

## PRESCRIBING INFORMATION

<sup>Pr</sup> **SEBIVO\***

telbivudine

Tablets (film-coated) 600 mg

Antiviral Agent

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Date of Preparation:  
November 20, 2006

Submission Control No: 104469

<sup>Pr</sup>SEBIVO\* is a registered trademark

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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	Microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate and colloidal silicon dioxide  Tablet coating: titanium dioxide, polyethylene glycol, talc and hypromellose

### 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 trial for 52 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.

#### **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.**

## 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.**

### **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.**

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

### **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. (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 studies of telbivudine treatment in patients with established adefovir - resistant Hepatitis B virus infection (see MICROBIOLOGY: 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. 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\* should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

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 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.

### **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.

### **Labour and Delivery**

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

### **Nursing 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  $\geq 65$  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 concomitant 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 in male or female rats at systemic exposures approximately 14 times those observed in humans at the therapeutic dose (see Toxicology: Reproductive Toxicology).

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Assessment of adverse reactions is primarily based on the pivotal 007 GLOBE study in which 680 patients received treatment with telbivudine 600mg / day and 687 patients received treatment with lamivudine 100mg / day for 52 weeks. The most common telbivudine related adverse event was CK elevation. There were also several cases of myopathy and uncomplicated myalgia in patients with CK elevations beyond week 52 in the 007 study (see WARNINGS AND PRECAUTIONS, Musculoskeletal).

### **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.*

Assessment of adverse reactions is primarily based on the pivotal 007 GLOBE study in which 1,367 patients with chronic hepatitis B received double-blind treatment with telbivudine 600 mg/day (n=680) or lamivudine 100 mg/day (n=687) for up to 52 weeks. Median duration of treatment in the 007 GLOBE study was 60 weeks for telbivudine- and lamivudine-treated patients.

In clinical studies telbivudine was generally well tolerated, with most adverse experiences classified as mild or moderate in severity. Frequently occurring adverse events regardless of attributability to telbivudine were upper respiratory tract infection (12%), nasopharyngitis (10%), fatigue (10%), headache (10%), dizziness (4%) and myalgia (3%). Frequently occurring adverse events regardless of attributability to lamivudine were headache (12%), upper respiratory tract infection (12%), nasopharyngitis (10%), fatigue (9%), dizziness (5%), and myalgia (2%).

In the 007 GLOBE study, discontinuation from the study due to any adverse event in the first 52 weeks was 0.3% for the telbivudine arm, and 0.7% for the lamivudine arm. In the telbivudine arm, there were more study drug discontinuations and interruptions due to musculoskeletal events associated with CK elevations than were in the lamivudine arm (see WARNINGS and PRECAUTIONS, Musculoskeletal, and Abnormal Hematologic and Clinical Chemistry Findings).

Clinical adverse events of moderate to severe intensity and considered at least possibly related to treatment during the pivotal 007 GLOBE study clinical trial are presented in Table 1.

**Table 1: Clinical Adverse Events Attributed to Study Drug in  $\geq 1\%$  of Patients with Chronic Hepatitis B Reported by Week 52 in the 007 GLOBE Study**

	<b>Telbivudine 600 mg n= 680 (%)</b>	<b>Lamivudine 100 mg n= 687 (%)</b>
<b>General</b>		
Fatigue	4.3	2.6
<b>Gastrointestinal</b>		
Nausea	2.8	2.2
Diarrhea	1.5	0.6
Abdominal Pain	1.0	0.1
<b>Nervous system</b>		
Headache	3.2	3.9
Dizziness	1.5	0.7
<b>Dermatological</b>		
Rash	1.3	1.0
<b>Respiratory system</b>		
Nasopharyngitis	1.0	0.6
Cough	1.0	0.4

Source: Study NV-02B-007 Table 14.3.1.3.2.1

### **Abnormal Hematologic and Clinical Chemistry Findings**

The most common lab abnormality associated with telbivudine treatment was CK (creatinine kinase) elevation. The majority of CK elevations were asymptomatic and decreased by the next visit while remaining on treatment. Grade 3-4 CK elevation occurred in 9% of telbivudine-treated patients and 3% of lamivudine-treated patients in Study 007 (including data on all patients to Week 52 and some patients from the ongoing second year of this study). In Study 007, 0.7% (5/680) of patients receiving telbivudine and 0% (0/687) of patients receiving lamivudine discontinued or dose interrupted due to CK elevations (see Table 3 for more details). Most CK elevations were asymptomatic but the mean recovery time was longer for subjects in telbivudine than subjects on lamivudine. Additional patients also discontinued or dose interrupted due to CK elevations in the ongoing second year of the GLOBE study. Some of these CK elevations were associated with myopathy and muscle weakness (see WARNINGS and PRECAUTIONS - Musculoskeletal).

**Table 2: Treatment-Emergent Grade 3-4<sup>1</sup> Laboratory Abnormalities<sup>2</sup> in Patients with Chronic Hepatitis B by Week 52 in the 007 GLOBE Study**

Test	Telbivudine 600 mg n=680 (%)	Lamivudine 100 mg n=687 (%)
Creatine Kinase (CK) $\geq 7.0$ x ULN	7.5	3.1
ALT (SGPT) > 3.0 x baseline	3.7	6.3
AST (SGOT) > 3.0 x baseline	2.6	4.7
Lipase >2.5 x ULN	1.8	3.2
Amylase > 3.0 x ULN	0.1	0.3
Total Bilirubin > 5.0 x ULN	0	0.3
Neutropenia <sup>3</sup> (ANC $\leq 749/\text{mm}^3$ )	0	0.1
Thrombocytopenia <sup>3</sup> (Platelets $\leq 49,999/\text{mm}^3$ )	0	0.1

<sup>1</sup> Grading system corresponds to the 1992 version of the DAIDS AE grading table

<sup>2</sup> On-treatment value worsened from baseline to Grade 3 or Grade 4 during therapy up to Week 52

<sup>3</sup> Confirmed on next laboratory value

**Table 3: Treatment-Emergent New Onset CK Abnormalities<sup>1</sup> in Patients with Chronic Hepatitis B by Week 52 in the 007 GLOBE Study**

CK Toxicity Grade <sup>¥, 2</sup>	Telbivudine 600 mg n=680 (%)	Lamivudine 100 mg n=687 (%)
Grade 1 (1 to 3.0 x ULN)	42.2	29.5
Grade 2 (>3.0 to 7.0 x ULN)	18.1	6.6
Grade 3 (>7.0 to 10.0 x ULN)	4.1	1.0
Grade 4 (> 10 x ULN)	3.4	2.0
Total of Grades 1-4 ( $\geq 1$ x ULN)	67.8	39.2
Discontinuation/Interruption due to CK <sup>3</sup>	0.7*	0

<sup>1</sup> On-treatment value worsened from baseline to Grade 1 to 4 during therapy up to Week 52

<sup>2</sup> 22% of patients had pre-treatment Grade 1-4 CK elevations.

<sup>3</sup> Additional discontinuations / dose interruptions have occurred after week 52 in this study

\*Two patients on telbivudine had study drug interrupted, while three patients had study drug discontinued.

¥ CK toxicity grade corresponds to the 1992 version of the DAIDS AE grading table,

The incidence of ALT flares was similar in the two treatment arms in the first six months but was lower for telbivudine after Week 24 as shown in Table 4 below.

**Table 4: Analysis of Categories of ALT Flares After Week 24 in Patients with Chronic Hepatitis B in the 007 GLOBE Study**

ALT Flare Category <sup>1</sup>	Telbivudine 600 mg n=680 (%)	Lamivudine 100 mg n=687 (%)
ALT $\geq 2$ x Baseline & $\geq 2$ x ULN <sup>2</sup>	0.3%	1.0%
ALT $\geq 3$ x Baseline & $\geq 3$ x ULN	0.1%	1.9%
ALT $\geq 500$ IU/L & $\geq 2$ x Baseline	0.1%	1.2%
ALT $\geq 2$ x Baseline & bilirubin $\geq 2$ x Baseline & $\geq 2$ x ULN	0%	0.4%
Total Week 24 to Week 52	0.6%	4.5%

<sup>1</sup> Each patient can only be represented in one category

<sup>2</sup> Upper Limit of Normal

### **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.

### **Drug abuse and dependence**

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

## **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 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 peginterferon alfa - 2a: 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 C<sub>max</sub> and AUC 0 to 168 h of peginterferon were increased by approximately 64% and 40%, respectively, when coadministered with multiple dose of telbivudine (600mg) 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.

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 / insufficiency below).

### **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.

The optimal treatment duration has not been established.

Renal impairment/insufficiency: (See WARNINGS & 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  $\geq 50$  mL/min ( $\geq 0.835$  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**

<b>Creatinine clearance (mL/min)</b>	<b>Dose of SEBIVO*</b>
$\geq 50$	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**

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 ( $EC_{50} = 0.4\text{-}1.3 \mu\text{M}$ ) and second-strand ( $EC_{50} = 0.12\text{-}0.24 \mu\text{M}$ ) synthesis, and shows a distinct preference for inhibiting second-strand production. By contrast, telbivudine-5'-triphosphate at concentrations up to 100  $\mu\text{M}$  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  $\mu\text{M}$  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 ( $C_{\text{max}}$ ) of telbivudine was  $3.69 \pm 1.25 \mu\text{g/mL}$  (Mean  $\pm$  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  $26.1 \pm 7.2 \mu\text{g}\cdot\text{h/mL}$  (Mean  $\pm$  SD), and trough plasma concentrations ( $C_{\text{trough}}$ ) were approximately 0.2-0.3  $\mu\text{g/mL}$ . 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  $^{14}\text{C}$ -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  $41.8 \pm 11.8$  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 retained wild-type phenotypic activity (1.2-fold reduction) against the M204V single mutant versus a 25-fold reduction in activity for lamivudine. 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  $> 1049 + / 226$ ).

Telbivudine showed a 2-fold enhanced activity against the N236T mutation, the most common form of adefovir-resistance 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 infected patients, nucleoside analogues such as lamivudine can induce YMDD-based (M184V) HIV resistant strains. Because telbivudine is not active against HIV, there is no risk for telbivudine to induce YMDD-based cross-resistant HIV strains.

### Clinical Resistance

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 ( $\geq 1000$  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  $\geq 16$  weeks of treatment. The rtM204I substitution was the most frequent mutation and was associated with virologic rebound ( $\geq 1 \log_{10}$  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.

## Cross-resistance

Cross-resistance has been observed among HBV nucleoside analogues. 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 6, 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 6: 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 <sub>max</sub> (µg/mL)	3.4±0.9	3.2±0.9	2.8±1.3	1.6±0.8	2.1±0.9
AUC <sub>0-∞</sub> (µg•h/mL)	28.5±9.6	32.5±10.1	36.0±13.2	32.5±13.2	67.4±36.9
CL <sub>RENAL</sub> (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

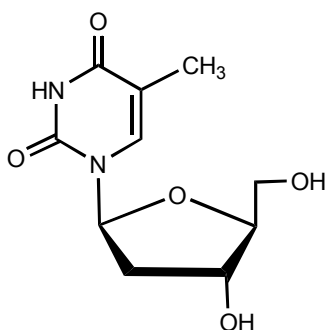
#### Drug Substance

Proper name: telbivudine

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

Molecular formula and molecular mass: C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub> (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 189°C. 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 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.

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. 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  $\geq 7$ , mean serum HBV DNA as measured by Roche COBAS Amplicor<sup>®</sup> PCR assay was 9.52 log<sub>10</sub> 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  $\geq 7$ , mean serum HBV DNA as measured by Roche COBAS Amplicor<sup>®</sup> PCR assay was 7.54 log<sub>10</sub> copies/mL and mean serum ALT was approximately 140 IU/litre. Pre- and post-liver biopsy samples were adequate for 92% of patients.

### Study results

Virological, biochemical and histological efficacy endpoints were evaluated separately in the HBeAg-positive and HBeAg-negative patient populations in Study 007. The primary endpoint termed “Therapeutic Response” at Week 52 was a composite serological endpoint requiring suppression of HBV DNA to  $< 5$  log<sub>10</sub> copies/mL in conjunction with either loss of serum HBeAg or ALT normalisation.

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% vs. 77.2% responders;  $p = 0.6187$ ).

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

In the Phase 3 global registration trial (007 GLOBE study), 60.0% of HBeAg-positive and 88.3% of HBeAg-negative patients receiving telbivudine 600 mg/day achieved nondetectable serum HBV DNA levels ( $< 300$  copies/mL) by Week 52.

**Table 7: Virological, biochemical and serological endpoints at week 52 (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 <sub>10</sub> copies/mL) ± SEM <sup>1,2</sup>	-6.45 (0.11) *	-5.54 (0.11)	-5.23 (0.13) *	-4.40 (0.13)
% Patients HBV DNA negative by PCR	60%*	40%	88%*	71%
ALT normalisation <sup>3</sup>	77%	75%	74%	79%
HBeAg seroconversion <sup>4</sup>	23%	22%	NA	NA
HBeAg loss <sup>4</sup>	26%	23%	NA	NA

<sup>1</sup> Roche COBAS Amplicor® PCR Assay (lower limit of quantification {LLOQ} ≤300 copies/mL)

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

<sup>3</sup> HBeAg-positive: n = 440 and 446, HBeAg-negative: n = 203 and 207, for telbivudine and lamivudine groups, respectively. ALT normalisation assessed only in patients with ALT > ULN at baseline

<sup>4</sup> 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

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 8. In HBeAg-negative patients telbivudine was statistically non-inferior to lamivudine for histological response.

**Table 8: 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) <sup>1</sup>	Lamivudine 100 mg (n = 386) <sup>1</sup>	Telbivudine 600 mg (n = 199) <sup>1</sup>	Lamivudine 100 mg (n = 207) <sup>1</sup>
<b>Histological response<sup>2</sup></b>				
Improvement	71%*	61%	71%	70%
No Improvement	17%	24%	21%	24%
<b>Ishak Fibrosis Score<sup>3</sup></b>				
Improvement	42%	47%	49%	45%
No change	39%	32%	34%	43%
Worsening	8%	7%	9%	5%
<b>Missing week 52 biopsy</b>	12%	15%	9%	7%
<sup>1</sup> Patients with ≥ one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Histological Activity Index (HAI) score >3				
<sup>2</sup> Histological response defined as ≥2 point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score				
<sup>3</sup> For Ishak Fibrosis Score, improvement defined as a ≥1 point reduction in Ishak Fibrosis Score from baseline to week 52				
*p = 0.0024				

## 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<sub>50</sub>) 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<sub>50</sub> value >200 μM).

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<sub>10</sub> 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<sub>10</sub> 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 9: 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 10: 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 10: 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 in male or female rats at systemic exposures approximately 14-times those observed 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 11: Reproductive Toxicology).

**Table 9: 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 10: Genetic Toxicology and Carcinogenicity**

Study Type	Species	Route	Doses	Findings
Ames test	Salmonella typhimurium strains TA98, TA100, TA1535, TA1537. E. coli strain WP2uvrA	<i>In vitro</i>	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	<i>In vitro</i>	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	<i>In vitro</i>	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 11: 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 2 <sup>nd</sup> 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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