommended during treatment.

Table 3 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 (see section CLINICAL STUDIES) 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. Grade 3/4 CK elevations occurred in 15.9% of patients (104/655) treated with telbivudine in study CLDT600A2303. Most grade 3/4 CK elevations were asymptomatic (74% patients without any muscle related adverse reaction) and transient (97.5% episodes lasted one or two visits (visit interval 2-12 weeks) and 86.6% patients had one or two episodes). Most grade 3/4 CK elevations (93.2%) resolved spontaneously or returned to baseline levels. Two cases of myopathy and two cases of myositis were reported in the 655 telbivudine-treated patients.

Exacerbations of hepatitis B 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 B after discontinuation of telbivudine treatment (see section WARNINGS AND PRECAUTIONS). However, severe acute exacerbations of hepatitis have been reported in patients who have discontinued anti-hepatitis B therapy.

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 exacerbations of hepatitis B upon telbivudine withdrawal were reported.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reaction has been derived from post-marketing experience with Sebivo via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA within each system organ class. ADRs are presented in order of decreasing seriousness.

Table 4 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Musculoskeletal, connective tissue and bone disorders
Rhabdomyolysis
Metabolism and nutrition disorders
Lactic acidosis

INTERACTIONS

Since telbivudine is eliminated primarily by renal excretion, co-administration of Sebivo with substances that affect renal function may affect plasma concentrations of telbivudine and/or the co-administered substance.

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, 2D26, 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.

The steady-state pharmacokinetics of telbivudine was unaltered following multiple dose administration in combination with lamivudine, adefovir dipivoxil, cyclosporine, pegylated interferon-alfa 2a or tenofovir disoproxil fumarate. In addition, telbivudine does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil, cyclosporine 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 WARNINGS AND PRECAUTIONS).

A pilot 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 of developing peripheral neuropathy (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Cyclosporine concentrations in blood should be monitored if cyclosporine is administered concurrently with telbivudine.

WOMEN OF CHILD BEARING POTENTIAL, PREGNANCY, BREAST FEEDING AND FERTILITY

Pregnancy (Category B1)

For telbivudine, very limited clinical trial data on exposed pregnancies are available. Data (from registry, literature and spontaneous post-marketing reports) on exposure to telbivudine during

pregnancy are available in 1696 women (173 in first trimester and 1523 in second and/or third trimester). Neither increased rates of live birth defects, spontaneous abortion or elective termination, nor fetal/neonatal toxicity have been reported during telbivudine treatment.

Telbivudine crossed the placenta in rats. Developmental toxicity studies revealed no evidence of harm to the embro or foetus of rats or rabbits at plasma levels (based on plasma AUC values) up to 6 (rats) and 37 (rabbits) times higher than those observed with the therapeutic dose (600mg/day) in humans. An increase in early deliveries and abortions was observed in rabbits at plasma levels 37 times higher than those in humans treated with the therapeutic dose, but this was correlated with maternal body weight loss. Sebivo should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

There are no data on the effect of telbivudine on transmission of HBV from mother to infant. Therefore, appropriate infant immunisation should be used to prevent neonatal acquisition of HBV.

Breast-feeding

Telbivudine is execreted 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.

Effects on Fertility

There are no clinical data on the effects of telbivudine on male or female fertility. In reproductive toxicology studies, fertility was slightly reduced when both male and female rats received telbivudine at systemic exposures greater than 2.5 times those achieved in humans at the therapeutic dose (see section NON-CLINICAL SAFETY DATA).

Effects on ability to drive and use machines

If patients experience dizziness or fatigue while using Sebivo they should refrain from driving or using machinery.

OVERDOSAGE

Overdose experience with Sebivo is very limited. Tested doses up to 1,800 mg/day, three times greater than the recommended daily dose, have been well tolerated. A maximum tolerated dose of telbivudine has not been determined. In the event of an overdose, Sebivo should be discontinued and appropriate general supportive treatment applied as necessary.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Antiviral for systemic use.

PHARMACODYNAMICS (PD)

Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase. It is phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours. Telbivudine-5’-triphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5’-triphosphate. Incorporation of telbivudine-5'-triphosphate into viral DNA causes DNA chain termination, resulting in the 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.*

The *in vitro* antiviral activity of telbivudine was assessed in the HBV-expressing human hepatoma cell line 2.2.15. The concentration of telbivudine that effectively inhibited 50% of viral synthesis (EC_{50}) was approximately 0.2 µM. The antiviral activity of telbivudine is specific to the hepatitis B virus and related hepadnaviruses. Telbivudine was not active against HIV *in vitro*. The

absence of activity of telbivudine against HIV has not been evaluated in clinical trials.

In vitro resistance

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. Reductions of at least 1,049 fold in telbivudine phenotypic susceptibility were observed against lamivudine resistant HBV strains containing either the M204l mutation or the L180M/M204V double mutation. M204l mutations have been identified in telbivudine resistant patients.

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 (most common adefovir-resistance mutations seen in HBV-infected patients). HBV encoding an A181V amino acid substitution showed 3- to 5-fold reduced susceptibility to telbivudine in cell culture.

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 absence of telbivudine activitiy against HIV has not been evaluated in clinical trials.

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 or rtA181V had around 0.3- and 4-fold change in susceptibility to telbivudine in cell culture, respectively.

PHARMACOKINETICS

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

Absorption and Bioavailability

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

Effect of food on oral absorption

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

Biotransformation/ 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 section INTERACTIONS).

Elimination

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

Special population

Gender

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

Race

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

Pediatrics and geriatric (65 years age and above)

Pharmacokinetic studies have not been conducted in pediatric or elderly subjects.

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 5, adjustment of the dose for telbivudine is recommended in patients with creatinine clearance of <50 mL/min (see section DOSAGE REGIMEN AND ADMINISTRATION).

Table 5 Pharmacokinetic parameters (mean ± SD) of telbivudine in subjects with various degrees of renal function

	Renal function (creatinine clearance in mL/min)				
	Normal (>80) (n=8) 600 mg	Mild (50–80) (n=8) 600 mg	Moderate (30–49) (n=8) 400 mg	Severe (<30) (n=6) 200 mg	ESRD/ Hemodialysis (n=6) 200 mg
Cmax (microg/mL)	3.4±0.9	3.2±0.9	2.8±1.3	1.6±0.8	2.1±0.9
$AUC_{0\text{-}INF}$ (microg•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 hemodialysis

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

Hepatic impairment

The pharmacokinetics of telbivudine following a single 600 mg dose has 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 section DOSAGE REGIMEN AND ADMINISTRATION).

Clinical studies

The safety and efficacy of long term (104 weeks) Sebivo treatment were evaluated in two active-

controlled clinical studies that included 1,699 patients with chronic hepatitis B and compensated liver disease (007 GLOBE and NV-02B-015)

Study 007 "GLOBE"

The 007 "GLOBE" study was a Phase III, randomized, double-blind, multinational study of telbivudine 600 mg/d compared to lamivudine 100 mg/d for a treatment period of up to 104 weeks 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 received 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 alfa-interferon therapy.

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 alfa-interferon therapy

Clinical results at week 52

Clinical and virological efficacy endpoints were evaluated separately in the HBeAg-positive and HBeAg-negative patient populations. The primary endpoint of therapeutic response was a composite serological endpoint requiring suppression of HBV DNA to < 5 $\log_{10}$ copies/ml in conjunction with either loss of serum HBeAg or ALT normalized. Secondary endpoints included histological response, ALT normalization, and various measures of antiviral efficacy.

Regardless of baseline characteristics, the majority of patients taking Sebivo showed histological, virological, biochemical, and serological responses to treatment. Baseline ALT levels > 2x ULN and baseline HBV DNA < 9 $\log_{10}$ copies/ml were associated with higher rates of HBeAg seroconversion in HBeAg-positive patients. Patients who achieve HBV DNA levels < 3 $\log_{10}$ copies/ml by week 24 had optimal responses to treatment; conversely patients with HBV DNA levels > 4 $\log_{10}$ copies/ml at 24 weeks had less favourable outcomes at week 52.

In HBeAg-positive patients, telbivudine was superior to lamivudine in therapeutic response (75.3% vs 67.0% responders; p = 0.0047). In HBeAg-negative patients, telbivudine was non-inferior to lamivudine (75.2% and 77.2% responders; p = 0.6187).

At week 24, 203 HBeAg-positive and 177 HBeAg-negative subjects achieved non-detectable HBV DNA levels. Of those HBeAg-positive subjects, 95% achieved non-detectable HBV DNA, 39% achieved HBeAg seroconversion, 90% achieved ALT normalization at week 52 and 0.5% exhibited resistance at week 48. Similarly of those HBeAg-negative subjects, 96% achieved non-detectable HBV DNA, 79% achieved ALT normalization at week 52 and 0% exhibited resistance at week 48.

Selected virological, biochemical and serological outcome measures are shown in Table 6 and histological response in Table 7.

Table 6 **Virological, biochemical and serological endpoints at week 52 in 007 (GLOBE) study**

Response parameter	HBeAg-positive (n = 921)		HBeAg-negative (n = 446)	
	Telbivudine 600 mg (n = 458)	Lamivudine 100 mg (n = 463)	Telbivudine 600 mg (n = 222)	Lamivudine 100 mg (n = 224)
Mean HBV DNA reduction from baseline ($\log_{10}$ copies/ml) ± SEM[1,2,3]	-6.45 (0.11) *	-5.54 (0.11)	-5.23 (0.13) *	-4.40 (0.13)
% Patients HBV DNA undetectable by PCR	60%*	40%	88%*	71%
ALT normalization[4]	77%	75%	74%	79%
HBeAg seroconversion[4]	23%	22%	-	-
HBeAg loss[5]	26%	23%	-	-

[1] SEM: Standard error of mean

[2] Roche COBAS Amplicor® PCR Assay (lower limit of quantification ≤ 300 copies/ml).

[3] HBeAg-positive n = 443 and 444, HBeAg-negative n = 219 and 219, for both telbivudine and lamivudine groups, respectively. The difference in populations is due to patient discontinuation from the study and missing HBV DNA assessment at week 52.

[4] HBeAg-positive n = 440 and 446, HBeAg-negative n = 203 and 207, for telbivudine and lamivudine groups, respectively. ALT normalization assessed only in patients with ALT > ULN at baseline.
[5] n = 432 and 442, for telbivudine and lamivudine groups, respectively. HBeAg seroconversion and loss assessed only in patients with detectable HBeAg at baseline.
*p < 0.0001

Table 7 Histological improvement and change in Ishak fibrosis score at week 52 in 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 a ≥ 2 point decrease in Knodell necroinflammatory score from baseline with no worsening of the Knodell Fibrosis Score.
[3] For Ishak fibrosis score, improvement measured as ≥ 1 point reduction in Ishak fibrosis score from baseline to week 52.
*p = 0.0024

Clinical results at week 104

Overall, clinical results at week 104 in telbivudine-treated patients were consistent with those at week 52, demonstrating durability of efficacy responses for telbivudine-treated patients with continued treatment.

Among HBeAg-positive patients, therapeutic response (63% vs 48%; $p < 0.0001$) and key secondary endpoints (mean $\log_{10}$ HBV DNA reduction: -5.74 vs -4.42; $p < 0.0001$, HBV DNA undetectability: 56% vs 39%; $p < 0.0001$ and ALT normalization of 70% vs 62%) demonstrated a widening difference at week 104 between telbivudine and lamivudine, respectively. A trend towards higher rates of HBeAg loss (35% vs 29%) and seroconversion (30% vs 25%) was also observed for telbivudine. Moreover, in the subgroup of patients with baseline ALT levels ≥ 2x ULN (320), a significantly higher proportion of telbivudine patients than lamivudine patients achieved HBeAg seroconversions at week 104 (36% vs 28%, respectively).

Among HBeAg-negative patients, differences in therapeutic response (78% vs 66%) and key secondary endpoints (mean $\log_{10}$ HBV DNA reduction: -5.00 vs -4.17, and HBV DNA undetectability: 82% vs 57%; $p < 0.0001$) were higher for telbivudine up to week 104. ALT normalization rates (78% vs 70%) continued to be higher by week 104.

Predictability at week 24

At week 24, 203 HBeAg-positive (44%) and 177 HBeAg-negative (80%) telbivudine-treated subjects achieved undetectable HBV DNA levels.

For both HBeAg-positive and HBeAg-negative patients, week 24 HBV DNA results were a predictor of long-term favourable outcomes. Telbivudine-treated patients who achieve undetectable HBV DNA by PCR by week 24 had the highest rates of HBV DNA undetectability and HBeAg seroconversion (in HBeAg-positive patients), and the lowest overall rates of virological breakthrough at week 104.

Outcome results at week 104, based on level of HBV DNA at week 24, for either HBeAg positive or HBeAg-negative patients are presented in Table 8.

Table 8 **Key efficacy endpoints at week 104 by serum HBV DNA levels at week 24, telbivudine-treated patients in 007 (GLOBE) study**

HBV DNA at week 24	Outcome for key efficacy end points at 104 weeks based on week 24 results				
	Therapeutic response n/N (%)	**HBV DNA undetectability n/N (%)**	**HBeAg seroconversion n/N (%)**	**ALT normalization n/N (%)**	**Virological breakthrough* n/N (%)**
HBeAg-positive					
< 300 copies/ml	172/203 (85)	166/203 (82)	84/183 (46)	160/194 (82)	22/203 (11)
300 copies/ml to < 3 log_{10} copies/ml	36/57 (63)	35/57 (61)	21/54 (39)	40/54 (74)	18/57 (32)
≥ 3 log_{10} copies/ml	82/190 (43)	54/190 (28)	23/188 (12)	106/184 (58)	90/190 (47)
HBeAg-negative					
< 300 copies/ml	146/177 (82)	156/177 (88)	N/A	131/159 (82)	11/177 (6)
300 copies/ml to < 3 log_{10} copies/ml	13/18 (72)	14/18 (78)	N/A	13/17 (76)	4/18 (22)
≥ 3 log_{10} copies/ml	13/26 (50)	12/26 (46)	N/A	14/26 (54)	12/26 (46)

N/A = not applicable
* Virological breakthrough: "1 log above nadir" definition assessed at week 104

Study NV-02B-015

NV-02B-015 was a Phase III, randomized, double-blind study of telbivudine 600 mg/d compared to lamivudine 100 mg/d 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 9. Efficacy results from study NV-02B-015 are consistent with the 007 "GLOBE" study results at week 52 and week 104 respectively.

Table 9 **Virological, Biochemical and Serologic Endpoints and Therapeutic Response at Weeks 52 and 104 (NV-02B-015)**

Response Parameter	HBeAg-positive (n= 289)				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/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 Negative 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≤300 copies/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 ≤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 156 and 208, the majority of patients maintained undetectable HBV DNA levels (< 300 copies/ml) and normalized ALT. HBeAg- positive patients with undetectable HBV DNA at week 24 had better outcomes at 156 and 208 weeks (Table 10).

Table 10 Virological, biochemical and serological endpoints up to week 208 (CLDT600A2303)

	Week 52	Week 104	Week 156	Week 208
HBeAg-positive patients (N = 293*)				
Maintained undetectable HBV DNA (< 300 copies/ml)	70.3% (206/293)	77.3% (218/282)	75.0% (198/264)	76.2% (163/214)
Maintained undetectable HBV DNA (< 300 copies/ml) with undetectable HBV DNA at week 24	99.4% (161/162)	94.9% (150/158)	86.7% (130/150)	87.9% (109/124)
Cumulative HBeAg seroconversion rates (%)	27.6% (81/293)	41.6% (122/293)	48.5% (142/293)	53.2% (156/293)
Cumulative HBeAg seroconversion rates in patients with undetectable HBV DNA at week 24 (%)	40.1% (65/162)	52.5% (85/162)	59.3% (96/162)	65.4% (106/162)
Maintained ALT normalization	81.4% (228/280)	87.5% (237/271)	82.9% (209/252)	86.4% (178/206)
HBeAg-negative patients (n = 209*)				
Maintained undetectable HBV DNA (< 300 copies/ml)	95.2% (199/209)	96.5% (195/202)	84.7% (160/189)	86.0% (14/164)
Maintained undetectable HBV DNA (< 300 copies/ml) with undetectable HBV DNA at week 24	97.8% (175/179)	96.5% (166/172)	86.7% (143/165)	87.5% (126/144)
Maintained ALT normalization	80.3% (151/188)	89.0% (161/181)	83.5% (142/170)	89.6% (129/144)

* The population without viral resistance at entry into study CLDT600A2303 consisted of 502 patients (293 HBeAg - positive and 209 HBeAg-negative)

Liver histology response - Study CLDT600ACN04E1

In study CLDT600ACN04E1, 57 chronic hepatitis B patients with compensated liver disease and with paired liver biopsies at baseline and after mean treatment of 260.8 weeks were evaluated for changes in liver histology (38 HBeAg- positive and 19 HBeAg-negative patients).

- The mean Knodell necroinflammatory score of 7.6 (SD 2.9) at baseline improved ($p < 0.0001$) to 1.4 (SD 0.9) with a mean change of -6.3 (SD 2.8). Knodell necroinflammatory score ≤ 3 (no or minimal necroinflammation) was observed in 98.2% (56/57) of patients.
- The mean Ishak score of 2.2 (SD 1.1) at baseline improved ($p < 0.0001$) to 0.9 (SD 1.0) with a mean change of -1.3 (SD 1.3). Ishak fibrosis score ≤ 1 (no or minimal fibrosis) was observed in 84.2% (48/57) of patients.

Changes in Knodell necroinflammatory and Ishak scores were similar for HBeAg-positive and HBeAg-negative patients.

Off-treatment durability of HBeAg response - CLDT600A2303

Study CLDT600A2303 included off-treatment follow up of 59 HBeAg-positive patients from studies 007 "GLOBE" and NV-02B-015. These patients had completed ≥ 52 weeks of telbivudine treatment, and had exhibited HBeAg loss for ≥ 24 weeks with HBV DNA < 5 $\log_{10}$ copies/ml at the last on-treatment visit. The median treatment duration was 104 weeks After a median off-treatment follow-up period of 120 weeks, the majority of HBeAg-positive telbivudine treated-patients showed sustained HBeAg loss (83.3%), and sustained HBeAg seroconversion (79.2%). Patients with sustained HBeAg seroconversion had a mean HBV DNA of 3.3 $\log_{10}$ copies/ml; and 73.7% had HBV DNA < 4 $\log_{10}$ copies/ml.

Clinical resistance

Genotypic resistance rates

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 $\log_{10}$ 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 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 2.4% for HBeAg-negative patients (Table 11).

Table 11 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 <7 $\log_{10}$, 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 Year 4 was 20.0% in the overall population (n=310); 22.3% in HBeAg-positive and 16.0% in HBeAg-negative patients.

Genotypic mutation pattern

Genotypic analysis of 203 evaluable sample pairs with HBV DNA ≥ 1,000 copies/ml at week 104 (NV-02B-007 (GLOBE)) 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. 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 of 50 HBV isolates from telbivudine-treated patients at week 208 (CLDT600A2303) revealed a similar resistance profile as reported at week 104. Conversions at position 80, 180 and polymorphic positions 91, 229 were always detected in sequences that harboured the M204I mutation that confers genotypic resistance. These mutations most likely are compensatory mutations. One isolated rtM204V mutation and two rtM204I/V/M mutations were reported in telbivudine-treated patients experiencing viral breakthrough up to week 208. No novel mutation was reported.

Cardiac safety

There is no evidence of cardiotoxicity for telbivudine. In an *in vitro* hERG model, telbivudine was negative at concentrations up to 10,000 microM. In a thorough QTc prolongation clinical study in healthy subjects, telbivudine had no effect on QT intervals or other electrocardiographic parameters after multiple daily doses up to 1,800 mg.

NON-CLINICAL SAFETY DATA

Carcinogenicity

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 human at the therapeutic dose of 600 mg/day.

Genotoxicity

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 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 achieved in humans at the therapeutic dose) and mated with untreated rats.

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 1,000 (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.

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 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.

INCOMPATIBILITIES

Not applicable.

STORAGE

Do not store above 30°C. Protect from moisture.

Sebivo should not be used after the date marked “EXP” on the pack.

Manufacturer:

See folding box

International Package Leaflet

Information issued: Jan 2017.SIN

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