ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sebivo 600 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg telbivudine.

For the full list of excipients, see section 6.1.

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 adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

Initiation of Sebivo treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.

See section 5.1 for details of the study and specific patient characteristics on which this indication is based.

4.2 Posology and method of administration

Therapy must be initiated by a physician experienced in the management of chronic hepatitis B infection.

<u>Posology</u>

Adults
The recommended dose of Sebivo is 600 mg (one tablet) once daily.

Sebivo oral solution may be considered for patients who have difficulties swallowing tablets.

Monitoring during treatment
On-treatment response at week 24 has been shown to be predictive of longer-term response (see Table 7 in section 5.1). HBV DNA levels should be monitored at 24 weeks of treatment to assure complete viral suppression (HBV DNA less than 300 copies/ml). For patients with detectable HBV DNA after 24 weeks of therapy, treatment modification should be considered.

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

Duration of therapy
The optimal treatment duration is unknown. Treatment discontinuation should be considered as follows:

- In HBeAg-positive patients without cirrhosis, treatment should be administered for at least 6-12 months after HBeAg seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBsAg seroconversion or there is evidence of loss of efficacy. Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.
- In HBeAg-negative patients without cirrhosis, treatment should be administered at least until HBsAg seroconversion or until there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuation of the selected therapy remains appropriate for the patient.

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.

Elderly (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).

Renal impairment
No adjustment of the recommended dose of telbivudine is necessary in patients whose creatinine clearance is ≥ 50 ml/min. Adjustment of the dose is required in patients with creatinine clearance < 50 ml/min, including those with end-stage renal disease (ESRD) on haemodialysis. A reduction of the daily dose using Sebivo oral solution, as detailed in Table 1 below, is recommended. If use of the oral solution is not possible, Sebivo film-coated tablets could be used as an alternative and dosing should be adjusted by increasing the time interval between doses, as detailed in Table 1.

Table 1 Dosing regimen adjustment of Sebivo in patients with renal impairment

Creatinine clearance (ml/min)	Telbivudine 20 mg/ml oral solution Daily dose adjustment	Telbivudine 600 mg film-coated tablet Alternative** dose adjustment with increased dose intervals
≥ 50	600 mg (30 ml) once daily	600 mg once daily
30-49	400 mg (20 ml) once daily	600 mg once every 48 hours
< 30 (not requiring dialysis)	200 mg (10 ml) once daily	600 mg once every 72 hours
ESRD*	120 mg (6 ml) once daily	600 mg once every 96 hours

* End stage renal disease
** In case use of the oral solution is not possible

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

End-stage renal disease patients
For patients with ESRD, Sebivo should be administered after haemodialysis (see section 5.2).

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

Paediatric population
The safety and efficacy of Sebivo in the paediatric population have not yet been established. No data are available.

Method of administration

Sebivo is to be taken orally, with or without food. The tablet should not be chewed, 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 with 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.

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 or4 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 (EC_{50}) was approximately 0.2 μM. The antiviral activity of telbivudine is specific to the hepatitis B virus and related hepadnaviruses. Telbivudine was not active against HIV *in vitro*. The absence of activity of telbivudine against HIV has not been evaluated in clinical trials. 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 $\log_{10}$ 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 $\log_{10}$ copies/ml were associated with higher rates of HBeAg seroconversion in HBeAg-positive patients. Patients who achieve HBV DNA levels < 3 $\log_{10}$ copies/ml by week 24 had optimal responses to treatment; conversely patients with HBV DNA levels > 4 $\log_{10}$ copies/ml at 24 weeks had less favourable outcomes at week 52.

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

Response parameter	HBeAg-positive (n = 921)		HBeAg-negative (n = 446)	
	Telbivudine 600 mg (n = 458)	**Lamivudine 100 mg (n = 463)**	**Telbivudine 600 mg (n = 222)**	**Lamivudine 100 mg (n = 224)**
Mean HBV DNA reduction from baseline (log_{10} copies/ml) ± SEM[1,2,3]	-6.45 (0.11) *	-5.54 (0.11)	-5.23 (0.13) *	-4.40 (0.13)
% Patients HBV DNA undetectable by PCR	60%*	40%	88%*	71%
ALT 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 $\log_{10}$ 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 $\log_{10}$ HBV DNA reduction: -5.00 vs -4.17, and HBV DNA undetectability: 82% vs 57%; $p < 0.0001$) were higher for telbivudine up to week 104. ALT 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 $\log_{10}$ copies/ml at the last on-treatment visit. The median treatment duration was 104 weeks. After a median off-treatment follow-up period of 120 weeks, the majority of HBeAg-positive telbivudine treated-patients showed sustained HBeAg loss (83.3%; 25/30), and sustained HBeAg seroconversion (79.2%; 19/24). Patients with sustained HBeAg seroconversion had a mean HBV DNA of 3.3 $\log_{10}$ copies/ml; and 73.7% had HBV DNA < 4 $\log_{10}$ copies/ml.

Clinical resistance

Genotypic resistance test was performed in study NV-02B-007 (GLOBE; n = 680) in patients with virological rebound (confirmed increase of ≥ 1 $\log_{10}$ 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 ≥ 1,000 copies/ml at week 104 (NV-02B-007 (GLOBE)) demonstrated that the primary mutation associated with telbivudine resistance was rtM204I, often associated with mutations rtL180M and rtL80I/V and infrequently with rtV27A, rtL82M, rtV173L, rtT184I and rtA200V. Baseline factors associated with development of genotypic drug resistance included: lamivudine treatment, higher baseline HBV DNA, lower baseline serum ALT, and increased body weight/BMI. On-treatment response parameters at week 24 that predicted emergence of drug resistant virus by week 104 were HBV DNA > 300 copies/ml and elevation of serum ALT.

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

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 (C_{max}) 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 ($AUC_{0-\infty}$) was 28.0 ± 8.5 µg•h/ml (mean ± SD). Inter-subject variability (CV%) for measures of systemic exposures (C_{max}, 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 ($t_{1/2}$) of 41.8 ± 11.8 hours. Telbivudine is eliminated primarily by urinary excretion of unchanged substance. The renal clearance of telbivudine approaches normal glomerular filtration rate, suggesting that 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 ± 36.9
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

<u>Tablet core</u>

Cellulose microcrystalline
Povidone
Sodium starch glycolate
Silica, colloidal anhydrous
Magnesium stearate

<u>Tablet film coat</u>

Titanium dioxide (E171)
Macrogol
Talc
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium blisters

Pack sizes: 28 or 98 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/388/001
EU/1/07/388/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 April 2007
Date of latest renewal: 16 December 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Sebivo 20 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 20 mg telbivudine.

Excipient with known effect: A 600 mg dose (30 ml) of oral solution contains approximately 47 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sebivo is indicated for the treatment of chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

Initiation of Sebivo treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.

See section 5.1 for details of the study and specific patient characteristics on which this indication is based.

4.2 Posology and method of administration

Therapy must be initiated by a physician experienced in the management of chronic hepatitis B infection.

Posology

Adults
The recommended dose of Sebivo is 30 ml, providing a dose equivalent to 600 mg, once daily.

Monitoring during treatment
On-treatment response at week 24 has been shown to be predictive of longer-term response (see Table 7 in section 5.1). HBV DNA levels should be monitored at 24 weeks of treatment to assure complete viral suppression (HBV DNA less than 300 copies/ml). For patients with detectable HBV DNA after 24 weeks of therapy, treatment modification should be considered.

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

Duration of therapy
The optimal treatment duration is unknown. Treatment discontinuation should be considered as follows:

- In HBeAg-positive patients without cirrhosis, treatment should be administered for at least 6-12 months after HBeAg seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBsAg seroconversion or there is evidence of loss of efficacy. Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.
- In HBeAg-negative patients without cirrhosis, treatment should be administered at least until HBsAg seroconversion or until there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuation of the selected therapy remains appropriate for the patient.

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.

Elderly (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).

Renal impairment
No adjustment of the recommended dose of telbivudine is necessary in patients whose creatinine clearance is ≥ 50 ml/min. Adjustment of the dose is required in patients with creatinine clearance < 50 ml/min, including those with end-stage renal disease (ESRD) on haemodialysis. A reduction of the daily dose using Sebivo oral solution, as detailed in Table 1 below, is recommended. If use of the oral solution is not possible, Sebivo film-coated tablets could be used as an alternative and dosing should be adjusted by increasing the time interval between doses, as detailed in Table 1.

Table 1 Dosing regimen adjustment of Sebivo in patients with renal impairment

Creatinine clearance (ml/min)	Telbivudine 20 mg/ml oral solution Daily dose adjustment	Telbivudine 600 mg film-coated tablet Alternative** dose adjustment with increased dose intervals
≥ 50	600 mg (30 ml) once daily	600 mg once daily
30-49	400 mg (20 ml) once daily	600 mg once every 48 hours
< 30 (not requiring dialysis)	200 mg (10 ml) once daily	600 mg once every 72 hours
ESRD*	120 mg (6 ml) once daily	600 mg once every 96 hours

* End stage renal disease
** In case use of the oral solution is not possible

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

End-stage renal disease patients
For patients with ESRD, Sebivo should be administered after haemodialysis (see section 5.2).

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

Paediatric population
The safety and efficacy of Sebivo in the paediatric population have not yet been established. No data are available.

Method of administration

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

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 with 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.

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.

Excipients

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

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 or4 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 (EC_{50}) was approximately 0.2 μM. The antiviral activity of telbivudine is specific to the hepatitis B virus and related hepadnaviruses. Telbivudine was not active against HIV *in vitro*. The absence of activity of telbivudine against HIV has not been evaluated in clinical trials. 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 $\log_{10}$ 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 $\log_{10}$ copies/ml were associated with higher rates of HBeAg seroconversion in HBeAg-positive patients. Patients who achieve HBV DNA levels < 3 $\log_{10}$ copies/ml by week 24 had optimal responses to treatment; conversely patients with HBV DNA levels > 4 $\log_{10}$ copies/ml at 24 weeks had less favourable outcomes at week 52.

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

Response parameter	HBeAg-positive (n = 921)		HBeAg-negative (n = 446)	
	Telbivudine 600 mg (n = 458)	**Lamivudine 100 mg (n = 463)**	**Telbivudine 600 mg (n = 222)**	**Lamivudine 100 mg (n = 224)**
Mean HBV DNA reduction from baseline (log_{10} copies/ml) ± SEM[1,2,3]	-6.45 (0.11) *	-5.54 (0.11)	-5.23 (0.13) *	-4.40 (0.13)
% Patients HBV DNA undetectable by PCR	60%*	40%	88%*	71%
ALT 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 $\log_{10}$ 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 $\log_{10}$ HBV DNA reduction: -5.00 vs -4.17, and HBV DNA undetectability: 82% vs 57%; $p < 0.0001$) were higher for telbivudine up to week 104. ALT 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 $\log_{10}$ copies/ml at the last on-treatment visit. The median treatment duration was 104 weeks. After a median off-treatment follow-up period of 120 weeks, the majority of HBeAg-positive telbivudine treated-patients showed sustained HBeAg loss (83.3%; 25/30), and sustained HBeAg seroconversion (79.2%; 19/24). Patients with sustained HBeAg seroconversion had a mean HBV DNA of 3.3 $\log_{10}$ copies/ml; and 73.7% had HBV DNA < 4 $\log_{10}$ copies/ml.

Clinical resistance

Genotypic resistance test was performed in study NV-02B-007 (GLOBE; n = 680) in patients with virological rebound (confirmed increase of ≥ 1 $\log_{10}$ 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 ≥ 1,000 copies/ml at week 104 (NV-02B-007 (GLOBE)) demonstrated that the primary mutation associated with telbivudine resistance was rtM204I, often associated with mutations rtL180M and rtL80I/V and infrequently with rtV27A, rtL82M, rtV173L, rtT184I and rtA200V. Baseline factors associated with development of genotypic drug resistance included: lamivudine treatment, higher baseline HBV DNA, lower baseline serum ALT, and increased body weight/BMI. On-treatment response parameters at week 24 that predicted emergence of drug resistant virus by week 104 were HBV DNA > 300 copies/ml and elevation of serum ALT.

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

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 (C_{max}) 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 ($AUC_{0-\infty}$) was 28.0 ± 8.5 µg•h/ml (mean ± SD). Inter-subject variability (CV%) for measures of systemic exposures (C_{max}, AUC) was typically approximately 30%. Film-coated tablets containing 600 mg telbivudine are bioequivalent to 30 ml telbivudine oral solution (20 mg/ml).

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 ($t_{1/2}$) of 41.8 ± 11.8 hours. Telbivudine is eliminated primarily by urinary excretion of unchanged substance. The renal clearance of telbivudine approaches normal glomerular filtration rate, suggesting that 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 ± 36.9
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

Benzoic acid (E210)
Sodium saccharin
Passion fruit flavouring
Sodium hydroxide
Citric acid anhydrous
Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Use within 2 months of opening the bottle.

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze.

6.5 Nature and contents of container

300 ml brown glass bottle with a child-resistant closure, including a polyethylene sealing disc and a guarantee ring, a polypropylene dosing cup with embossed graduations from 5 to 30 ml in 5 ml increments, and a polypropylene oral syringe with graduations of 1 ml to 10 ml in 0.5 ml increments.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/388/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 April 2007
Date of latest renewal: 16 December 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Sebivo 600 mg film-coated tablets
telbivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One tablet contains 600 mg telbivudine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not chew, split or crush the tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/388/001	28 film-coated tablets
EU/1/07/388/002	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sebivo 600 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sebivo 600 mg film-coated tablets
telbivudine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

FOLDING BOX AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Sebivo 20 mg/ml oral solution
telbivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 20 mg telbivudine.

3. LIST OF EXCIPIENTS

Also contains sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

1 bottle containing 300 ml oral solution [folding box only]
1 cup + 1 oral syringe [folding box only]

300 ml [bottle label only]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 2 months of opening the bottle.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/388/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sebivo 20 mg/ml [folding box only]

17. UNIQUE IDENTIFIER – 2D BARCODE [folding box only]

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA [folding box only]

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Sebivo 600 mg film-coated tablets
Telbivudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Sebivo is and what it is used for
2. What you need to know before you take Sebivo
3. How to take Sebivo
4. Possible side effects
5. How to store Sebivo
6. Contents of the pack and other information

1. What Sebivo is and what it is used for

Sebivo contains the active substance telbivudine. Sebivo belongs to a group of medicines called antiviral medicines, which are used to treat infections caused by viruses.

Sebivo is used to treat adults with chronic hepatitis B. Starting treatment with Sebivo should only be considered when it is not possible or appropriate to use an alternative medicine to which the hepatitis B virus is less likely to develop resistance. Your doctor will decide which treatment is most appropriate for you.

Hepatitis B is caused by infection with the hepatitis B virus, which multiplies in the liver and causes liver damage. Treatment with Sebivo reduces the amount of hepatitis B virus in the body by blocking its growth, resulting in less liver damage and improved liver function.

2. What you need to know before you take Sebivo

Do not take Sebivo
- if you are allergic to telbivudine or any of the other ingredients of this medicine (listed in section 6).
- if you are being treated with pegylated or standard interferon alfa (see “Taking other medicines”).

If this applies to you, **do not take Sebivo. Talk to your doctor**.

Warnings and precautions
Talk to your doctor before taking Sebivo:
- if you have or have had any kidney problems. Your doctor may order laboratory tests to check your kidneys are working properly before and during treatment. Depending on the results of these tests your doctor may advise you to change how often you take Sebivo.
- if you suffer from cirrhosis of the liver (a serious condition which causes liver "scarring"). In this case your doctor will want to monitor you more closely.
- if you have had a liver transplant.
- if you are taking any medicines that may cause muscle problems (talk to your doctor or pharmacist if you are unsure).
- if you are infected with HIV, hepatitis C or D, or are being treated with any antiviral medicines.

If any of these applies to you, **tell your doctor before you take Sebivo**.

During the treatment with Sebivo:
- Sebivo can cause persistent unexplained muscle weakness or muscle pain (myopathy). Muscle symptoms may progress and become serious, sometimes leading to muscle breakdown (rhabdomyolysis) which can cause kidney damage.
- Uncommonly Sebivo can induce numbness, tingling, pain and/or burning sensations in the arms and/or legs (peripheral neuropathy).

If you experience any of these symptoms during your treatment with Sebivo, **call your doctor immediately**.

Other side effects of this type of medicine
Sebivo can cause an excess of lactic acid in the blood (lactic acidosis) which is usually associated with an enlargement of the liver (hepatomegaly). Lactic acidosis is a rare but serious side effect which can occasionally be fatal. Your doctor will monitor you regularly while you are receiving Sebivo. If you experience muscle pain, severe and persistent stomach pain with nausea and vomiting, severe and persistent trouble breathing, tiredness or abdominal discomfort while taking Sebivo, **call your doctor immediately**.

Some people may get very serious hepatitis symptoms when they stop taking medicines like Sebivo. Your doctor will monitor your health and do regular blood tests to check your liver after you stop treatment with Sebivo. Tell your doctor immediately about any new or unusual symptoms that you notice after stopping treatment (see "If you stop taking Sebivo" in section 3 of this leaflet).

Take care not to infect other people
Even if you take Sebivo, you may still infect others with hepatitis B virus (HBV) through sexual contact or exposure to contaminated blood or other body fluids. If you have sexual intercourse with a partner who is not immune against hepatitis B, always use condoms and avoid any other exchange of body fluids. Never share needles. Do not share personal items that could have blood or body fluids on them, such as toothbrushes or razor blades. A vaccine is available to prevent infection with HBV.

Children and adolescents
Sebivo is not recommended for use in children and adolescents.

Other medicines and Sebivo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Your doctor or pharmacist needs to know about other medicines because some medicines could affect your kidneys and because Sebivo mainly leaves the body via the kidneys in the urine.

Do not take Sebivo if you are using pegylated or standard interferon alfa (see "Do not take Sebivo"), because the combination of these medicines may increase your risk of developing peripheral neuropathy (numbness, tingling, and/or burning sensations in the arms and/or legs). Tell your doctor or pharmacist if you are being treated with interferon.

Pregnancy and breast-feeding

- Do not use Sebivo during pregnancy unless your doctor recommends it. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you the potential risks of taking Sebivo during pregnancy.

- If you have hepatitis B and become pregnant, talk to your doctor about how you can best protect your baby. Sebivo may reduce the risk of passing your hepatitis B virus on to your unborn baby if taken in combination with Hepatitis B immune globulin and Hepatitis B vaccine.

- Do not breast-feed during treatment with Sebivo. Tell your doctor if you are breast- feeding.

Driving and using machines

Sebivo has minor influence on the ability to drive and use machines. If you feel dizzy while taking this medicine, do not drive a vehicle or use any tools or machines.

3. How to take Sebivo

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much Sebivo to take

The recommended dose of Sebivo is one 600 mg tablet once a day. Take the tablet at about the same time each day.

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

You may need to take Sebivo less frequently if you have kidney problems. Tell your doctor if you have, or have ever had, any kidney problems.

How long to take Sebivo

Continue taking Sebivo every day for as long as your doctor tells you. Do not change your dose or stop taking Sebivo without talking to your doctor. This medicine is intended for long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you take more Sebivo than you should

If you have taken too much Sebivo, or if someone else accidentally takes your tablets, go to your doctor or hospital for advice straight away. Take the pack of tablets with you and show it to your doctor.

If you forget to take Sebivo

- If you forget to take Sebivo, take it as soon as you remember and then take your next dose at its regular time.
- However, if it is within 4 hours before your next dose, skip the dose you missed and take the next one at the usual time.

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

If you stop taking Sebivo
Stopping treatment with Sebivo may result in a worsening of your hepatitis B infection i.e. progression of the disease and abnormal test results (increase of viral load, ALT increase). Do not stop Sebivo unless your doctor tells you to. While you are taking Sebivo, make sure you do not run out of Sebivo.

Your doctor will monitor your health and do regular blood tests to check your liver after you stop treatment with Sebivo since your hepatitis B infection may get worse or become very serious after stopping treatment. Tell your doctor immediately about any new or unusual symptoms that you notice after stopping treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious:
- Persistent muscle weakness or muscle pain
- Numbness, tingling, pain and/or burning sensation in the arms and/or legs

If you experience any of these, **call your doctor immediately**.

Sebivo may also cause other side effects:
Common (may affect up to 1 in 10 people)
- Dizziness, headache
- Cough
- Diarrhoea, feeling sick (nausea), stomach (abdominal) pain
- Skin rash
- Tiredness (fatigue)
- Blood test results show higher levels of some liver enzymes (e.g. ALT, AST), amylase, lipase or creatine kinase

Uncommon (may affect up to 1 in 100 people)
- Joint pain
- Persistent muscle weakness or muscle pain (myopathy/myositis), muscle cramp
- Back, neck and flank pain
- Numbness, tingling, pain and/or burning sensation in the arms and/or legs or around the mouth
- Pain in lower back or hip that may radiate into the leg (sciatica)
- Taste disturbance
- Feeling unwell (malaise)

Rare (may affect up to 1 in 1,000 people)
- Excess of lactic acid in the blood (lactic acidosis)
- Muscle breakdown (rhabdomyolysis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Sebivo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not use this medicine if the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Sebivo contains
- The active substance is telbivudine. Each tablet contains 600 mg telbivudine.
- The other ingredients are: cellulose, microcrystalline; povidone; sodium starch glycolate; silica, colloidal anhydrous; magnesium stearate; hypromellose; titanium dioxide (E171); talc; macrogol.

What Sebivo looks like and contents of the pack
Sebivo film-coated tablets are white to slightly yellowish, oval, film-coated tablets with "LDT" imprinted on one side.

Sebivo film-coated tablets are supplied in packs of 28 or 98 tablets. Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Pharma Services Inc.
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
Novartis Pharma Services Inc.
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website:
http://www.ema.europa.eu

Package leaflet: Information for the user

Sebivo 20 mg/ml oral solution
Telbivudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Sebivo is and what it is used for
2. What you need to know before you take Sebivo
3. How to take Sebivo
4. Possible side effects
5. How to store Sebivo
6. Contents of the pack and other information

1. What Sebivo is and what it is used for

Sebivo contains the active substance telbivudine. Sebivo belongs to a group of medicines called antiviral medicines, which are used to treat infections caused by viruses.

Sebivo is used to treat adults with chronic hepatitis B. Starting treatment with Sebivo should only be considered when it is not possible or appropriate to use an alternative medicine to which the hepatitis B virus is less likely to develop resistance. Your doctor will decide which treatment is most appropriate for you.

Hepatitis B is caused by infection with the hepatitis B virus, which multiplies in the liver and causes liver damage. Treatment with Sebivo reduces the amount of hepatitis B virus in the body by blocking its growth, resulting in less liver damage and improved liver function.

2. What you need to know before you take Sebivo

Do not take Sebivo
- if you are allergic to telbivudine or any of the other ingredients of this medicine (listed in section 6).
- if you are being treated with pegylated or standard interferon alfa (see “Taking other medicines”).

If this applies to you, **do not take Sebivo. Talk to your doctor**.

Warnings and precautions
Talk to your doctor before taking Sebivo:
- if you have or have had any kidney problems. Your doctor may order laboratory tests to check your kidneys are working properly before and during treatment. Depending on the results of these tests your doctor may advise you to change how often you take Sebivo.
- if you suffer from cirrhosis of the liver (a serious condition which causes liver "scarring"). In this case your doctor will want to monitor you more closely.
- if you have had a liver transplant.
- if you are taking any medicines that may cause muscle problems (talk to your doctor or pharmacist if you are unsure).
- if you are infected with HIV, hepatitis C or D, or are being treated with any antiviral medicines.

If any of these applies to you, **tell your doctor before you take Sebivo.**

During the treatment with Sebivo:
- Sebivo can cause persistent unexplained muscle weakness or muscle pain (myopathy). Muscle symptoms may progress and become serious, sometimes leading to muscle breakdown (rhabdomyolysis) which can cause kidney damage.
- Uncommonly Sebivo can induce numbness, tingling, pain and/or burning sensations in the arms and/or legs (peripheral neuropathy).

If you experience any of these symptoms during your treatment with Sebivo, **call your doctor immediately**.

Other side effects of this type of medicine
Sebivo can cause an excess of lactic acid in the blood (lactic acidosis) which is usually associated with an enlargement of the liver (hepatomegaly). Lactic acidosis is a rare but serious side effect which can occasionally be fatal. Your doctor will monitor you regularly while you are receiving Sebivo. If you experience muscle pain, severe and persistent stomach pain with nausea and vomiting, severe and persistent trouble breathing, tiredness or abdominal discomfort while taking Sebivo, **call your doctor immediately**.

Some people may get very serious hepatitis symptoms when they stop taking medicines like Sebivo. Your doctor will monitor your health and do regular blood tests to check your liver after you stop treatment with Sebivo. Tell your doctor immediately about any new or unusual symptoms that you notice after stopping treatment (see "If you stop taking Sebivo" in section 3 of this leaflet).

Take care not to infect other people
Even if you take Sebivo, you may still infect others with hepatitis B virus (HBV) through sexual contact or exposure to contaminated blood or other body fluids. If you have sexual intercourse with a partner who is not immune against hepatitis B, always use condoms and avoid any other exchange of body fluids. Never share needles. Do not share personal items that could have blood or body fluids on them, such as toothbrushes or razor blades. A vaccine is available to prevent infection with HBV.

Children and adolescents
Sebivo is not recommended for use in children and adolescents.

Other medicines and Sebivo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Your doctor or pharmacist needs to know about other medicines because some medicines could affect your kidneys and because Sebivo mainly leaves the body via the kidneys in the urine.

Do not take Sebivo if you are using pegylated or standard interferon alfa (see "Do not take Sebivo"), because the combination of these medicines may increase your risk of developing peripheral neuropathy (numbness, tingling, and/or burning sensations in the arms and/or legs). Tell your doctor or pharmacist if you are being treated with interferon.

Pregnancy and breast-feeding

- Do not use Sebivo during pregnancy unless your doctor recommends it. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you the potential risks of taking Sebivo during pregnancy.

- If you have hepatitis B and become pregnant, talk to your doctor about how you can best protect your baby. Sebivo may reduce the risk of passing your hepatitis B virus on to your unborn baby if taken in combination with Hepatitis B immune globulin and Hepatitis B vaccine.

- Do not breast-feed during treatment with Sebivo. Tell your doctor if you are breast- feeding.

Driving and using machines
Sebivo has minor influence on the ability to drive and use machines. If you feel dizzy while taking this medicine, do not drive a vehicle or use any tools or machines.

Sebivo contains sodium
Sebivo oral solution contains approximately 47 mg of sodium per 600 mg dose (30 ml). If you are on a controlled sodium diet, ask your doctor for advice.

3. How to take Sebivo

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much Sebivo to take
The recommended dose of Sebivo is 30 ml of oral solution (600 mg telbivudine) once a day. Take Sebivo at about the same time each day. It can be taken with or without food.

For full instructions on how to take Sebivo, see section “Instructions for use” at the end of this leaflet.

Remove the dosing cup and open the bottle. Slowly and carefully pour the solution from the bottle into the dosing cup until it reaches the prescribed amount. Swallow the entire contents of the dosing cup immediately.

If you cannot measure the prescribed amount precisely using the dosing cup alone, you should use the oral syringe. Detailed instructions on how to use this are given in the section “Instructions for use”.

Your dose may be reduced if you have kidney problems. Tell your doctor if you have, or have ever had, any kidney problems.

How long to take Sebivo
Continue taking Sebivo every day for as long as your doctor tells you. Do not change your dose or stop taking Sebivo without talking to your doctor. This medicine is intended for long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you take more Sebivo than you should
If you have taken too much Sebivo, or if someone else accidentally takes your oral solution, go to your doctor or hospital for advice straight away. Take the pack with you and show it to the doctor.

If you forget to take Sebivo
- If you forget to take Sebivo, take it as soon as you remember and then take your next dose at its regular time.
- However, if it is within 4 hours before your next dose, skip the dose you missed and take the next one at the usual time.

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

If you stop taking Sebivo
Stopping treatment with Sebivo may result in a worsening of your hepatitis B infection i.e. progression of the disease and abnormal test results (increase of viral load, ALT increase). Do not stop Sebivo unless your doctor tells you to. While you are taking Sebivo, make sure you do not run out of Sebivo.

Your doctor will monitor your health and do regular blood tests to check your liver after you stop treatment with Sebivo since your hepatitis B infection may get worse or become very serious after stopping treatment. Tell your doctor immediately about any new or unusual symptoms that you notice after stopping treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious:
- Persistent muscle weakness or muscle pain
- Numbness, tingling, pain and/or burning sensation in the arms and/or legs

If you experience any of these, **call your doctor immediately**.

Sebivo may also cause other side effects:
Common (may affect up to 1 in 10 people)
- Dizziness, headache
- Cough
- Diarrhoea, feeling sick (nausea), stomach (abdominal) pain
- Skin rash
- Tiredness (fatigue)
- Blood test results show higher levels of some liver enzymes (e.g. ALT, AST), amylase, lipase or creatine kinase

Uncommon (may affect up to 1 in 100 people)
- Joint pain
- Persistent muscle weakness or muscle pain (myopathy/myositis), muscle cramp
- Back, neck and flank pain
- Numbness, tingling, pain and/or burning sensation in the arms and/or legs or around the mouth
- Pain in lower back or hip that may radiate into the leg (sciatica)
- Taste disturbance
- Feeling unwell (malaise)

Rare (may affect up to 1 in 1,000 people)
- Excess of lactic acid in the blood (lactic acidosis)
- Muscle breakdown (rhabdomyolysis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Sebivo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label. The expiry date refers to the last day of that month.

Do not store above 30°C. Do not freeze.

Use within 2 months of opening the bottle.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Sebivo contains
- The active substance is telbivudine. 30 ml oral solution contain 600 mg telbivudine.
- The other ingredients are: benzoic acid, sodium saccharin, passion fruit flavouring, sodium hydroxide, citrc acid anhydrous, water.

What Sebivo looks like and contents of the pack
Sebivo 20 mg/ml oral solution is supplied as 300 ml of a clear, colourless to pale yellow solution in an brown glass bottle with a child-resistant white polypropylene closure, including a polyethylene sealing disc and a guarantee ring. The pack contains an oral dosing cup made of polypropylene with embossed graduations from 5 to 30 ml in 5 ml increments and a polypropylene oral syringe with graduations of 1 ml to 10 ml in 0.5 ml increments.

Marketing Authorisation Holder
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Pharma Services Inc.
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
Novartis Pharma Services Inc.
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

This leaflet was last revised in

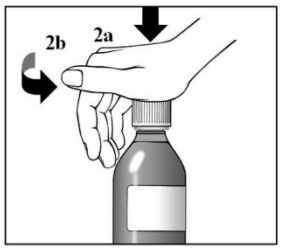
Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website:
http://www.ema.europa.eu

INSTRUCTIONS FOR USE

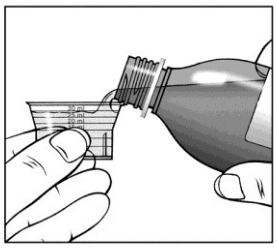
Please read these instructions carefully so that you know how to use the solution correctly.

1. Bottle containing the oral solution.
2. Child-resistant screw cap with a guarantee-ring. Always close the bottle with the cap after use.
3. Oral dosing cup for measuring out the dose. Always put the dosing cup back onto the cap after use and cleaning.
4. Oral syringe for measuring out doses that cannot be precisely measured using the cup.

Preparing a dose of medicine using the dosing cup

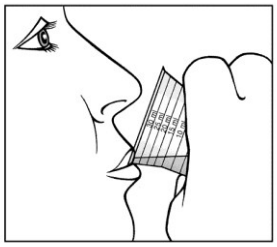


1. Remove the dosing cup.
2. Simultaneously press down (2a) and turn the child-resistant cap (2b) to the left to open the bottle.

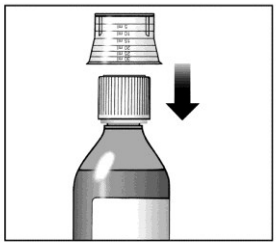


3. Before pouring any solution into the cup, please check the position of the appropriate graduation to avoid any potential waste or spillage.
   Holding the cup at eye level, carefully and slowly pour the prescribed amount of solution from the bottle into the dosing cup until the solution reaches the top of the appropriate graduation.

Note: If the amount poured into the cup exceeds the required dose, discard the excess in the sink. Do not pour it back into the bottle.

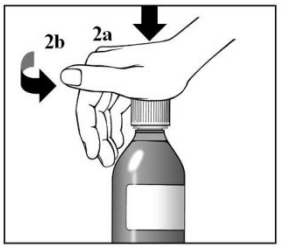


4. Drink the solution or administer it to the patient immediately.
5. Close the bottle by screwing the cap back on tightly.

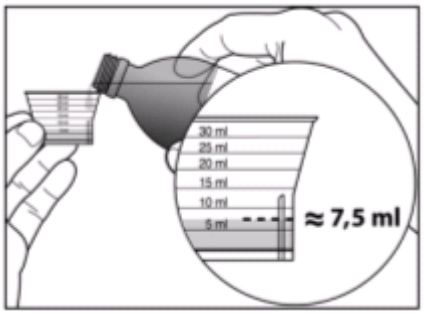


6. Immediately rinse the dosing cup with water.
7. Remove the water from the dosing cup, wipe it with a clean tissue and place it back on top of the cap.

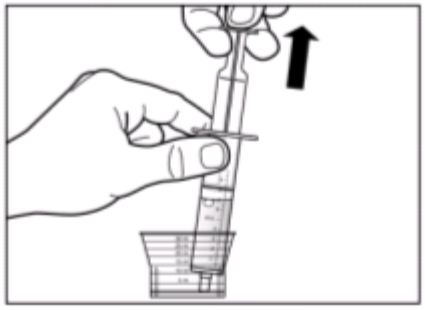
Preparing a 6 ml dose of medicine using the oral syringe



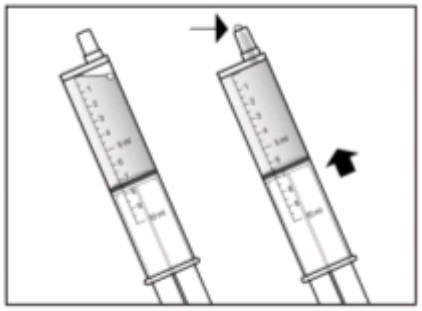
1. Remove the dosing cup.
2. Simultaneously press down (2a) and turn the child-resistant cap (2b) to the left to open the bottle.



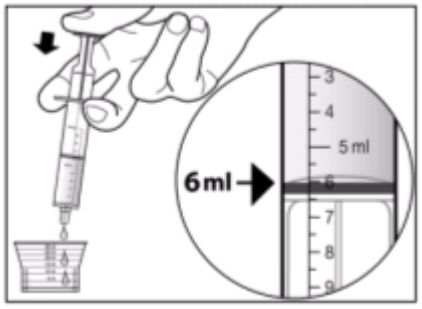
3. Before pouring any solution into the cup, please check the position of the 5 and 10 ml marks to avoid any potential waste or spillage.
   Holding the cup at eye level, carefully and slowly pour the solution from the bottle into the cup until it comes to about halfway between the 5 ml and 10 ml marks.



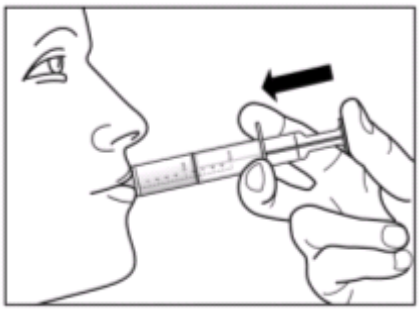
4. Withdraw all the solution from the cup into the syringe.



5. Turn the syringe to the upright position and incline it slightly so that the air bubbles rise to the top.
6. Push the plunger carefully and slowly to remove the air until a droplet of solution appears.



7. Hold the syringe above the cup.
8. Push the plunger slowly and carefully until the solution reaches the 6 ml mark.



9. Immediately swallow the solution direct from the syringe.
10. Discard the solution left in the cup into the sink. Do not pour it back into the bottle as this could cause contamination.
11. Close the bottle firmly.
12. Rinse the cup and syringe with clean water.
13. Dry the cup with a clean tissue and place it back over the cap of the bottle.
14. Allow the syringe to air-dry and store with the bottle.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for telbivudine, the scientific conclusions of CHMP are as follows:

Based on a cumulative review submitted by the MAH with this PSUR, a total of 96 cases of lactic acidosis were reported with telbivudine, including 54 cases as a secondary event of a serious underlying condition, such as rhabdomyolysis or myopathy and 26 cases with no evident primary cause, although CPK elevation were often associated. Moreover, one literature case report of severe refractory lactic acidosis was reported during the review period in a patient receiving telbivudine monotherapy and for whom no underlying serious condition was reported. In cumulative, seven fatal cases of lactic acidosis were recorded including six cases where lactic acidosis was reported as a symptom or secondary to rhabdomyolysis. Overall, it is acknowledged that it remains difficult to clearly conclude whether lactic acidosis causes muscle events or lactic acidosis follows muscular damage.

Based on the available evidence, the PRAC considered that the telbivudine SmPC should be updated to reinforce the current warning in section 4.4 of the SmPC on lactic acidosis, notably by highlighting the potential fatal outcome of telbivudine-induced lactic acidosis in a context of rhabdomyolysis and to delete the current information in section 4.8 of the SmPC that lactic acidosis has been reported with telbivudine exclusively as a secondary event (since it is not always the case).

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing telbivudine were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for telbivudine the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing telbivudine is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.