

NEW ZEALAND DATA SHEET

SEBIVO[®]

(telbivudine)

600 mg Film-Coated Tablets

20 mg/mL Oral Solution

Qualitative and quantitative composition

Each film-coated tablet contains 600 mg telbivudine.

Each mL of oral solution contains 20 mg telbivudine.

A 600 mg dose (30 mL) of Sebivo oral solution contains approximately 47 mg of sodium.

For a full list of excipients, see List of excipients.

Pharmaceutical form

Film-coated tablet

White to slightly yellowish-coloured, ovaloid-shaped, film-coated tablet, imprinted with "LDT" on one side.

Oral Solution

Clear, colourless to pale yellow, passion fruit flavoured liquid.

Clinical particulars

Therapeutic indications

Sebivo[®] is indicated for the treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation.

This indication is based on virological, serological, biochemical and histological responses in adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B.

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

- For HBeAg-positive patients, Sebivo treatment should only be initiated in patients with baseline HBV DNA < 9log₁₀ copies/mL and baseline ALT ≥ 2x ULN.
- For HBeAg-negative patients, Sebivo treatment should only be initiated in patients with baseline HBV DNA < 7log₁₀ copies/mL.

Dosage and method of administration

Adults

The recommended dose of Sebivo for the treatment of chronic hepatitis B is 600 mg once daily, taken orally, with or without food.

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

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

Monitoring and duration of treatment

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

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

The optimal treatment duration has not been established.

Renal impairment/insufficiency

Sebivo may be used for the treatment of chronic hepatitis B in patients with impaired renal function. No adjustment of the recommended dose of telbivudine is necessary in patients whose creatinine clearance is ≥ 50 mL/min. Dose adjustment is required in patients with creatinine clearance < 50 mL/min including those with end stage renal disease (ESRD) on haemodialysis. Dose adjustment may be achieved either by changing of the tablet dose interval or by a dose reduction using oral solution presentation, as shown in Table 1:

Table 1 Dose adjustment of Sebivo in patients with renal impairment

Creatinine clearance (mL/min)	Oral Solution Dose (20 mg/mL)	Tablet Dose (1 tablet = 600 mg)
≥ 50	600 mg once daily (30 mL)	600 mg once daily
30 – 49	400 mg once daily (20 mL)	600 mg once every 48 hours
< 30 (not requiring dialysis)	200 mg once daily (10 mL)	600 mg once every 72 hours
ESRD*	120 mg once daily (6 mL)	600 mg once every 96 hours

* End stage renal disease

ESRD patients

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

Hepatic impairment

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

Paediatric patients (age below 16 years)

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

Elderly patients (age above 65 years)

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

Contraindications

Hypersensitivity to telbivudine or to any of the excipients.

Combination of telbivudine 600 mg daily with pegylated interferon alfa-2a, 180 micrograms once weekly (see Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction).

Special warnings and precautions for use

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy. Hepatic function must be monitored closely, with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside/nucleotide analogues alone or in combination with antiretrovirals.

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

Uncomplicated myalgia has been reported in telbivudine-treated patients (see Adverse effects). Myopathy, defined as persistent unexplained muscle aches and/or muscle weakness regardless of the degree of increases in creatine kinase (CK) levels, should be considered in any patient with unexplained diffuse myalgias, muscle tenderness or muscle weakness. Among patients with telbivudine-associated myopathy, there has not been a uniform pattern with regard to the degree or timing of CK elevations. In addition, the predisposing factors for the development of myopathy among telbivudine recipients are unknown. Patients should be advised to report promptly any persistent unexplained muscle aches, pain, tenderness or weakness. Telbivudine therapy should be discontinued if myopathy is diagnosed.

It is not known if the risk of myopathy during treatment with drugs in this class is increased with concurrent administration of other drugs associated with myopathy. Physicians considering concomitant treatment with other agents associated with myopathy should weigh carefully the potential benefits and risks and should monitor patients for any signs or symptoms of unexplained muscle pain, tenderness, or weakness.

In one study, an increased risk of developing peripheral neuropathy has been observed with the combination use of telbivudine, 600 mg daily, and pegylated interferon alfa-2a, 180 micrograms once weekly compared to telbivudine or pegylated interferon alfa-2a, 180 micrograms once weekly alone (see Contraindications and Interaction with other medicinal products and other forms of interaction). Such risk cannot be excluded for other dose regimens of pegylated interferon alfa-2a, or other alfa interferons (pegylated or standard). The potential benefit of this combination therapy remains to be established.

Renal function

Telbivudine is eliminated primarily by renal excretion, therefore dose adjustment is recommended in patients with creatinine clearance <50 mL/min, including patients on haemodialysis (see Dosage and method of administration). In addition, co-administration of Sebivo with substances that affect renal function may alter plasma concentrations of telbivudine and/or the co-administered substance (see Interaction with other medicinal products and other forms of interaction).

Patients with antiviral resistant HBV infection

There are no adequate and well controlled studies of telbivudine treatment in patients with established lamivudine-resistant hepatitis B virus infection. In vitro, telbivudine was not active against hepatitis B virus (HBV) strains containing rtM204V/rtL180M or rtM204I mutations (see Pharmacodynamic properties).

There are no adequate and well controlled studies of telbivudine treatment in patients with established adefovir-resistant hepatitis B virus infection. HBV encoding the adefovir resistance-associated substitution rtN236T and rtA181V remain fully susceptible to telbivudine, with 0.5- and 1.0-fold susceptibility, respectively, in cell culture.

Liver transplant recipients

The safety and efficacy of telbivudine in liver transplant recipients are unknown. The steady state pharmacokinetics of telbivudine were not altered following multiple dose administration in combination with cyclosporin. If telbivudine treatment is considered necessary in a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporin or tacrolimus, renal function must be monitored both before and during treatment with Sebivo (see Interaction with other medicinal products and other forms of interaction).

Use in elderly patients

Clinical studies of telbivudine did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger subjects. In general, caution must be exercised when prescribing Sebivo to elderly patients in view of the greater frequency of decreased renal function due to concomitant disease or concomitant use of other medicinal products.

Other special populations

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

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

Information for Patients

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

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 may affect plasma concentrations of telbivudine and/or the co-administered substance.

At concentrations up to 12 times that used in humans, telbivudine did not inhibit in vitro metabolism mediated by any of the following human hepatic microsomal cytochrome P450 (CYP) isoenzymes known to be involved in human drug metabolism: 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. Telbivudine does not induce cytochrome P450 isoenzymes in animals. Based on the above results and the known elimination pathway of telbivudine, the potential for CYP450-mediated interactions involving Sebivo with other medicinal products is low.

The steady-state pharmacokinetics of telbivudine were unaltered following multiple dose administration in combination with lamivudine, adefovir dipivoxil, cyclosporin, pegylated interferon-alfa 2a or tenofovir disoproxil fumarate. In addition, telbivudine does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil, cyclosporin or tenofovir disoproxil fumarate. No definitive conclusion could be drawn regarding the effects of telbivudine on the pharmacokinetics of pegylated interferon-alfa 2a due to the high inter-individual variability of pegylated interferon-alfa 2a concentrations (see Special warnings and precautions for use).

A pilot clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy (see Contraindications and Special warnings and precautions for use).

Pregnancy and lactation

Pregnancy

For telbivudine no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see Preclinical safety data). Sebivo should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

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

Women of child-bearing potential

No special requirements.

Lactation

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

Fertility

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

Effects on ability to drive and use machines

No specific recommendations.

Adverse effects

Approximately 1,500 subjects have been treated with telbivudine in clinical studies at a dose of 600 mg once daily. Assessment of adverse reactions is primarily based on two studies (007 GLOBE and NV-02B-015) in which 1,699 patients with chronic hepatitis B received double-blind treatment with telbivudine 600 mg/day (n=847) or lamivudine (n=852) for 104 weeks. The safety profiles of telbivudine and lamivudine were generally comparable in these studies.

In the 104 week clinical studies telbivudine was generally well tolerated, with most adverse experiences classified as mild or moderate in severity. In the 007 GLOBE and NV-02B-015 studies patient discontinuations for adverse events, clinical disease progression or lack of efficacy were 1.5% for telbivudine and 4.1% for lamivudine.

Table 2 lists the adverse reactions recorded in the pooled 104 week 007 GLOBE and NV-02B-015 studies by system organ class and by frequency using the following convention: common ($\geq 1/100$; $< 1/10$); uncommon ($\geq 1/1,000$; $< 1/100$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

Nervous System Disorders	
Common	Dizziness, headache
Uncommon	Peripheral neuropathy
Gastrointestinal Disorders	
Common	Blood amylase increased, diarrhoea, lipase increased, nausea
Hepato-biliary disorders	
Common	Alanine aminotransferase increased
Uncommon	Aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	
Common	Rash
Musculoskeletal, connective tissue and bone disorders	
Common	Blood creatine phosphokinase increased
Uncommon	Myopathy, myositis, arthralgia, myalgia
General disorders and administration site conditions	
Common	Fatigue
Uncommon	Malaise

Creatine kinase elevation

Creatine kinase (CK) elevations occurred in both treatment arms. However, median CK levels were higher in telbivudine-treated patients. In the pooled analysis from 007 GLOBE and NV-02B-015, by 104 weeks of treatment, Grade 3/4 CK elevations occurred in 12.6% of

telbivudine-treated patients (n=847) and 4.0% of lamivudine-treated patients. Most CK elevations were asymptomatic and CK values typically decreased by the next visit on continued treatment. Analysis of clinical adverse events in patients with CK elevations indicated no significant difference between telbivudine-treated and lamivudine-treated patients.

In an open-label study in 2,206 Chinese patients (CLDT600ACN03), grade 3/4 CK elevations were reported in 3.1% of telbivudine-treated patients by week 52.

ALT flares

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

Table 3 Summary of ALT flares¹ by 6-month intervals in the pooled 007 GLOBE and NV-02B-015 studies

	Telbivudine 600 mg (n = 847)	Lamivudine 100 mg (n = 852)
Overall	4.8 %	7.9 %
Baseline to week 24	3.0 %	2.9 %
Week 24 to week 52	0.4 %	1.7 %
Week 52 to week 76	0.7 %	2.0 %
Week 76 to week 104	1.3 %	2.0 %
Week 24 to end of treatment	2.0 %	5.3%

¹ intermittent elevations of aminotransferase activity to >10x upper limit of normal and >2x baseline value.

Results at 208 weeks

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

The overall safety profile from the pooled analysis up to 104 and 208 weeks was similar. Grade 3/4 CK elevations occurred in 15.9% of patients (104/655) treated with telbivudine in study CLDT600A2303. Most grade 3/4 CK elevations were asymptomatic (74% patients without any muscle related adverse reaction) and transient (97.5% episodes lasted one or two visits (visit interval 2-12 weeks) and 86.6% patients had one or two episodes). Most grade 3/4 CK elevations (93.2%) resolved spontaneously or returned to baseline levels. Two cases of myopathy and 2 cases of myositis were reported in the 655 telbivudine-treated patients.

Exacerbations of hepatitis B after discontinuation of treatment

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy. There are insufficient data on post-treatment exacerbations of hepatitis B after discontinuation of telbivudine treatment (see Special warnings and precautions for use).

Post-marketing experience

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

Musculoskeletal, connective tissue and bone disorders

Rhabdomyolysis has been very rarely reported.

Overdose

No case of overdose with Sebivo has been reported. 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.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, ATC code: J05AF11

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

The in vitro antiviral activity of telbivudine was assessed in the HBV-expressing human hepatoma cell line 2.2.15, as well as in primary duck hepatocytes infected with duck hepatitis B virus (DHBV). The concentration of telbivudine that effectively inhibited 50% of viral synthesis (EC_{50}) in both systems was approximately 0.2 μM . The antiviral activity of telbivudine is specific to hepatitis B virus and related hepadnaviruses. No activity was noted against multiple other RNA and DNA viruses, including human immunodeficiency virus (HIV) type 1 (EC_{50} value $>200\ \mu\text{M}$). The absence of activity of telbivudine against HIV has not been evaluated in clinical trials.

In 4- and 12-week studies of hepadnavirus-infected woodchucks (*marmota monax*), a relevant animal model for HBV, telbivudine significantly reduced viral DNA levels. Within 28 days, at oral doses of 10 mg/kg/day, serum viral DNA levels decreased by as much as 8 \log_{10} to undetectable levels ($<300\ \text{copies/mL}$ by PCR). Following telbivudine withdrawal, viral rebound occurred within four weeks. When telbivudine was given orally to woodchucks at

lower doses (1 mg/kg/day) for 12 weeks viral load reductions of at least 6 log₁₀ were seen in all telbivudine-treated animals.

In vitro resistance

The activity of telbivudine was assessed in cell-based assays against a number of HBV genomic variants associated with lamivudine and adefovir resistance in HBV-infected patients. The M204V mutant is a key intermediate leading to the emergence of the L180M/M204V lamivudine resistant strain. Reductions of at least 1049 fold in telbivudine phenotypic susceptibility were observed against lamivudine resistant HBV strains containing either the M204I mutation or the L180M/M204V double mutation.

In cell culture, telbivudine showed a 2-fold enhanced activity against HBV containing the N236T mutation and wild type activity against HBV containing the A181T mutation, the most common adefovir-resistance mutations seen in HBV-infected patients.

In HIV-1 infected patients, nucleoside analogues such as lamivudine and entecavir can induce YMDD-based (M184V) HIV drug resistant strains. Telbivudine does not demonstrate activity against HIV-1 in cell culture. The absence of activity of telbivudine against HIV has not been evaluated in clinical trials.

Clinical experience

The safety and efficacy of long term (104 week) telbivudine treatment were evaluated in two active-controlled clinical studies that included 1,699 patients with chronic hepatitis B (007 GLOBE and NV-02B-015). All patients were 16 years of age or older, with chronic hepatitis B, evidence of HBV infection with viral replication (HBsAg-positive, HBeAg-positive or HBeAg-negative, HBV DNA detectable by PCR assay), elevated ALT levels ≥ 1.3 times the upper limit of normal (ULN), and chronic inflammation on liver biopsy compatible with chronic viral hepatitis.

Study 007 “GLOBE”

The 007 “GLOBE” study is a Phase III, randomised, double-blind, multinational study of telbivudine 600 mg once daily compared to lamivudine 100 mg once daily for a treatment period of up to 104 weeks in 1,367 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative patients. The primary data analysis was conducted after all patients had reached week 52.

HBeAg-positive patients: The mean age of patients was 32 years, 74% were male, 82% were Asian, 12% were Caucasian, and 6% had previously received alpha-interferon therapy. At baseline, patients had a mean Knodell Necroinflammatory Score ≥ 7 , mean serum HBV DNA as measured by Roche COBAS AmpliCor[®] PCR assay was 9.52 log₁₀ copies/mL, and mean serum ALT was approximately 153 IU/litre. Pre- and post-liver biopsy samples were adequate for 86% of patients.

HBeAg-negative patients: The mean age of patients was 43 years, 79% were male, 65% were Asian, 23% were Caucasian, and 11% had previously received alpha-interferon therapy. At baseline, patients had a mean Knodell Necroinflammatory Score ≥ 7 , mean serum HBV DNA as measured by Roche COBAS AmpliCor[®] PCR assay was 7.54 log₁₀ copies/mL, and mean serum ALT was approximately 140 IU/litre. Pre- and post-liver biopsy samples were adequate for 92% of patients.

007 GLOBE - Clinical results at Week 52

Clinical and virological efficacy endpoints were evaluated separately in the HBeAg-positive and HBeAg-negative patient populations in Study 007. The primary endpoint of therapeutic response at week 52 is a composite serological endpoint 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.

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

Selected virological, biochemical and serological outcome measures are shown in Table 4. In both the HBeAg-positive and HBeAg-negative patient populations, telbivudine was superior to lamivudine for antiviral efficacy, as assessed by HBV DNA suppression. Telbivudine showed a greater reduction than lamivudine in viral load as early as Week 12 in HBeAg-positive patients ($p=0.0157$) and Week 8 in HBeAg-negative patients ($p=0.0242$).

Table 4 Virological, biochemical and serological endpoints at week 52 (007 GLOBE study)

Response parameter	HBeAg-positive (n = 921)		HBeAg-negative (n = 446)	
	Telbivudine 600 mg (n = 458)	Lamivudine 100 mg (n = 463)	Telbivudine 600 mg (n = 222)	Lamivudine 100 mg (n = 224)
Mean HBV DNA reduction from baseline (\log_{10} copies/mL) \pm SEM ^{1,2}	-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 ³	77%	75%	74%	79%
HBeAg seroconversion ⁴	23%	22%	NA	NA
HBeAg loss ⁴	26%	23%	NA	NA

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

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

³ 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

⁴ n = 432 and 442, for telbivudine and lamivudine groups, respectively. HBeAg seroconversion and loss assessed only in patients with detectable HBeAg at baseline

* $p < 0.0001$

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

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

	HBeAg-positive (n = 921)		HBeAg-negative (n = 446)	
	Telbivudine 600 mg (n = 384) ¹	Lamivudine 100 mg (n = 386) ¹	Telbivudine 600 mg (n = 199) ¹	Lamivudine 100 mg (n = 207) ¹
Histological response²				
Improvement	71%*	61%	71%	70%

No Improvement	17%	24%	21%	24%
Ishak Fibrosis Score³				
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 \geq one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Histological Activity Index (HAI) score >3				
² Histological response defined as ≥ 2 point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score				
³ For Ishak Fibrosis Score, improvement defined as a ≥ 1 point reduction in Ishak Fibrosis Score from baseline to week 52				
*p = 0.0024				

007 GLOBE - 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; $p < 0.0001$, PCR negativity: 56% vs 39%; $p < 0.0001$ and mean ALT normalization of 70% vs 62%) demonstrated a widening difference at Week 104 between telbivudine and lamivudine, respectively. Proportionally higher rates of HBeAg loss (35% vs 29%) and seroconversion (30% vs 25%) were also observed for telbivudine. Interferon eligible patients (screening ALT $\geq 2 \times \text{ULN}$; $n=320$), showed a better treatment response to telbivudine in all categories as compared to the overall HBeAg-positive population, including a significantly higher proportion of telbivudine patients achieving HBeAg seroconversion at Week 104 than lamivudine patients (36% vs 28%, respectively). Seroconversion rates were sustained 52-weeks post-treatment in the majority of HBeAg-positive patients who discontinued therapy due to efficacy.

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 PCR negativity: 82% vs 57%; $p < 0.0001$) were consistently high for telbivudine through Week 104. ALT normalization rates (78% vs 70%) continued to be proportionally higher by Week 104.

Patients who achieved non-detectable HBV DNA levels and/or normalized ALT at 24 weeks were more likely to undergo e-antigen seroconversion, achieve undetectable levels of HBV DNA, normalize ALT, and minimize resistance at one and two years.

Study NV-02B-015

NV-02B-015 is a Phase III, randomized, 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. The primary efficacy endpoint was serum HBV DNA reduction at Week 52, defined as the reduction (in \log_{10} copies/mL) in serum HBV DNA levels from baseline values. Therapeutic Response was a key secondary endpoint.

Study NV-02B-015 - Clinical results Outcomes at Week 52

Selected virological, biochemical and serological outcome measures are shown in Table 6. Efficacy results from study NV-02B-015 are consistent with the 007 GLOBE study results at week 52.

Table 6 Virological, Biochemical and Serologic Endpoints and Therapeutic Response at Week 52 (NV-02B-015)

Response Parameter	HBeAg-positive (n= 290)		HBeAg-negative (n=42)	
	Telbivudine 600 mg (n=147)	Lamivudine 100 mg (n=143)	Telbivudine 600 mg (n=20)	Lamivudine 100 mg (n=22)
Mean HBV DNA Reduction from Baseline (log ₁₀ copies/mL) ± SEM ¹	-6.33 (0.18)	-5.49 (0.18)	-5.49 (0.40)	-4.81 (0.38)
% Subjects HBV DNA undetectable by PCR	67%*	38%	85%	77%
ALT Normalization ²	87%	75%	100%	78%
HBeAg Seroconversion ³	25%	18%	NA	NA
HBeAg Loss ³	31%	20%	NA	NA
Therapeutic Response	85%*	62%	100%	82%
¹ Roche COBAS Amplicor® Assay (LLOQ≤300 copies/mL)				
² n=142 and 135, for telbivudine and lamivudine groups, respectively. ALT normalization assessed only in subjects with ALT > ULN at baseline				
³ n = 138 for both telbivudine and lamivudine groups. HBeAg seroconversion and loss assessed only in subjects with detectable HBeAg at baseline				
* p <0.0001				

Study NV-02B-015 - Clinical results Outcomes at Week 104

Among HBeAg-positive subjects, results for therapeutic response (66% vs 41%; p <0.0001), mean log₁₀ HBV DNA reduction (-5.47 vs -3.97; p =0.0001), PCR negativity (58% vs 34%; p <0.0001), ALT normalization (73% vs 59%), HBeAg loss (40% vs 28%) and HBeAg seroconversion (29% vs 20%) were consistently high for telbivudine.

Although the number of HBeAg-negative subjects in this study is small (n=42), results for key endpoints remain consistent for telbivudine at Week 104 (therapeutic response: 90% vs 68%, mean log₁₀ HBV DNA reduction: -5.59 vs -4.20, PCR negativity: 90% vs 68%, and ALT normalization: 95% vs 78%).

Study CLDT600A2303 - Clinical results up to week 208

Study CLDT600A2303 is an open-label 104-week extension study of up to 208 weeks of continuous telbivudine treatment in patients who were previously treated in studies 007 GLOBE and NV-02B-015. A subset of 502 patients (293 HBeAg-positive and 209 HBeAg-negative, excluding those with virological breakthrough and confirmed genotypic resistance at entry into study CLDT600A2303) were analyzed. At week 156 and 208, the majority of patients maintained undetectable HBV DNA levels (< 300 copies/ml) and normalized ALT. Patients with undetectable HBV DNA at week 24 had better outcomes at 156 and 208 weeks (Table 7).

In 293 HBeAg-positive patients the cumulative HBeAg seroconversion rate increased with duration of treatment: 27.6% at week 52, 41.6% at week 104, 48.5% at week 156 and 53.2% at week 208. Higher rates of seroconversion were observed in HBeAg-positive patients who

achieved undetectable HBV DNA at week 24 (40.1% at week 52, 52.5% at week 108, 59.3% at week 156 and 65.4% at week 208) (Table 7).

Table 7 Virological, biochemical and serological endpoints up to week 208 (CLDT600A2303)

	Week 52	Week 104	Week 156	Week 208
HBeAg-positive patients (N = 293*)				
Maintained undetectable HBV DNA (< 300 copies/ml)	70.3%	77.3%	75.0%	76.2%
Maintained undetectable HBV DNA (< 300 copies/ml) with undetectable HBV DNA at week 24 (n = 162)	99.4%	94.9%	86.7%	87.9%
Cumulative HBeAg seroconversion rates	27.6%	41.6%	48.5%	53.2%
Cumulative HBeAg seroconversion rates in patients with undetectable HBV DNA at week 24 (n = 162)	40.1%	52.5%	59.3%	65.4%
Maintained ALT normalisation	81.4%	87.5%	82.9%	86.4%
HBeAg-negative patients (n = 209*)				
Maintained undetectable HBV DNA (< 300 copies/ml)	95.2%	96.5%	84.7%	86.0%
Maintained undetectable HBV DNA (< 300 copies/ml) with undetectable HBV DNA at week 24 (n = 179)	97.8%	96.5%	86.7%	87.5%
Maintained ALT normalisation	80.3%	89.0%	83.5%	89.6%

Liver histology response - Study CLDT600ACN04E1

In study CLDT600ACN04E1, 57 patients with paired liver biopsies at baseline and after 5 years of telbivudine treatment) were evaluated for changes in liver histology. The Knodell necroinflammation and Ishak fibrosis scores showed a statistical significant improvement versus baseline (Table 8). After treatment 98.2% of patients had no or minimal liver necroinflammation (Knodell necroinflammatory score ≤ 3), and 84.2% of patients had no or minimal liver fibrosis (Ishak fibrosis score ≤ 1).

Table 8 Histological improvement in patients after 5 years of telbivudine treatment

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

Off-treatment durability of response - CLDT600A2303

Study CLDT600A2303 included off-treatment follow up of 59 HBeAg-positive patients from studies 007 GLOBE and NV-02B-015. These patients had completed ≥ 52 weeks of telbivudine treatment, and had exhibited HBeAg loss for ≥ 24 weeks with HBV DNA $< 5 \log_{10}$ copies/ml at the last on-treatment visit. The median treatment duration was 104 weeks.

After a median off-treatment follow-up period of 120 weeks, the majority of patients showed sustained HBeAg loss (83.3%), and sustained HBeAg seroconversion (79.2%). Patients with sustained HBeAg seroconversion had a mean HBV DNA of 3.3 log₁₀ copies/ml; and 73.7% had HBV DNA < 4 log₁₀ copies/mL.

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

The glomerular filtration rate (GFR) analysis from 007 GLOBE and CLDT600A2303 showed no renal toxicity with telbivudine treatment.

Renal function improved steadily over 104 weeks of telbivudine treatment (Table 9), particularly a majority (72.3%) of patients with baseline GFR between 60 to 90 mL/min shifted to > 90 mL/min/1.73 m². Improvement in renal function continued with a mean increase of 14.9 mL/min/1.73 m² at 208 weeks vs. baseline (Table 9).

Table 9 GFR improvement in patients with telbivudine treatment

Treatment duration	Study	Patients No.	BL mean GFR (MDRD)	GFR Change from BL	% of patients with baseline GFR 60-90 mL/min shifted to >90mL/min	
1 year	007 GLOBE:	LDT	680	98.3	5.1 ^a	61.7% (n=256)
		LAM	687	99.8	-1.0 ^a	-
2 year	007 GLOBE:	LDT	680	98.3	6.7 ^a	72.3% (n=256)
		LAM	687	99.8	-1.8 ^a	-
4 year	2303	LDT	511	95 ^b	14.9	

^a Least Square mean change, Telbivudine (LDT) vs lamivudine (LAM), P <0.0001.

^b Based on 655 patients with available baseline GFR values

Monitoring of HBV DNA at week 24 - Study CLDT600A2410

Study CLDT600A2410 evaluated the addition of once daily tenofovir 300 mg to once daily telbivudine 600 mg in HBeAg-positive patients.

At week 24, HBV DNA was undetectable in 54% of patients (55/101); telbivudine monotherapy was continued for these patients. For the remaining 46 patients, tenofovir was added to telbivudine at week 24.

At week 52, 93% (94/101) had undetectable HBV DNA, 38% HBeAg seroconversion, and 6% HBsAg loss. At week 52 HBV DNA was undetectable in all 55 patients who continued telbivudine monotherapy. The addition of tenofovir to telbivudine monotherapy in 46 patients with detectable HBV DNA at week 24 resulted in a further decline in HBV DNA of 1.71 log₁₀ copies/ml. In the total population (n = 101) no virological breakthrough (1 log above nadir) or resistance was reported over 52 weeks.

Of the 46/101 patients with detectable HBV DNA at week 24, 12/46 patients had baseline HBV DNA < 9 log₁₀ copies/ml. All 12 patients achieved undetectable HBV DNA at week 52.

Study NV-02B-018

NV-02B-018 is a Phase IIIb, randomized, open-label, multi-center study of treatment with telbivudine 600 mg once daily compared to adefovir dipivoxil 10 mg once daily for a

treatment period of 52 weeks in 135 adult subjects with HBeAg-positive compensated chronic hepatitis B. The primary endpoint was serum HBV DNA reduction from baseline at Week 24 with a secondary comparison at Week 52.

In study NV-02B-018, the mean age of subjects was 32 years, 76% were male, 92% were Asian, 4% were Caucasian, and 1% had previously received alfa-interferon therapy. At baseline, 95 % of subjects were diagnosed with chronic hepatitis B ≥ 9 years ago, mean serum HBV DNA as measured by Roche COBAS Amplicor[®] PCR assay was 9.67 log₁₀ copies/mL, and mean serum ALT was 173 IU/L.

At Week 24, the mean reduction of serum HBV DNA from baseline was -6.29 vs -4.92 log₁₀ copies/mL for telbivudine (n= 45) and adefovir dipivoxil (n=90), respectively.

Clinical resistance

Genotypic resistance rates

One and 2 year data from 007 GLOBE – Subpopulation considering baseline characteristics and week 24 HBV DNA, and excluding patients with detectable HBV DNA at beginning of years 2

Cumulative genotypic resistance rates were assessed in patients from study 007 GLOBE (n = 680) by baseline factors (HBV DNA < 9 log₁₀ copies/ml and ALT ≥ 2 x ULN for HBeAg positive; HBV DNA < 7 log₁₀ copies/ml for HBeAg negative) where only patients with undetectable HBV DNA at week 24 and at the beginning of year 2 were included. At week 52, resistance rates were 0% for both HBeAg-positive and HBeAg-negative patients; at week 104, the resistance rates were 1.8% for HBeAg-positive and 2.4% for HBeAg-negative patients (Table 10).

Table 10 Efficacy responses and resistance rates at weeks 52 and 104 by baseline factors and on-treatment response at week 24 (007 GLOBE)

	HBeAg-positive ¹	HBeAg-negative ²
Year 1/week 52	n = 57	N = 86
Undetectable serum HBV DNA	96.5%	97.7%
HBeAg seroconversion	39.6%	-
Genotypic resistance	0%	0%
Year 2/week 104³	n = 55	n = 84
Undetectable serum HBV DNA	90.9%	92.9%
HBeAg seroconversion	53.2%	-
Cumulative genotypic resistance	1.8%	2.4%

¹ HBeAg-positive patients with baseline HBV DNA < 9 log₁₀ copies/ml, baseline ALT ≥ 2 xULN, and undetectable HBV DNA at treatment week 24.

² HBeAg-negative patients with baseline HBV DNA < 7 log₁₀ copies/ml and undetectable HBV DNA at week 24.

³ Includes patients with undetectable HBV DNA at the beginning of year 2.

Four year data from CLDT600A2303 - Subpopulation excluding patients with detectable HBV DNA at beginning of years 2, 3 and 4

Cumulative genotypic resistance rates up to 208 weeks were calculated for study CLDT600A2303, excluding patients with detectable HBV DNA at beginning of years 2, 3

and 4. The overall cumulative resistance rate at 4 year was 20.0% in the overall population (n=310); 22.3% in HBeAg positive and 16.0% in HBeAg negative patients.

This retrospective data was confirmed in a prospective study CLDT600A2410 in 101 patients (see Pharmacodynamic properties, Monitoring of HBV DNA at week 24 - Study CLDT600A2410).

Genotypic mutation pattern

In study 007 GLOBE study, 55.7% (255/458) of treatment-naïve HBeAg-positive and 82.0% (182/222) of treatment-naïve HBeAg-negative patients receiving telbivudine 600 mg once daily achieved non-detectable serum HBV DNA levels (<300 copies/mL) by Week 104. Genotypic analysis of 203 evaluable sample pairs with HBV DNA \geq 1000 copies/mL 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 from telbivudine-treated patients at week 208 (CLDT600A2303) showed no novel mutation.

Cross-resistance

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, lamivudine-resistant HBV strains containing either the rtM204I mutation or the rtL180M/rtM204V double mutation had \geq 1,000-fold reduced susceptibility to telbivudine. HBV encoding the adefovir resistance-associated substitutions at rtN236T and A181V had 0.5- and 1.0- fold change in susceptibility to telbivudine in cell culture, respectively. Substitution at rtA194T had 0.99-fold shift in susceptibility to telbivudine in cell culture.

ALT Flares

In the 007 GLOBE study, the incidence of alanine aminotransferase (ALT) flares was similar in the telbivudine and lamivudine treatment arms in the first six months of treatment, but was lower for telbivudine after week 24 (see Adverse effects, Table 3).

Cardiac safety

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

Pharmacokinetic properties

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

Absorption and Bioavailability

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

Effect of food on oral absorption

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

Distribution

In vitro binding of telbivudine to human plasma proteins is low (3.3%). After oral dosing, the estimated apparent volume of distribution is in excess of total body water, suggesting that telbivudine is widely distributed into tissues. Telbivudine was equally partitioned between plasma and blood cells.

Biotransformation

No metabolites of telbivudine were detected following administration of ^{14}C -telbivudine in humans. Telbivudine is not a substrate, inhibitor or inducer of the cytochrome P450 (CYP450) enzyme system (see Interaction with other medicinal products and other forms of interaction).

Elimination

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

Characteristics in patients

Gender

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

Race

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

Paediatrics and geriatrics

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

Renal impairment

The single-dose pharmacokinetics of telbivudine have been evaluated in patients (without chronic hepatitis B) with various degrees of renal impairment (as assessed by creatinine clearance). Based on the results shown in Table 11, adjustment of the dose for telbivudine is recommended in patients with creatinine clearance of <50 mL/min (see Dosage and method of administration).

Table 11 Pharmacokinetic parameters (mean \pm 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} (microg/mL)	3.4 \pm 0.9	3.2 \pm 0.9	2.8 \pm 1.3	1.6 \pm 0.8	2.1 \pm 0.9
AUC _{0-∞} (microg•h/mL)	28.5 \pm 9.6	32.5 \pm 10.1	36.0 \pm 13.2	32.5 \pm 13.2	67.4 \pm 36.9
CL _{RENAL} (L/h)	7.6 \pm 2.9	5.0 \pm 1.2	2.6 \pm 1.2	0.7 \pm 0.4	-

Renally impaired patients on haemodialysis

Haemodialysis (up to 4 hours) reduces systemic telbivudine exposure by approximately 23%. Following dose adjustment for creatinine clearance, no additional dose modification is necessary during routine haemodialysis (see Dosage and method of administration). Telbivudine should be administered after haemodialysis.

Hepatic impairment

The pharmacokinetics of telbivudine following a single 600 mg dose have been studied in patients (without chronic hepatitis B) with various degrees of hepatic impairment. There were no changes in telbivudine pharmacokinetics in hepatically impaired subjects compared to unimpaired subjects. Results of these studies indicate that no dosage adjustment is necessary for patients with hepatic impairment (see Dosage and method of administration).

Preclinical safety data

Carcinogenicity

Telbivudine has shown no carcinogenic potential. Long-term oral carcinogenicity studies with telbivudine were negative in mice and rats at exposures up to 14 times those observed in humans at the therapeutic dose of 600 mg/day.

Genotoxicity

There was no evidence of genotoxicity based on in vitro or in vivo tests. Telbivudine was not mutagenic in the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli* strains with or without metabolic activation. Telbivudine was not clastogenic in mammalian cell gene mutation assays, including human lymphocyte cultures and a transformation assay with Chinese hamster ovary cells with or without metabolic activation. Furthermore, telbivudine was negative in an in vivo micronucleus study in mice.

Reproductive toxicity

In reproductive toxicology studies, no evidence of impaired fertility was seen when either male or female rats were treated with telbivudine at doses up to 2000 mg/kg/day (systemic exposures approximately 14 times those achieved in humans at the therapeutic dose) and mated with untreated rats.

A separate study indicated reduced fertility when both male and female rats were treated with telbivudine doses of 500 or 1000 mg/kg/day. A lower fertility index was noted in pairs given 500 (76%) or 1000 (72%) mg/kg/day when compared to concurrent controls (92%). There were no abnormalities in sperm morphology or function, and the testes and ovaries were histologically unremarkable.

Fertility was assessed as part of a juvenile toxicology study in which rats treated from Day 14 to Day 70 were mated with rats from other litters receiving the same treatment. The mean number of days to mating was slightly higher at 1000 and 2000 mg/kg/day. The fertility indices were reduced at 1000 mg/kg (40%) and 2000 mg/kg/day (50%) compared to the 80% value in the control group. In this study, the mating index and conception rate were slightly reduced, however the ovarian and uterine parameters of those females mating successfully were unaffected by administration of telbivudine. There was no effect on fertility or mating parameters at 250 mg/kg/day where the exposure was 2.5 to 2.8 times higher than exposure achieved in humans at the therapeutic dose.

Telbivudine is not teratogenic and has shown no adverse effects in developing embryos and fetuses in preclinical studies. Studies in pregnant rats and rabbits showed that telbivudine crosses the placenta. Developmental toxicity studies revealed no evidence of harm to the foetus in rats and rabbits at doses up to 1,000 mg/kg/day, providing exposure levels 6- to 37-times higher, respectively, than those observed with the therapeutic dose (600 mg/day) in humans.

Cardiac safety

There is no evidence of cardiotoxicity for telbivudine. In an in vitro hERG model, telbivudine was negative at concentrations up to 10,000 microM.

Pharmaceutical particulars

List of excipients

Tablet core:

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

Tablet film coat:

Titanium dioxide (E171)
Macrogol
Talc
Hypromellose

Oral solution:

Citric acid anhydrous
Benzoic acid
Passion fruit flavour
Sodium saccharin
Sodium hydroxide
Water, purified

Incompatibilities

Not applicable.

Shelf life**Film-coated tablet:**

3 years.

Oral solution:

3 years. Use within 2 months after first opening of the bottle.

Special precautions for storage**Film-coated tablet:**

Store at or below 30°C
Store in the original package.

Oral solution:

Do not store above 30°C. Do not freeze.
For storage conditions of the opened bottle, see Shelf life.
Sebivo must be kept out of the reach and sight of children.

Nature and contents of container**Film-coated tablet:**

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

Oral solution:

300 mL brown glass bottles with child-resistant closures with guarantee ring and a polypropylene dosing cup with embossed graduations from 5 to 30 mL in 5 mL increments. The pack includes a clear polypropylene oral dosing syringe with graduations from 0.5 mL to 10 mL in 0.5 mL increments.

Special precautions for disposal

No special requirements.

Medicine classification

Prescription Medicine

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