NOVARTIS

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו באוגוסט2017

SEBIVO®

(telbivudine)

600 mg film coated tablets

Prescribing Information

1 Name of the medicinal product

SEBIVO®.

2 Qualitative and quantitative composition

Each film-coated tablet contains 600 mg telbivudine.

For the full list of excipients, see section 6.1.

The product contains less than 1mMol sodium (23mg) per tablet.

3 Pharmaceutical form

Film-coated tablet.

White to slightly yellowish, oval film-coated tablet, imprinted with “LDT” on one side.

4 Clinical particulars

4.1 Therapeutic indications

Sebivo is indicated for the treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation in adults over 16 years of age.

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

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

4.2 Posology and method of administration

Therapy must be initiated by a physician experienced in the management of chronic hepatitis B infection in adults over 16 years of age.

Adults

The recommended dose of Sebivo for the treatment of chronic hepatitis B is 600 mg once daily.

Due to risk of higher rates of resistance that may develop with longer term treatment among patients with incomplete viral suppression, treatment should only be initiated after baseline HBV DNA criteria are met (see section 4.1 Therapeutic indication).

Monitoring and duration of treatment

On-treatment response at week 24 has been shown to be predictive of longer-term response (see section 5.1 Pharmacodynamic properties). HBV DNA levels should be monitored at 24 weeks of treatment to assure complete viral suppression (HBV DNA less than 300 copies/mL). Alternate therapy should be initiated for patients who have detectable HBV DNA after 24 weeks of treatment.

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, alternate treatment should be instituted. Optimal treatment should be guided by resistance testing.

The optimal treatment duration has not been established.

Renal impairment/insufficiency

Sebivo may be used for the treatment of chronic hepatitis B in patients with impaired renal function. No adjustment of the recommended dose of telbivudine is necessary in patients whose creatinine clearance is ≥50 mL/min. Dose adjustment is required in patients with creatinine clearance <50 mL/min including those with end stage renal disease (ESRD) on haemodialysis. Dose adjustment may be achieved by changing of the tablet dose interval as shown below:

Table 1 Dose adjustment of Sebivo in patients with renal impairment

Creatinine clearance (mL/min)	**Tablet Dose (1 tablet = 600 mg)**
≥50	600 mg once daily
30 – 49	600 mg once every 48 hours
<30 (not requiring dialysis)	600 mg once every 72 hours
ESRD*	600 mg once every 96 hours

* End stage renal disease

The proposed dose modification is based on extrapolation and may not be optimal. The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, close clinical monitoring is recommended in these patients.

End Stage Renal Disease (ESRD) patients

For patients with ESRD, Sebivo should be administered after haemodialysis (see section 5.2 Pharmacokinetic properties).

Hepatic impairment

No adjustment of the recommended dose of Sebivo is necessary in patients with hepatic impairment (see section 5.2 Pharmacokinetic properties).

Paediatric patients (age below 16 years)

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

Elderly patients (age above 65 years)

No data are available to support a specific dose recommendation for patients over the age of 65 years (see section 4.4 Special warnings and precautions for use).

Missed Doses

If a dose is missed, the patient may take the missed dose only up to 4 hours prior to the next scheduled dose. The next dose should be taken at the usual time.

Method of Administration

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

The tablet should not be crushed, split or crushed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Combination of telbivudine with pegylated or standard interferon alfa (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Severe acute exacerbations of chronic hepatitis B are relatively frequent, and are characterised 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 section 4.8). On average, 4-5 weeks elapsed prior to the occurrence of an exacerbation in patients treated with telbivudine. Overall, ALT flares occurred more frequently in HBeAg-positive patients than in HBeAg-negative patients. In patients with compensated liver disease, this elevation of serum ALT is generally not accompanied by elevated levels of serum bilirubin or by other signs of hepatic decompensation. The risk of hepatic decompensation – and of a subsequent exacerbation of hepatitis – may be elevated in patients with cirrhosis. Such patients should therefore be closely monitored.

Exacerbations of hepatitis have also been reported in patients who have terminated treatment of hepatitis B. Post-treatment ALT flares are normally associated with increases in serum HBV DNA levels, and the majority of such cases have proven to be self-limiting. Nonetheless, there have also been reports of severe – and sometimes fatal – post-treatment disease exacerbations. Therefore, hepatic function should be monitored at regular intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy.

Lactic acidosis

Rare post-marketing cases of lactic acidosis have been reported with telbivudine. Cases were

more often secondary to other serious conditions (e.g. rhabdomyolysis) and/or associated muscle-related events (e.g. myopathy, myositis). When secondary to other conditions, some cases were also associated with pancreatitis, liver failure/hepatic steatosis and renal failure. In some cases, fatal outcomes were reported when lactic acidosis was secondary to rhabdomyolysis. Patients should be followed closely.

Treatment with telbivudine should be discontinued when metabolic/lactic acidosis of unknown aetiology occurs. Benign digestive symptoms, such as nausea, vomiting and abdominal pain, may be indicative of lactic acidosis development.

Muscular effects

Cases of myopathy and myalgia have been reported with telbivudine use several weeks to months after starting therapy (see section 4.8). Cases of rhabdomyolysis have been reported during post-marketing use of telbivudine (see section 4.8).

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 diffuse unexplained myalgias, muscle tenderness , muscle weakness or myositis (defined as myopathy with histological evidence of muscle damage). Patients should be advised to report promptly any persistent unexplained muscle aches, pain, tenderness or weakness. If any of these symptoms are reported, a detailed muscle examination should be performed in order to evaluate muscle function. Telbivudine therapy should be discontinued if myopathy is diagnosed.

It is not known whether the risk of myopathy during treatment with telbivudine is increased with concurrent administration of other medicinal products associated with myopathy (e.g. statins, fibrates, or ciclosporin). 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 suggestive of myopathy.

Peripheral neuropathy

Peripheral neuropathy has been uncommonly reported in telbivudine-treated patients. If peripheral neuropathy is suspected, treatment with telbivudine should be reconsidered (see section 4.8).

An increased risk of developing peripheral neuropathy has been observed in one study when telbivudine and pegylated interferon alfa-2a were co-administered (see section 4.5). Such increased risk cannot be excluded for other interferon alfa (pegylated or standard). Moreover, the benefit of the combination of telbivudine with interferon alfa (pegylated or standard) is not currently established.
Therefore, the combination of telbivudine with pegylated or standard interferon alfa is contraindicated (see section 4.3).

Renal function

Telbivudine is eliminated primarily by renal excretion, therefore dose interval adjustment is recommended in patients with creatinine clearance <50 mL/min, including patients on haemodialysis. The effectiveness of dosing interval adjustment has not been clinically evaluated. Therefore, virological response should be closely monitored in patients with increased dosage interval (see sections 4.2 and 5.2).

Patients with cirrhosis without decompensation

Due to the limited data available (about 3% of patients enrolled had cirrhosis), telbivudine should be used with particular caution in cirrhotic patients. These patients should be closely monitored for clinical, biochemical and virological parameters associated with hepatitis B during treatment and after treatment is discontinued.

Patients with cirrhosis with decompensation

There are no adequate efficacy and safety data in patients with decompensated cirrhosis. Sebivo is not indicated in patients with decompensated cirrhosis.

Patients with previous exposure to nucleoside/nucleotide analogues

In vitro, telbivudine was not active against the HBV strains containing rtM204V/rtL180M or rtM204I mutations (see section 5.1). Telbivudine monotherapy is not an option for patients with established lamivudine-resistant hepatitis B virus infection. Patients who failed to achieve virological response following treatment with lamivudine for more than 24 weeks are unlikely to benefit from telbivudine monotherapy. There is currently no clinical data to properly assess the benefit and risk of switching to telbivudine for lamivudine-treated patients who achieve complete viral suppression on lamivudine.
There are no data on telbivudine treatment in patients with established adefovir-resistant hepatitis B virus single mutations of rtN236T or A181V. Results from cell-based assays showed that the adefovir resistance-associated substitution A181V had 1.5- to approximately 4-fold reduced susceptibility to telbivudine.

Liver transplant recipients

The safety and efficacy of telbivudine in liver transplant recipients are unknown.

Elderly

Clinical studies of telbivudine did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger subjects. In general, caution must be exercised when prescribing Sebivo to older 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 human immunodeficiency virus [HIV], hepatitis C virus [HCV] or hepatitis D virus [HDV]).

General

Patients should be advised that treatment with Sebivo has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination.
Telbivudine is not recommended to be used with lamivudine because in a phase II study, the treatment response observed with combination therapy of telbivudine and lamivudine was lower than with telbivudine alone.

There are currently no efficacy and safety data for other antiviral combinations with telbivudine.

4.5 Interaction with other medicinal products and other forms of interaction

Since telbivudine is eliminated primarily by renal excretion, co-administration of Sebivo with substances that affect renal function (such as aminoglycosides, loop diuretics, platinum compounds, vancomycin, amphotericin B) may affect plasma concentrations of telbivudine and/or the co-administered substance. The combination of telbivudine with these medicinal products should be used with caution.

The steady-state pharmacokinetics of telbivudine were unaltered following multiple dose administration in combination with lamivudine, adefovir dipivoxil, tenofovir disoproxil fumarate , ciclosporin or pegylated interferon-alfa 2a. In addition, telbivudine does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil, tenofovir disoproxil fumarate or ciclosporin. No definitive conclusion could be drawn regarding the effects of telbivudine on the pharmacokinetics of pegylated interferon due to high interindividual variability of pegylated interferon-alfa 2a concentrations.
A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see section 4.4). The combination of telbivudine with any interferon alfa-containing product is contraindicated (see section 4.3).

Telbivudine is not a substrate, inhibitor or inducer of the cytochrome P450 (CYP450) enzyme system (see section 5.2). Therefore, the potential for CYP450-mediated drug interactions involving Sebivo is low.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Studies in pregnant rats and rabbits showed that telbivudine crosses the placenta. Studies in pregnant rabbits showed early delivery and/or abortion secondary to maternal toxicity.

Limited clinical data (less than 300 pregnancy outcomes) after exposure to telbivudine during the first trimester of pregnancy indicate no malformative toxicity and a large amount of data (more than 1000 pregnancy outcomes) after exposure during the second and third trimesters indicate no foetal/neonatal toxicity.

Sebivo should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

Literature shows that exposure to telbivudine in the second and/or third trimester of pregnancy has been shown to reduce the risk of HBV transmission from mother to infant if telbivudine is given in addition to Hepatitis B immune globulin and Hepatitis B vaccine.

Breast-feeding

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

Fertility

There are no clinical data on the effects of telbivudine on male or female fertility. In reproductive toxicology studies in adult animals, fertility was slightly reduced when both male and female rats received telbivudine. The adverse effects on fertility were greater in a separate study in juvenile animals when both sexes received telbivudine (see section 5.3).

4.7 Effects on ability to drive and use machines

Sebivo has minor influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is mainly based on two studies NV-02B-007 (GLOBE) and NV-02B-015, in which 1,699 patients with chronic hepatitis B received double-blind treatment with telbivudine 600 mg/day (n = 847) or lamivudine (n = 852) for 104 weeks. In the 104- week clinical studies, reported adverse reactions were usually classified as mild or moderate in severity. The most common adverse reactions were grade 3 or 4 blood creatine kinase elevations (6.8%), fatigue (4.4%), headache (3.0%) and nausea (2.6%).

Tabulated list of adverse reactions

Table 2 lists the adverse reactions according to MedDRA system organ class and frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse reactions

Metabolism and nutrition disorders	
Rare*	Lactic acidosis
Nervous System Disorders	
Common	Dizziness, headache
Uncommon	Peripheral neuropathy, dysgeusia, hypoaesthesia, paresthesia, sciatica
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Gastrointestinal Disorders	
Common	Diarrhoea, blood lipase increased, nausea, abdominal pain
Skin and subcutaneous tissue disorders	
Common	Rash
Musculoskeletal and connective tissue disorders	
Uncommon	Myopathy/myositis, arthralgia, myalgia, pain in the extremities, back pain, muscle spasm, neck pain, flank pain
Rare*	Rhabdomyolysis
General disorders and administration site conditions	
Common	Fatigue
Uncommon	Malaise
Investigations	
Common	Blood creatine phosphokinase increased, blood alanine aminotransferase increased, blood amylase increased

Uncommon	Aspartate aminotransferase increased

* This adverse reaction was identified through post-marketing surveillance but not observed in controlled clinical trials. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to telbivudine in clinical trials (n = 8,914).

Description of selected adverse reactions

Creatine kinase elevation

In the pooled analysis from NV-02B-007 (GLOBE) and NV-02B-015, by 104 weeks of treatment grade 3 or 4 CK elevations (> 7x ULN) occurred in 12.6% of telbivudine-treated patients (n = 847) and 4.0% of lamivudine-treated patients (n = 846). Most CK elevations were asymptomatic and CK values typically decreased by the next visit on continued treatment.

ALT flares

The incidence of on treatment alanine aminotransferase (ALT) flares in the two treatment arms according to AASLD (American Association for the Study of Liver Diseases) definition (ALT elevation > 2x baseline and > 10x ULN) are further described in Table 3 below.

Table 3 Summary of on-treatment ALT flares pooled NV-02B-007 (GLOBE) and NV-02B-015 studies

ALT flare: ALT elevation > 2x baseline and > 10x ULN	Lamivudine n/N (%)	Telbivudine n/N (%)
Overall	67/852 (7.9)	41/847 (4.8)
Baseline to week 24	25/852 (2.9)	25/847 (3.0)
Week 24 to end of study	44/837 (5.3)	17/834 (2.0)

Periodic monitoring of hepatic function is recommended during treatment (see section 4.4).

Exacerbations of hepatitis B after discontinuation of treatment
Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy including telbivudine (see section 4.4).

The incidence of post-treatment alanine aminotransferase (ALT) flares in the two treatment arms are further described in Table 4 below.

Table 4 Summary of post-treatment ALT flares – Pooled NV-02B-007 (GLOBE) and NV-02B-015 studies

	Lamivudine	Telbivudine
ALT flare	n/N (%)	n/N (%)
ALT elevation > 2x baseline and > 10x ULN	10/180 (5.6)	9/154 (5.8)

Results at 208 weeks

After 104 weeks of telbivudine therapy, 78% of patients (530/680) from study NV-02B-007 (GLOBE) and 82% (137/167) of patients from study NV-02B-015 enrolled into the extension study CLDT600A2303 (see section 5.1) to continue treatment for up to 208 weeks. The long-term safety population consisted of 655 patients, including 518 from NV-02B-007 (GLOBE) and 137 from NV-02B-015.

The overall safety profile from the pooled analysis up to 104 and 208 weeks was similar. Grade 3 or 4 CK elevations newly occurred in 15.9% of patients treated with telbivudine for 208 weeks. Most grade 3 or 4 CK elevations were asymptomatic and transient.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic
@moh.gov.il

4.9 Overdose

There is no information on intentional overdose of telbivudine, but one subject was given an unintentional overdose which was asymptomatic. Tested doses up to 1,800 mg/day, three times greater than the recommended daily dose, have been well tolerated. A maximum tolerated dose of telbivudine has not been determined. In the event of an overdose, Sebivo should be discontinued and appropriate general supportive treatment applied as necessary.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF11.

Mechanism of action

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.

Pharmacodynamic effects

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 cellular DNA polymerases α, β, or γ. In assays relating to mitochondrial structure, function and DNA content, telbivudine lacked appreciable toxic effect at concentrations up to at 10 μM and did not increase lactic acid production in vitro.

The in vitro antiviral activity of telbivudine was assessed in the HBV-expressing human hepatoma cell line 2.2.15. The concentration of telbivudine that effectively inhibited 50% of viral synthesis (EC50) was approximately 0.2 μM. The antiviral activity of telbivudine is specific to the hepatitis B virus and related hepadnaviruses. Telbivudine was not active against HIV in vitro. The absence of activity of telbivudine against HIV has not been evaluated in clinical trials. Transient reductions in HIV-1 RNA have been reported in a small number of patients after administration of telbivudine in the absence of antiretroviral therapy. The clinical significance of these reductions has not been determined.

Clinical experience

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

Study NV-02B-007 (GLOBE)

The NV-02B-007 (GLOBE) study is a randomised, double-blind, multinational phase III study of telbivudine compared to lamivudine for a treatment period of 104 weeks in 1,367 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative patients. The majority of the population enrolled was Asian. The most common HBV genotypes were B

(26%) and C (51%). A small number (total of 98) of Caucasian patients were treated with telbivudine. 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 alfa-interferon therapy.

HBeAg-negative patients: The mean age of patients was 43 years, 79% were male, 65% were Asian, 23% were Caucasian, and 11% had previously received alfa-interferon therapy.

Clinical results at week 52

Clinical and virological efficacy endpoints were evaluated separately in the HBeAg-positive and HBeAg-negative patient populations. The primary endpoint of therapeutic response was a composite serological endpoint requiring suppression of HBV DNA to <5 log10 copies/mL in conjunction with either loss of serum HBeAg or ALT normalised. Secondary endpoints included histological response, ALT normalisation, and various measures of antiviral efficacy. Regardless of baseline characteristics, the majority of patients taking Sebivo showed histological, virological, biochemical, and serological responses to treatment. Baseline ALT levels > 2x ULN and baseline HBV DNA < 9 log10 copies/ml were associated with higher rates of HBeAg seroconversion in HBeAg-positive patients. Patients who achieve HBV DNA levels < 3 log10 copies/ml by week 24 had optimal responses to treatment; conversely patients with HBV DNA levels > 4 log10 copies/ml at 24 weeks had less favourable outcomes at week 52.

In HBeAg-positive patients, telbivudine was superior to lamivudine in therapeutic response (75.3% vs 67.0% responders; p = 0.0047). In HBeAg-negative patients, telbivudine was non-inferior to lamivudine (75.2% and 77.2% responders; p = 0.6187). Caucasian ethnicity was associated with lower treatment response to both antiviral agents used in the NV-02B-007 (GLOBE) study; however the Caucasian patient population was very limited (n = 98).

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

Selected virological, biochemical and serological outcome measures are shown in Table 5 and histological response in Table 6.

Table 5 Virological, biochemical and serological endpoints at week 52 in NV-02B-007 (GLOBE) study

	HBeAg-positive (n = 921)	HBeAg-negative (n = 446)

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

[1] SEM: Standard error of mean
[2] Roche COBAS Amplicor® PCR Assay (lower limit of quantification ≤ 300 copies/ml).
[3] HBeAg-positive n = 443 and 444, HBeAg-negative n = 219 and 219, for both telbivudine and lamivudine groups, respectively. The difference in populations is due to patient discontinuation from the study and missing HBV DNA assessment at week 52.
[4] HBeAg-positive n = 440 and 446, HBeAg-negative n = 203 and 207, for telbivudine and lamivudine groups, respectively. ALT normalisation assessed only in patients with ALT > ULN at baseline.
[5] n = 432 and 442, for telbivudine and lamivudine groups, respectively. HBeAg seroconversion and loss assessed only in patients with detectable HBeAg at baseline.
*$p < 0.0001$

Table 6 Histological improvement and change in Ishak Fibrosis Score at week 52 in NV-02B-007 (GLOBE) study

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

[1] Patients with ≥ one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Histological Activity Index (HAI) score >3

[2] Histological response defined as a ≥2 point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.

[3] For Ishak Fibrosis Score, improvement measured as ≥1 point reduction in Ishak Fibrosis Score from baseline to week 52.

*p = 0.0024

Clinical results at Week 104

Overall, clinical results at week 104 in telbivudine-treated patients were consistent with those at week 52, demonstrating durability of efficacy responses for telbivudine-treated patients with continued treatment.
Among HBeAg-positive patients, therapeutic response (63% vs 48%; p <0.0001), and key secondary endpoints (mean log10 HBV DNA reduction: -5.74 vs -4.42; p <0.0001, HBV DNA undetectability: 56% vs 39%; p <0.0001 and ALT normalisation of 70% vs 62%) demonstrated a widening difference at week 104 between telbivudine and lamivudine, respectively. A trend towards higher rates of HBeAg loss (35% vs 29%) and seroconversion (30% vs 25%) was also observed for telbivudine. Moreover, in the subgroup of patients with baseline ALT levels ≥ 2x ULN (320), a significantly higher proportion of telbivudine patients than lamivudine patients achieved HBeAg seroconversions at week 104 (36% vs 28%, respectively).

Among HBeAg-negative patients, differences in therapeutic response (78% vs 66%) and key secondary endpoints (mean log10 HBV DNA reduction: -5.00 vs -4.17, and HBV DNA undetectability: 82% vs 57%; p <0.0001) were higher for telbivudine up to week 104. ALT normalisation rates (78% vs 70%) continued to be higher by week 104.

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

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

Outcome results at week 104, based on level of HBV DNA at week 24, for either HBeAg-positive or HBeAg-negative patients are presented in Table 7.

Table 7 Key efficacy endpoints at week 104 by serum HBV DNA levels at week 24, telbivudine-treated patients in NV-02B-007 (GLOBE) study

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

N/A = not applicable

* Virological breakthrough: "1 log above nadir" definition assessed at week 104

Study NV-02B-015

The efficacy and safety results of the NV-02B-007 (GLOBE) study were confirmed in study NV-02B-015. This study is a phase III, randomised, double-blind study of telbivudine 600 mg once daily compared to lamivudine 100 mg once daily for a treatment period of 104 weeks in 332 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative Chinese patients.

Study CLDT600A2303 – Clinical results over 208 weeks

Study CLDT600A2303 was an open-label 104-week extension study in patients with compensated chronic hepatitis B who were previously treated with telbivudine for 2 years including patients from studies NV-02B-007 (GLOBE) and NV-02B-015 , providing efficacy and safety data after 156 and 208 weeks of continuous telbivudine therapy. Patients with undetectable HBV DNA at week 24 had better outcomes at 156 and 208 weeks (Table 8).

Table 8 Efficacy analysis in pooled data from NV-02B-007 (GLOBE), NV-02B-015 and CLDT600A2303 studies

	Week 52	Week 104	Week 156	Week 208
HBeAg-positive patients (n = 293*)				
Maintained undetectable HBV DNA (< 300 copies/ml)	70.3% (206/293)	77.3% (218/282)	75.0% (198/264)	76.2% (163/214)
Maintained undetectable HBV DNA (< 300 copies/ml) with undetectable HBV DNA at week 24	99.4% (161/162)	94.9% (150/158)	86.7% (130/150)	87.9% (109/124)
Cumulative HBeAg seroconversion rates (%)	27.6% (81/293)	41.6% (122/293)	48.5% (142/293)	53.2% (156/293)
Cumulative HBeAg seroconversion rates in patients with undetectable HBV DNA at week 24 (%)	40.1% (65/162)	52.5% (85/162)	59.3% (96/162)	65.4% (106/162)
Maintained ALT normalisation	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	97.8% (175/179)	96.5% (166/172)	86.7% (143/165)	87.5% (126/144)
Maintained ALT normalisation	80.3% (151/188)	89.0% (161/181)	83.5% (142/170)	89.6% (129/144)

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

Study CLDT600ACN04E1- Impact of treatment on liver histology

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

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

- The mean Ishak score of 2.2 (SD 1.1) at baseline improved ($p < 0.0001$) to 0.9 (SD 1.0) with a mean change of -1.3 (SD 1.3). Ishak fibrosis score ≤ 1 (no or minimal fibrosis) was observed in 84.2% (48/57) of patients.

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

CLDT600A2303 - Off-treatment durability of HBeAg responses

Study CLDT600A2303 included HBeAg-positive patients from studies NV-02B-007 (GLOBE) or NV-02B-015 for off-treatment follow up. These patients had completed ≥ 52 weeks of telbivudine treatment, and had exhibited HBeAg loss for ≥ 24 weeks with HBV DNA < 5 log10 copies/ml at the last on-treatment visit. The median treatment duration was 104 weeks. After a median off-treatment follow-up period of 120 weeks, the majority of HBeAg-positive telbivudine treated-patients showed sustained HBeAg loss (83.3%; 25/30), and sustained HBeAg seroconversion (79.2%; 19/24). Patients with sustained HBeAg seroconversion had a mean HBV DNA of 3.3 log10 copies/ml; and 73.7% had HBV DNA < 4 log10 copies/ml.

Clinical resistance

Genotypic resistance test was performed in study NV-02B-007 (GLOBE; n = 680) in patients with virological rebound (confirmed increase of ≥ 1 log10 copies/ml HBV DNA from nadir).

At week 48 among HBeAg-positive and HBeAg-negative patients, 5% (23/458) and 2% (5/222), respectively, had virological rebound with detectable HBV resistance mutations.

Studies NV-02B-007 (GLOBE) and CLDT600A2303 - cumulative genotypic resistance rates

The original analysis for cumulative genotypic resistance at week 104 and 208 was based on the ITT population and included all patients who continued treatment until 4 years, regardless

of HBV DNA levels. Out of the 680 telbivudine-treated patients initially included in the pivotal study NV-02B-007 (GLOBE), 517 (76%) enrolled into study CLDT600A2303 for continued telbivudine treatment for up to 208 weeks. Out of these 517 patients 159 patients (HBeAg-positive=135, HBeAg-negative=24) 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 ITT population the cumulative resistance rates at year 4 for HBeAg-positive and HBeAg-negative patients, was 40.8% (131/321) and 18.9% (37/196), respectively.

Cumulative genotypic resistance rates were also assessed by applying a mathematical model where only patients with undetectable HBV DNA at the beginning of the respective year are considered. Cumulative resistance rates at year 4 were 22.3% for HBeAg-positive patients and 16.0% for HBeAg-negative patients in this analysis.

When considering patients with viral breakthrough by 104 weeks in NV-02B-007 (GLOBE), 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 48 weeks and 9% (18/203) at week 104, whilst in patients with HBV DNA ≥ 300 copies/ml resistance was 8% (20/247) at 48 weeks 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 48 weeks and 5% (9/177) at week 104, whilst in patients with HBV DNA ≥ 300 copies/ml resistance was 11% (5/44) at 48 weeks and 34% (15/44) at week 104.

Genotypic mutation pattern and cross-resistance

Genotypic analysis of 203 evaluable sample pairs with HBV DNA ≥ 1000 copies/mL at week 104 (NV-02B-007 (GLOBE)) demonstrated that the primary mutation associated with telbivudine resistance was rtM204I often associated with mutations rtL180M and rtL80I/V and infrequently with rtV27A, rtL82M, rtV173L, rtT184I, and rtA200V. Baseline factors associated with development of genotypic drug resistance included: lamivudine treatment, higher baseline HBV DNA, lower baseline serum ALT, and increased body weight/BMI. On treatment response parameters at week 24 that predicted emergence of drug resistant virus by week 104 were HBV DNA >300 copies/ml and elevation of serum ALT.

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

Cross-resistance has been observed among HBV nucleoside analogues (see section 4.4). In cell-based assays, lamivudine-resistant HBV strains containing either the rtM204I mutation or the rtL180M/rtM204V double mutation had ≥1,000-fold reduced susceptibility to telbivudine. HBV encoding the adefovir resistance-associated substitutions rtN236T or rtA181V had around 0.3- and 4-fold change in susceptibility to telbivudine in cell culture, respectively (see section 4.4).

5.2 Pharmacokinetic properties

The single- and multiple-dose pharmacokinetics of telbivudine were evaluated in healthy subjects and in patients with chronic hepatitis B. The pharmacokinetics of telbivudine were not evaluated with the recommended dose of 600 mg in patients with chronic hepatitis B. However telbivudine pharmacokinetics are similar between both populations.

Absorption

Following oral administration of a 600 mg single dose of telbivudine to healthy subjects (n = 42), the peak plasma concentration (Cmax) of telbivudine was 3.2 ± 1.1 μg/ml (mean ± SD) and occurred at median 3.0 hours post dose. The telbivudine area under the plasma concentration-time curve (AUC0-∞) was 28.0 ± 8.5 μg•h/ml (mean ± SD). Inter-subject variability (CV%) for measures of systemic exposures (Cmax, AUC) was typically approximately 30%.

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%).

Biotransformation

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

Elimination

After reaching peak concentration, plasma disposition of telbivudine declined in a bi-exponential manner with a terminal elimination half-life (t1/2) of 41.8 ± 11.8 hours. Telbivudine is eliminated primarily by urinary excretion of unchanged substance. The renal clearance of telbivudine approaches normal glomerular filtration rate, suggesting that

filtration 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. As 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 section 4.2).

Linearity/non-linearity

Telbivudine pharmacokinetics are dose proportional over the range of 25 to 1,800 mg. Steady state was achieved after 5 to 7 days of once-daily administration with an approximate 1.5-fold accumulation in systemic exposure, suggesting an effective accumulation half-life of approximately 15 hours. Following once-daily administration of telbivudine 600 mg, steady-state trough plasma concentrations were approximately 0.2-0.3 μg/ml.

Special populations

Gender

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

Race

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

Paediatrics and elderly (65 years age and above)

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

Renal impairment

The single-dose pharmacokinetics of telbivudine (200, 400 and 600 mg) 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 9, adjustment of the dose interval for telbivudine is recommended in patients with creatinine clearance of <50 mL/min (see sections 4.2 and 4.4).

Table 9 Pharmacokinetic parameters (mean ± SD) of telbivudine in subjects with various degrees of renal function

	Renal function (creatinine clearance in mL/min)				
	Normal (>80) (n = 8) 600 mg	Mild (50–80) (n = 8) 600 mg	Moderate (30–49) (n = 8) 400 mg	Severe (<30) (n = 6) 200 mg	ESRD/ 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
$AUC_{0-\infty}$ (μg•h/ml)	28.5 ± 9.6	32.5 ± 10.1	36.0 ± 13.2	32.5 ± 13.2	67.4 ±3 6.9
CL_{RENAL} (ml/min)	126.7 ± 48.3	83.3 ± 20.0	43.3 ± 20.0	11.7 ± 6.7	-

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 section 4.2). Telbivudine should be administered after haemodialysis.

Hepatic impairment

The pharmacokinetics of telbivudine have been studied in patients (without chronic hepatitis B) with various degrees of hepatic impairment and in some patients with decompensated liver disease. There were no significant changes in telbivudine pharmacokinetics in hepatically impaired subjects compared to unimpaired subjects. Results of these studies indicate that no dosage adjustment is necessary for patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Telbivudine did not show any carcinogenic potential. No evidence of a direct toxic effect of telbivudine was seen in standard tests of reproduction toxicology. In rabbits doses of telbivudine providing exposure levels of 37 times those observed in humans at the therapeutic dose (600 mg) were associated with an increased incidence of abortion and early delivery. This effect was considered to be secondary to maternal toxicity.

Fertility was assessed in conventional studies performed in adult rats, and as part of a juvenile toxicology study.

In adult rats, fertility was reduced when both male and female rats were treated with telbivudine at doses of 500 or 1000 mg/kg/day (lower fertility index compared to concurrent controls). There were no abnormalities in sperm morphology or function, and the testes and ovaries were histologically unremarkable.

No evidence of impaired fertility was seen in other studies when either male or female rats were treated at doses up to 2000 mg/kg/day and mated with untreated rats (systemic exposure levels approximately 6-14 times higher than those achieved in humans).

In the juvenile toxicology study, rats were treated from day 14 to day 70 post-partum and were mated with rats receiving the same treatment (no sibling mating). Fertility was reduced in pairs given ≥ 1000 mg/kg/day as shown by decreases in fertility and mating indices, and reduced conception rate. However the ovarian and uterine parameters of those females mating successfully were unaffected.

The *no observed adverse effect level* (NOAEL) for effects on fertility or mating parameters amounted to 250 mg/kg/day, which provided exposure levels 2.5 to 2.8 times higher than those achieved in humans with normal renal function at the therapeutic dose.

6 Pharmaceutical particulars

6.1 List of excipients

Tablet core

Cellulose microcrystalline

Povidone

Sodium starch glycolate

Magnesium stearate

Silica, colloidal anhydrous

Tablet film coat

Titanium dioxide (E171)

Macrogol 4000

Talc

Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is printed on the package materials.

6.4 Special precautions for storage

Store in the original package below 30°c.

Sebivo must be kept out of the reach and sight of children.

6.5 Nature and contents of container

PVC/aluminium blisters. Pack size: 28 film-coated tablets

6.6 Special precautions for disposal

No special requirements for disposal.

7 Registration Number

137 703 1522

8 Manufacturer:

Novartis Pharma Stein AG

Schaffhauserstrasse

CH-4332 Stein

Switzerland

9 Registration Holder:

Novartis Israel Ltd.

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