NOVARTIS

Sebivo®

Composition

Active substance: Telbivudine.

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

Oral solution excipients: citric acid anhydrous, benzoic acid, passion fruit flavour, sodium saccharin, sodium hydroxide, water purified
Information might differ in some countries.

Pharmaceutical form and quantity of active substance per unit

600 mg film-coated tablets
Oral solution containing 20 mg telbivudine per ml. Clear, colourless to pale yellow liquid with passion-fruit flavour.

Indications/Potential uses

Treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation. This indication is based on virological, serological, biochemical and histological responses in adult patients with HBeAg-positive and HBeAg-negative compensated chronic hepatitis B (see "**Clinical studies**").
The following points should be considered before initiating therapy with Sebivo:

- For HBeAg-positive patients, treatment should only be initiated if baseline HBV DNA <9 log$_{10}$ copies/ml and baseline ALT ≥2 × ULN.
- For HBeAg-negative patients, treatment should only be initiated if baseline HBV DNA <7 log$_{10}$ copies/ml.

There have thus far been no studies of the safety and efficacy of telbivudine in liver-transplant patients or in patients with decompensated chronic hepatitis B.

Dosage and Administration

Adults
The recommended dose for the treatment of chronic hepatitis B is 600 mg once daily. Sebivo may be taken with or without food.
The oral solution may be considered for patients who have trouble swallowing tablets.
Due to risk of higher rates of resistance that may develop with long-term treatment among patients with incomplete viral suppression, treatment should only be initiated after baseline HBV DNA criteria are met (see "**Indications/Potential uses**").

Monitoring and duration of treatment
On-treatment response at week 24 has been shown to be a good indicator of long-term response (see "**Pharmacodynamics**" under "**Properties and Actions**"). HBV DNA levels should be monitored at 24 weeks of treatment to assure complete viral suppression (HBV DNA less than 300 copies/ml). Alternative therapy should be initiated for patients who have detectable HBV DNA after 24 weeks of treatment.
HBV DNA should be monitored every 6 months to assure continued response. If patients are tested positive for HBV DNA at any time after their initial response, alternative treatment should be instituted. Optimal therapy should be guided by resistance testing.
The optimal treatment duration has not yet been determined.

Renal impairment
Sebivo may be used for the treatment of chronic hepatitis B in patients with renal impairment. Dose adjustment is achieved either by reducing the daily dose of the oral solution, or by extending the dose interval for the tablets. The oral solution is preferable to the tablets for the treatment of patients with renal impairment.
No adjustment of the recommended dose is necessary in patients whose creatinine clearance is ≥50 ml/minute (see "Pharmacokinetics"). However, dose adjustment is required in patients with creatinine clearance <50 ml/minute, including those with end-stage renal disease (ESRD) on haemodialysis, as shown below (see table 1). The recommended dose (600 mg) was not studied in these patients. The recommended dose adjustment is based on extrapolation of data from patients with varying degrees of renal dysfunction, including ESRD. The safety and efficacy of the dose adjustment guidelines have not yet been evaluated in phase III clinical trials. A single-dose pharmacokinetic study in patients with varying degrees of renal impairment was carried out to determine the dose adjustment obtained by the single-dose reduction achieved using the solution. Close monitoring of efficacy and safety must be ensured in patients with renal impairment.

Table 1: Dose adjustment of Sebivo in patients with renal impairment

Creatinine clearance (ml/minute)	Dose of oral solution (20 mg/ml)	Film-coated tablet (1 tablet = 600 mg)
≥50	600 mg once daily (30 ml)	600 mg once daily
30-49	400 mg once daily (20 ml)	600 mg once every 48 hours
<30 (not requiring dialysis)	200 mg once daily (10 ml)	600 mg once every 72 hours
ESRD*	120 mg once daily (6 ml)	600 mg once every 96 hours

* End-stage renal disease

ESRD patients
For patients with ESRD, Sebivo should be administered after haemodialysis (see "**Pharmacokinetics**").

Hepatic impairment
No adjustment of the recommended dose of Sebivo is necessary in patients with hepatic impairment (see "**Pharmacokinetics**").

Children (under 16 years of age)
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.

Elderly patients (over 65 years of age)
No data are available to support a specific dose recommendation for patients over the age of 65 years (see "**Warnings and Precautions**").

Contraindications

Hypersensitivity to the active substance or any of the excipients.
Combination of 600 mg telbivudine daily with 180 micrograms pegylated interferon alfa-2a once weekly (see "**Warnings and Precautions**" and "**Interactions**").

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 1 year, in patients who discontinue anti-hepatitis B therapy. If appropriate, anti-hepatitis B therapy should be resumed.
Exacerbations of hepatitis: Spontaneous 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 (see "**Adverse effects**"). On average, 4-5 weeks elapsed prior to the occurrence of an exacerbation in patients treated with telbivudine. In patients with compensated liver disease, this elevation of serum ALT is generally not accompanied by elevated levels of serum bilirubin or by 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.
Exacerbations of hepatitis have also been reported in patients who have terminated treatment of hepatitis B. Post-treatment exacerbations are normally associated with increases in HBV DNA, and the majority of such cases have proven to be self-limiting. Nonetheless, there have also been reports of severe – and sometimes fatal – exacerbations. No data are available yet concerning telbivudine.
In nucleoside-naive patients treated for hepatitis B with similar medicinal products, the median time to exacerbation was about half a year after treatment. Most of these exacerbations were reported in HBeAg-negative patients. Clinical and laboratory parameters of liver function should be monitored repeatedly for at least 1 year after discontinuation of hepatitis B treatment. Where appropriate, a resumption of hepatitis B treatment may be beneficial.
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.
Cases of myopathy have been reported with telbivudine use several weeks to months after starting therapy. Myopathy has also been reported with some other medicinal products in this therapeutic class. Isolated cases of rhabdomyolysis have been reported during post-marketing use of telbivudine (see "**Postmarketing experience**" under "**Adverse effects**").
Uncomplicated myalgia has been reported in telbivudine-treated patients (see "**Adverse effects**"). Myopathy, defined as persistent unexplained muscle aches and/or muscle weakness regardless of the degree of increases in creatine kinase (CK) levels, should be considered in any patient with unexplained diffuse myalgia, 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 any persistent unexplained muscle aches, pain, tenderness or weakness. Telbivudine therapy should be discontinued if myopathy is diagnosed.
It is not known whether the risk of myopathy during treatment with medicinal products in this class is increased with concurrent administration of other medicinal products associated with myopathy. Physicians considering concomitant treatment with 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.
In one study, an increased risk of developing peripheral neuropathy was observed with the combination of 600 mg telbivudine daily and 180 µg pegylated interferon alfa-2a once weekly, as compared with telbivudine alone or 180 µg pegylated interferon alfa-2a once weekly alone (see "**Contraindications**" and "**Interactions**"). Such risk cannot be ruled out for other dose regimens of pegylated interferon alfa-2a, or other alfa interferons (pegylated or standard). Use of this combination is therefore not currently advisable.

Renal function
Telbivudine is eliminated primarily via the kidneys, and dose adjustment is therefore recommended in patients with creatinine clearance <50 ml/minute, including patients on haemodialysis (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 "**Interactions**").

Patients with antiviral resistant hepatitis B virus (HBV) infection
There have been no studies of telbivudine in patients with established lamivudine-resistant HBV infection. *In vitro*, telbivudine was not active against HBV strains containing rtM204V/rtL180M or rtM204I mutations (see "**Pharmacodynamics**" and "**Cross-resistance**").
There have been no studies of telbivudine in patients with established adefovir-resistant HBV infection. HBV encoding the adefovir resistance-associated substitutions rtN236T and rtA181V remain fully susceptible to telbivudine, with 0.5- and 1.0-fold susceptibility, respectively, in cell cultures.

Liver transplant recipients
The safety and efficacy of telbivudine in liver transplant recipients have not been studied. The steady-state pharmacokinetics of telbivudine were not altered following multiple dose administration in combination with ciclosporin. 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 ciclosporin or tacrolimus, renal function must be monitored both before and during treatment with Sebivo (see "**Interactions**").

Patients with decompensated cirrhosis
The safety and efficacy of telbivudine have not been studied in patients with decompensated cirrhosis. Severe adverse hepatic effects have been reported more frequently in patients with decompensated cirrhosis than in patients with compensated hepatic function.

Ethnicity
Out of a total of 1367 patients who participated in the pivotal study, 209 patients (15%) were Caucasian. Of these, 98 (52 HBeAg-positive, 46 HBeAg-negative) were treated with telbivudine. Experience with telbivudine in Caucasian patients is limited.

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 patients. In general, caution is required 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.

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

Sebivo oral solution contains approximately 47 mg sodium per 600 mg dose (30 ml). This should be taken into account by patients on a controlled sodium diet.

Information for patients

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

Interactions

Since telbivudine is eliminated primarily via the kidneys, co-administration of Sebivo with substances that impair renal function may affect plasma concentrations of telbivudine and/or the co-administered substances (see "**Warnings and Precautions**").

At concentrations up to 12 times those normally used in humans, telbivudine did not inhibit *in vitro* metabolism mediated by any of the following human hepatic microsomal cytochrome P450 (CYP) isoenzymes: 1A2, 2C9, 2C19, 2D6, 2E1, 3A4. These isoenzymes are known to be involved in human metabolism. 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 of Sebivo with other medicinal products is low.

The steady-state pharmacokinetics of telbivudine were unaltered following administration in combination with lamivudine, adefovir dipivoxil, ciclosporin or pegylated interferon-alfa 2a. In addition, telbivudine does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil or ciclosporin. No definitive conclusions could be drawn regarding the effects of telbivudine on the pharmacokinetics of pegylated interferon-alfa 2a due to the high interindividual variability of pegylated interferon-alfa 2a concentrations (see "**Warnings and Precautions**").

In addition, telbivudine did not have a negative effect on the AUC of ciclosporin even though a slight, 16% increase in C_{max} was noted (783 ± 135 ng/ml alone vs 908 ± 173 ng/ml in combination with telbivudine). This obvious effect lies within the range of interindividual variability of the C_{max} of ciclosporin (CV% = 17%) and was therefore not considered to be clinically significant.

Although pegylated interferon-alfa 2a shows great variability, no significant pharmacokinetic interaction was found between telbivudine and pegylated interferon-alfa 2a. Exposure to pegylated interferon-alfa 2a, when administered alone, resulted in a C_{max} of 8.0 ± 5.5 ng/ml and an AUC of 957 ± 658 ng×hours/ml. When telbivudine was concomitantly administered, the C_{max} was 11.4 ± 8.3 ng/ml and the AUC was 1343 ± 1010 ng×hours/ml. Mean C_{max} was 164% (90% CI: 94.2-287.0) and mean AUC was 140% (90% CI: 78.0-249.8). The clinical relevance of the increase in the mean value, with marked scatter, is unclear.

A pilot clinical trial investigating the combination of 600 mg telbivudine daily with 180 µg pegylated interferon alfa-2a once weekly, by subcutaneous administration, indicated that this combination is associated with an increased risk of developing peripheral neuropathy. The combination therapy was discontinued because of peripheral neuropathy occurring in 8 out of 48 patients (severe in 5 cases). Clinical results are currently unknown (see "**Contraindications**" and "**Warnings and Precautions**").

Pregnancy/Lactation

Pregnancy

No clinical data are available on exposure to telbivudine during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development (see "**Preclinical data**"). Sebivo should not be used in pregnancy unless it is absolutely necessary.

There are no data on the effect of telbivudine on transmission of HBV from mother to infant.

Therefore, appropriate measures should be used to prevent neonatal acquisition of HBV infection.

Women of childbearing potential

No special requirements.

Lactation

Telbivudine is excreted in the milk of rats. It is not known whether telbivudine is also excreted in human milk. Women should not breastfeed if they are taking Sebivo.

Effects on ability to drive and use machines

Patients who experience dizziness or fatigue during Sebivo therapy should not drive or use machines.

Adverse effects

In clinical studies, approximately 1500 subjects have been treated with telbivudine at doses of 600 mg/day. Assessment of adverse effects is primarily based on two studies (007 GLOBE study and study NV-02B-015) in which 1699 patients with chronic hepatitis B received double-blind treatment with 600 mg telbivudine per day (n = 847) or 100 mg lamivudine per day (n = 852) for 104 weeks.

In the 104 weeks of the clinical studies, most adverse effects were classified as mild or moderate in severity. In the 007 GLOBE study and study NV-02B-015, treatment was discontinued in 1.5% of patients on telbivudine and 4.1% of patients on lamivudine due to adverse effects, clinical disease progression or lack of efficacy. Common adverse effects, whether or not associated with telbivudine, were infections of the upper respiratory tract (15.2%), nasopharyngitis (19.2%), fatigue (12.5%), headache (9.8%) and elevated blood levels of creatine kinase (10.6%). Common adverse effects, whether or not associated with lamivudine, were headache (11.2%), infections of the upper respiratory tract (14.3%), nasopharyngitis (16.0%) and fatigue (11.2%).

Clinical adverse effects seen in the pooled 104-week 007 GLOBE and NV-02B-015 studies – which are at least potentially treatment-related – are listed below:

Frequencies

Very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10 000 to <1/1000), very rare (<1/10 000).

Nervous system disorders
Common: Dizziness, headache.
Uncommon: Peripheral neuropathy.

Gastrointestinal disorders
Common: Increased serum amylase, diarrhoea, increased serum lipase, nausea.

Hepatobiliary disorders
Common: Increased serum alanine aminotransferase.
Uncommon: Increased serum aspartate aminotransferase.

Skin disorders
Common: Rash.

Musculoskeletal disorders
Common: Increased serum creatine kinase.
Uncommon: Myopathy, myositis, arthralgia, myalgia.

General disorders
Common: Fatigue.
Uncommon: Malaise

Creatine kinase (CK) elevation

Serum creatine kinase (CK) elevations occurred in both treatment arms. Median CK levels were higher in patients treated with telbivudine. In the pooled analysis of the 007 GLOBE and NV-02B-015 studies, 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.

Most CK elevations were asymptomatic and CK values 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.

Table 2: Percentage of patients with new grade 3/4 CK elevations* at 6-month intervals (007 GLOBE study)

Period**	Telbivudine 600 mg (n = 680)	Lamivudine 100 mg (n = 687)
Week 0 to week 24	1.8%	1.5%
Week 24 to week 52	6.3%	1.9%
Week 52 to week 76	3.8%	0.5%
Week 76 to week 104	5.6%	1.0%
In total	12.9%	4.1%

* New CK elevations are defined as grade 3 or 4 CK elevations during therapy when a normal or lower CK grade was present prior to the start of treatment.

** Patients with multiple grade 3/4 CK episodes occurring in more than one period were counted once in each period.

In an open-label study in 2206 Chinese patients (CLDT600ACN03), grade 3/4 CK elevations were reported in 3.1% of telbivudine-treated patients by week 52.

Alanine aminotransferase (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 treatment arms after week 24, with a lower incidence in the telbivudine arm (2.0%) than in the lamivudine arm (5.3%; see table 3). Regular 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

ALT flare category[1]	**Telbivudine 600 mg (n = 847)**	**Lamivudine 100 mg (n = 852)**
In total	4.8%	7.9%
Baseline to week 24	3.0%	2.9%
Weeks 24-52	0.4%	1.7%
Weeks 52-76	0.7%	2.0%
Weeks 76-104	1.3%	2.0%-
Week 24 to end of treatment	2.0%	5.3%

[1] Aminotransferase flares to >10 × upper limit of normal and >2 × baseline.

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 "**Properties and Actions**") 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 of data 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 2 cases of myositis were reported in the 655 telbivudine-treated patients.

Exacerbations of hepatitis B after discontinuation of treatment

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy. There are insufficient data on exacerbations of hepatitis B after discontinuation of telbivudine treatment (see "**Warnings and Precautions**").

Postmarketing experience

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

Musculoskeletal disorders

There have been very rare reports of rhabdomyolysis.

Overdose

No case of overdose with Sebivo has been reported. Tested doses of up to 1800 mg/day, i.e. three times higher 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 measures applied as necessary.

Properties and Actions

ATC code: J05AF11, Antiviral for systemic use

Mechanism of action/Pharmacodynamics

Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase. It is efficiently phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours. Telbivudine-5'-triphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5'-triphosphate. Incorporation of telbivudine-5'-triphosphate into viral DNA causes DNA chain termination, resulting in inhibition of HBV replication. Telbivudine is an inhibitor of both HBV first-strand (EC_{50} = 0.4-1.3 µM) and second-strand (EC_{50} = 0.12-0.24 µM) synthesis, and shows a distinct preference for inhibiting second-strand production. By contrast, telbivudine-5'-triphosphate at concentrations up to 100 µM did not inhibit human cellular DNA polymerases alpha, beta, or gamma. In assays relating to human mitochondrial structure, function and DNA content, telbivudine lacked an appreciable toxic effect at concentrations up to 10 µM and did not increase lactic acid production *in vitro*.

The *in vitro* antiviral activity of telbivudine was assessed in the HBV-expressing human hepatoma cell line 2.2.15, as well as in primary duck hepatocytes infected with duck hepatitis B virus (DHBV). The concentration of telbivudine that effectively inhibited 50% of viral synthesis (EC_{50}) in both systems was approximately 0.2 µM. The antiviral activity of telbivudine is specific to hepatitis B virus and related hepadnaviruses. No activity was noted against multiple other RNA and DNA viruses, including human immunodeficiency virus (HIV) type 1 (EC_{50} value >200 µM). The *in vitro* data showing no telbivudine activity against HIV require clinical evaluation.

In 4- and 12-week studies of hepadnavirus-infected woodchucks (Marmota monax), 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 8 $\log_{10}$ to undetectable levels (<300 copies/ml by PCR). Following telbivudine withdrawal, viral rebound occurred within four weeks. When telbivudine was given orally to woodchucks at lower doses (1 mg/kg/day) for 12 weeks, viral load reductions of at least 6 $\log_{10}$ were seen in all telbivudine-treated animals.

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 an intermediate leading to the emergence of the L180M/M204V lamivudine resistant strain. In cell-based studies, telbivudine activity was reduced by at least 1049 times as compared with lamivudine-resistant HBV strains containing either the M204I mutation or the L180M/M204V double mutation.
In cell cultures, telbivudine showed 2-fold enhanced activity against HBV containing the N236T mutation, and wild type activity against HBV containing the A181T mutation, the most common adefovir-resistance mutations in HBV-infected patients.
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 cultures. The *in vitro* data showing no telbivudine activity against HIV require clinical evaluation.
There has been no clinical experience with telbivudine in patients with HIV infection or HIV/HBV co-infection.

Clinical efficacy
The safety and efficacy of long term telbivudine treatment (104 weeks) were evaluated in two active-controlled clinical studies (007 GLOBE and NV-02B-015) in 1699 patients with chronic hepatitis B. The patients were 16 years of age or older, with chronic hepatitis B confirmed by liver biopsy. They showed evidence of HBV infection with viral replication (HBsAg-positive, HBeAg-positive or HBeAg-negative, HBV DNA detectable by PCR assay), and had elevated ALT levels ≥1.3 times the upper limit of normal (ULN).
Patients showing evidence of hepatic decompensation or co-infection with the hepatitis C virus (HCV), the hepatitis D virus (HDV) or HIV were excluded from the studies.

007 "GLOBE" study
The 007 "GLOBE" study is a randomized, double-blind, multinational, phase III study that compared 600 mg telbivudine once daily with 100 mg lamivudine once daily for a period of 104 weeks in the treatment of 1367 nucleoside-naive 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 ≥7, mean serum HBV DNA as measured by Roche COBAS Amplicor® PCR assay was 9.52 $\log_{10}$ copies/ml, and mean serum ALT was approximately 153 IU/litre. Pre- and post-liver biopsy samples were adequate for 86% of patients.

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

007 GLOBE – Clinical results at weeks 52 and 104
Clinical and virological efficacy parameters were evaluated separately in the HBeAg-positive and HBeAg-negative patient populations in Study 007. The primary endpoint of therapeutic response at week 52 is a composite serological endpoint, defined as suppression of HBV DNA to <5 $\log_{10}$ copies/ml in conjunction with either loss of serum HBeAg (in HBeAg-positive patients) or ALT normalization (in HBeAg-negative patients). Secondary endpoints included histological response, ALT normalization, and various measures of antiviral efficacy. After 52 weeks, telbivudine was superior to lamivudine in terms of therapeutic response in HBeAg-positive patients (75% vs 67% responders; 95.68% CI*: 2.4, 14.2; p = 0.0047). In HBeAg-negative patients, telbivudine was shown to be non-inferior to lamivudine (75% vs 77% responders; 95% CI*: -10.6, 5.7; p = 0.6187). In addition, selected virological, biochemical and serological outcome measures are shown in table 4. In both the HBeAg-positive and HBeAg-negative patient populations, telbivudine was superior to lamivudine for antiviral efficacy, as assessed by HBV DNA suppression. Telbivudine showed a greater reduction than lamivudine in viral load as early as week 12 in HBeAg-positive patients (p = 0.0157) and week 8 in HBeAg-negative patients (p = 0.0242).
*: 2-sided control intervals (CI) for the treatment difference (telbivudine-lamivudine)

Table 4: Virological, biochemical and serological endpoints at weeks 52 and 104 (007 GLOBE study)

Response parameter	HBeAg-positive (n = 921)				HBeAg-negative (n = 446)			
	Sebivo 600 mg (n = 458)		Lamivudine 100 mg (n = 463)		Sebivo 600 mg (n = 222)		Lamivudine 100 mg (n = 224)	
Time (week)	52	104	52	104	52	104	52	104
Mean HBV DNA reduction from baseline ($\log_{10}$ copies/ml) ± SEM[1]	-6.45 (0.11)	-5.74 (0.15)	-5.54 (0.11)	-4.42 (0.15)	-5.23 (0.13)	-5.00 (0.15)	-4.40 (0.13)	-4.17 (0.16)
% Patients HBV DNA undetectable by PCR	60%	56%	40%	39%	88%	82%	71%	57%
ALT normalization[2]	77%	70%	75%	62%	74%	78%	79%	70%
HBeAg seroconversion[3]	23%	30%	22%	25%	NA	NA	NA	NA
HBeAg loss[3]	26%	35%	23%	29%	NA	NA	NA	NA
Therapeutic response	75%	63%	67%	48%	75%	78%	77%	66%

[1] Roche COBAS Amplicor® Assay (lower limit of quantification [LLOQ] ≤300 copies/ml)
[2] ALT normalization assessed only in patients with ALT >ULN at baseline.
[3] HBeAg seroconversion and loss assessed only in patients with undetectable HBeAg at baseline.

Telbivudine was superior to lamivudine in HBeAg-positive patients for the key secondary endpoint of histological response, as shown in table 5. In HBeAg-negative patients telbivudine was shown to be statistically non-inferior to lamivudine for histological response.

Table 5: Histological improvement and change in Ishak Fibrosis Score at week 52 (007 GLOBE study)

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

[1] Patients with ≥1 dose of study drug with evaluable baseline liver biopsies and baseline Knodell Histological Activity Index (HAI) score >3
[2] Histological response defined as ≥2 point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score
[3] For Ishak Fibrosis Score, improvement defined as a ≥1 point reduction in Ishak Fibrosis Score from baseline to week 52
*p = 0.0024

007 GLOBE – Subpopulation considering baseline characteristics and week 24 HBV DNA, excluding patients with detectable HBV DNA after 2 years
Patients who had achieved non-detectable HBV DNA levels at week 24 were more likely to undergo e-antigen seroconversion and achieve undetectable levels of HBV DNA, normalized ALT, and minimized resistance after one and two years.
Efficacy in 007 GLOBE study patients (n = 680) was assessed by baseline factors (HBV DNA <9 $\log_{10}$ copies/ml and ALT ≥2 × ULN for HBeAg-positive, and HBV DNA <7 $\log_{10}$ copies/ml for HBeAg-negative patients), considering only those patients with undetectable serum HBV DNA levels at week 24 and after 2 years. Undetectable HBV DNA rates were 96.5% for HBeAg-negative and 97.7% for HBeAg-positive patients at week 52, and 90.4% for HBeAg-negative and 92.9% for HBeAg-positive patients at week 104 (Table 6).

Table 6: Efficacy response and resistance rates at weeks 52 and 104 by baseline factors and on-treatment response at week 24 (007 GLOBE)

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

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

Study NV-02B-015
Study NV-02B-015 confirmed the safety and efficacy findings of the GLOBE (NV-02B-007) study. Study NV-02B-015 is a randomized, double-blind, phase III study that compared 600 mg telbivudine once daily with 100 mg lamivudine once daily for a period of 104 weeks in the treatment of 332 nucleoside-naive chronic hepatitis B HBeAg-positive and HBeAg-negative Chinese patients (summarized in table 7).

Table 7: Virological, biochemical and serological endpoints and therapeutic response at weeks 52 and 104 (NV-02B-015 study)

Response parameter	HBeAg-positive (n = 147)				HBeAg-negative (n = 42)			
	Telbivudine 600 mg (n = 147)		Lamivudine 100 mg (n = 142)		Telbivudine 600 mg (n = 20)		Lamivudine 100 mg (n = 22)	
Time (week)	52	104	52	104	52	104	52	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)
% Patients HBV DNA undetectable by PCR	67%*	58%*	38%	34%	85%	90%	77%	68%
ALT normalization[2]	87%	73%	75%	59%	100%	95%	78%	78%
HBeAg seroconversion[3]	25%	29%	18%	20%	NA	NA	NA	NA
HBeAg loss[3]	31%	40%	20%	28%	NA	NA	NA	NA
Therapeutic response	85%*	66%*	62%	41%	100%	90%	82%	68%

[1] Roche COBAS Amplicor® Assay (LLOQ ≤300 copies/ml)
[2] n = 142/18 and 135/18 for telbivudine and lamivudine groups, respectively. ALT normalization 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 patients who were previously treated in studies 007 GLOBE or NV-02B-015. A subset of 502 patients (293 HBeAg-posi-

tive and 209 HBeAg-negative, excluding those with virological breakthrough and confirmed genotypic resistance at entry into study CLDT600A2303) were analyzed. At weeks 156 and 208, the majority of patients had undetectable HBV DNA levels (<300 copies/ml) and normalized ALT. Patients with undetectable HBV DNA at week 24 had better outcomes at 156 and 208 weeks (see table 8).

Table 8: Virological, biochemical and serological endpoints up to week 208 (CLDT600A2303 study)

	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) in patients with undetectable HBV DNA at week 24 (n = 162)	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 (n = 162)	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% (178/106)
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% (141/164)
Maintained undetectable HBV DNA (<300 copies/ml) with undetectable HBV DNA at week 24 (n = 179)	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)

Liver histology response – Study CLDT600ACN04E1

In study CLDT600ACN04E1, 57 patients with paired liver biopsies (at baseline and after 5 years of telbivudine treatment) were evaluated for changes in liver histology. The Knodell necroinflammatory and Ishak fibrosis scores showed a statistically significant improvement versus baseline (see table 9). After treatment 98.2% of patients had no or minimal liver necroinflammation (Knodell necroinflammatory score ≤3), and 84.2% of patients had no or minimal liver fibrosis (Ishak fibrosis score ≤1).

Table 9: Improvement in liver histology in patients after 5 years of telbivudine treatment

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

Off-treatment durability of 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 patients showed sustained HBeAg loss (83.03%), 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.

Glomerular filtration rate (GFR) – Studies 007 GLOBE and CLDT600A2303

The glomerular filtration rate (GFR) analysis from 007 GLOBE and CLDT600A2303 showed no renal toxicity with telbivudine treatment. Renal function improved steadily over 104 weeks of telbivudine treatment; in particular, a majority (72.3%, 185/256) of patients with baseline GFR 60 to 90 ml/minute increased to >90 ml/minute/1.73 m^2. None of these patients experienced worsening of renal function to GFR <60 ml/minute/1.73 m^2. MDRD-calculated GFR had increased by 11.3 ml/minute/1.73 m^2 after 104 weeks of treatment with Sebivo. Improvement in renal function in the CLDT600A2303 study patients continued with a mean increase of 14.9 ml/minute/1.73 m^2 at 208 weeks vs baseline.

Clinical resistance

Cumulative genotypic resistance rates – NV-02B-007 (GLOBE) and CLDT600A2303

The original analysis for cumulative genotypic resistance at week 104 and 208 was based on patients who continued treatment until 4 years, regardless of HBV DNA levels. Of the original 680 telbivudine-treated patients in the 007 GLOBE study, 517 (76%) were enrolled in study CLDT600A2303 and continued treatment with telbivudine until week 208. Of these 517 patients, 159 (135 HBeAg-positive, 24 HBeAg-negative) had detectable HBV DNA.

The cumulative genotypic rates by week 104 were 25.1% (115/458) for HBeAg-positive patients and 10.8% (24/222) for HBeAg-negative patients.

In the overall population the cumulative genotypic rates at year 4 were 40.8% (131/321) for HBeAg-positive and 18.9% (37/196) for HBeAg-negative patients.

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. Cumulative resistance rates at year 4 were 22.3% for HBeAg-positive patients and 16.0% for HBeAg-negative patients in this analysis.

Among patients with viral breakthrough by 104 weeks in the NV-02B-007 GLOBE study, the rate of resistance was lower in patients with HBV DNA <300 copies/ml at week 24 than in patients with HBV DNA ≥300 copies/ml at week 24. In HBeAg-positive patients with HBV DNA <300 copies/ml at week 24, resistance was 1% (3/203) at week 48 and 9% (18/203) at week 104, whilst in patients with HBV DNA ≥300 copies/ml resistance was 8% (20/247) at week 48 and 39% (97/247) at week 104. In HBeAg-negative patients with HBV DNA <300 copies/ml at week 24, resistance was 0% (0/177) at week 48 and 5% (9/177) at week 104, whilst in patients with HBV DNA ≥300 copies/ml resistance was 11% (5/44) at week 48 and 34% (15/44) at week 104.

Genotypic mutation pattern

In the Phase III global registration study (007 GLOBE study), 55.7% (255/458) of treatment-naive HBeAg-positive patients and 82.0% (182/222) of treatment-naive HBeAg-negative patients receiving 600 mg telbivudine once daily achieved non-detectable serum HBV DNA levels (<300 copies/ml) at week 104.

Genotypic analysis of 203 evaluable sample pairs with HBV-DNA ≥1000 copies/ml showed that the primary mutation associated with telbivudine resistance, rtM204I, was often associated with mutations rtL180M and rtL80I/V and rarely 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. Treatment-related parameters at week 24 that predicted emergence of drug resistant virus at week 104 included HBV DNA >300 copies/ml and elevated serum ALT.

Genotypic analysis from telbivudine-treated patients at week 208 (CLDT600A2303) showed no novel mutation.

Cross-resistance

Cross-resistance has been observed among HBV nucleoside analogues. Tests in cell cultures showed that lamivudine-resistant HBV strains containing either the rtM204I mutation or the rtL180M/rtM204V double mutation showed a greater than 1000-fold reduced susceptibility to telbivudine. HBV encoding the adefovir resistance-associated substitutions at rtN236T and A181V showed a 0.5- and 1.0-fold change, respectively, in susceptibility to telbivudine in cell cultures. Substitution at rtA194T produced a 0.99-fold shift in susceptibility to telbivudine in cell cultures. Very similar IC50 values for telbivudine and lamivudine against these mutant strains in *in vitro* studies mean that no efficacy can be expected from telbivudine in patients with established lamivudine resistance. Therefore, until further clinical data become available, such patients should only be treated with telbivudine in the context of a well controlled clinical study.

ALT flares

In the pooled 007 GLOBE and NV-02B-015 studies, the incidence of alanine aminotransferase (ALT) flares was similar in the telbivudine and lamivudine treatment arms during the first six months of treatment, but was lower for telbivudine after week 24 (see “**Adverse effects**”).

Cardiac safety

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

Pharmacokinetics

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

Absorption and bioavailability

Following oral administration of 600 mg telbivudine once daily in healthy subjects (n = 12), steady state peak plasma concentrations (C_{max}) of 3.69 ± 1.25 µg/ml (mean ± SD) were reached after 1-4 hours (median 2 hours). The AUC was 26.1 ± 7.2 µg×hours/ml (mean ± SD), and trough plasma concentrations (C_{trough}) were approximately 0.2-0.3 µg/ml. Steady state was achieved, after approximately 5 to 7 days of once-daily administration, with an approximately 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 8.2 ± 4.1 litres/kg, which is in excess of total body water. Telbivudine was equally partitioned between plasma and blood cells.

Metabolism

No metabolites of telbivudine were detected following administration of 14C-telbivudine in humans. Telbivudine is not a substrate, inhibitor or inducer of the cytochrome P450 (CYP450) enzyme system (see “**Interactions**”).

Elimination

After reaching a peak, plasma concentrations of telbivudine decline in a bi-exponential manner with an initial distribution/elimination half-life of 2.0 ± 0.3 hours and a terminal elimination half-life ($t_{1/2}$) of 40-49 hours. The AUC under the terminal phase represents <10% of $AUC_{0\text{-}INF}$. Plasma levels generally fall to about 5% of C_{max} 24 hours after dose administration, and systemic exposure during this phase is 80-85% of total exposure ($AUC_{0\text{-}INF}$). Telbivudine is eliminated primarily by urinary excretion of unchanged substance. The renal clearance of telbivudine approaches the normal glomerular filtration rate, suggesting that passive diffusion is the main mechanism of excretion. Following a single oral dose of 600 mg, about 42% of the dose is excreted over the following 7 days in the urine as unchanged telbivudine, with 36% of the dose being excreted within the first 24 hours. Because renal excretion is the predominant route of elimination, patients with moderate to severe renal impairment and those undergoing haemodialysis require dose adjustment (see “**Dosage and Administration**”).

Pharmacokinetics in special patient populations

Sex

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

Race

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

Paediatrics and geriatrics

Pharmacokinetic studies have not been conducted in paediatric or elderly patients.

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 10, adjustment of the dose of telbivudine is recommended in patients with creatinine clearance <50 ml/minute (see “**Dosage and Administration**”).

Table 10: Pharmacokinetic parameters (mean ± SD) of telbivudine in patients with various degrees of renal impairment

	Renal function (creatinine clearance in ml/minute)				
	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/Haemodialysis (n = 6) 200 mg
C_{max} (µg/ml)	3.4±0.9	3.2±0.9	2.8±1.3	1.6±0.8	2.1±0.9

AUC$_{0\text{-INF}}$ (µg×hours/ ml)	28.5±9.6	32.5±10.1	36.0±13.2	32.5±13.2	67.4±36.9
CL$_{\text{RENAL}}$ (litres/ hour)	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 adjustment for creatinine clearance, no additional dose modification is necessary during routine haemodialysis (see "**Dosage and Administration**"). Telbivudine should be administered after haemodialysis.

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 with unimpaired subjects. Results of these studies indicate that no dosage adjustment is necessary for patients with hepatic impairment (see "**Dosage and Administration**").

Preclinical 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 humans given a 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 toxicity studies, there was no evidence of impaired fertility when either male or female rats given telbivudine at doses up to 2000 mg/kg/day (systemic exposure approximately 14 times that reached at therapeutic doses in humans) mated with untreated rats.

A separate study indicated reduced fertility when both male and female rats were given telbivudine at doses of 500 or 1000 mg/kg/day. A lower fertility index was noted in pairs given 500 (76%) or 1000 (72%) mg/kg/day, as compared with similar controls (92%). There were no abnormalities in sperm morphology or function, and the testes and ovaries were histologically unremarkable. Systemic exposure in rats was 2.5 times higher than in humans given the same therapeutic dose.

Telbivudine is not teratogenic and showed 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 given doses of up to 1000 mg/kg/day, with exposure levels 6 to 37 times higher, respectively, than those observed with the therapeutic dose (600 mg/day) in humans.

Cardiac safety
There is no evidence that telbivudine is cardiotoxic. In an *in vitro* hERG model, telbivudine was negative at concentrations of up to 10 000 µM.

Other information

Shelf-life
Do not use after the expiry date (= EXP) printed on the pack.
Oral solution: Once the bottle has been opened, the contents must be used within 2 months.

Special precautions for storage
Store in the original package. Keep out of the reach of children.

Film-coated tablet
Do not store above 30°C.

Oral solution
Do not store above 30°C. Do not freeze.
Instructions for use and handling
No special requirements.

Pack sizes

Country specific pack sizes.

Manufacturer

See folding box.

Information last revised

March 2013

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This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists