Drugs 2007; 67 (13): 1917-1929
0012-6667/07/0013-1917/$49.95/0

Telbivudine

Susan J. Keam

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Contents

Abstract

▲ Telbivudine, the unmodified L-enantiomer of the naturally occurring nucleoside D-thymidine, is a potent synthetic nucleoside analogue. It acts as a hepatitis B virus (HBV) polymerase inhibitor and preferentially inhibits HBV second strand (DNA-dependent) compared with first strand (RNA-dependent) DNA synthesis.

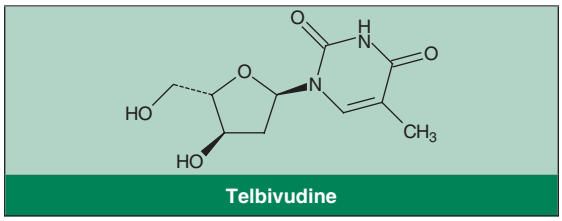
▲ More telbivudine than lamivudine recipients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B and similar proportions of telbivudine or lamivudine recipients with HBeAg-negative disease achieved a therapeutic response at 52 weeks in the large 2-year GLOBE trial. In a phase III trial in Chinese patients, greater reductions in serum HBV DNA occurred with telbivudine than lamivudine at 52 weeks.

▲ Reductions in serum HBV DNA at 24 weeks were greater with telbivudine than adefovir in the 1-year switching trial. A lower residual viral load at 52 weeks was seen in patients who received telbivudine or who switched from adefovir to telbivudine at 24 weeks than in patients receiving adefovir.

▲ In the 1-year lamivudine switching trial in patients with serum HBV DNA levels >3 $\log_{10}$ copies/mL despite having received prior treatment with lamivudine for a mean of ≈7 months, those randomised to telbivudine therapy achieved greater reductions in serum HBV DNA levels at 24 weeks than patients randomised to continue lamivudine therapy.

▲ Telbivudine was generally well tolerated and most adverse events were of mild or moderate severity. The incidence of severe ALT flares with telbivudine was half that seen with lamivudine at both 52 and 104 weeks in the GLOBE trial.

Features and properties of telbivudine	
Approved indication	
Treatment of hepatitis B e antigen (HBeAg)-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum ALT levels and/or (Global/US) histological evidence of active inflammation and/or fibrosis	
Mechanism of action	
Synthetic thymidine nucleoside analogue that acts as a hepatitis B virus (HBV) polymerase inhibitor. Preferentially inhibits HBV second strand (DNA-dependent) compared with first strand (RNA-dependent) DNA	
Dosage and administration	
Route	Oral
Dosage	600 mg/d
Pharmacokinetic profile (single oral 600mg dose in healthy volunteers; mean values unless stated otherwise)	
Peak plasma concentration (μg/mL)	3.2
Median time to peak plasma concentration (h)	3.0
Area under the plasma-concentration-time curve from time zero to infinity (μg • h/mL)	28.0
Trough plasma concentration at steady state (μg/mL)	≈0.2–0.3
Terminal elimination half-life (h)	≈40
Most frequent adverse events possibly or probably related to telbivudine therapy in the GLOBE trial	
Creatine kinase elevations, fatigue, headache, nausea	



Telbivudine

Chronic infection with the hepatitis B virus (HBV), a small, partially double-stranded hepadnavirus, is estimated to affect >350 million individuals worldwide[1] and to result in >500 000 deaths due to hepatic cirrhosis or hepatocellular carcinoma each year.[2] Prevalence of the disease varies from region to region, ranging from 0.1–2% in Western Europe to ≥8% in Sub-Saharan Africa and South-East Asia.[3]

Patients with chronic hepatitis B have a detectable HBV load, experience intermittent or persistent serum ALT elevations, are hepatitis B surface antigen (HBsAg)-positive and are either hepatitis B e antigen (HBeAg)-positive or HBeAg-negative.[4,5] Although HBeAg seroconversion (loss of HBeAg and emergence of antibodies against HBe [anti-HBe]) is usually associated with a reduction in viral load, at least 15–20% of HBeAg-negative/anti-HBe positive patients continue to have detectable HBV DNA due to the emergence of mutant HBV strains that express little or no HBeAg (mutations in the pre-core or core promoter regions) during seroconversion.[5,6]

Irrespective of HBeAg status, patients with chronic hepatitis B have an increased risk of developing hepatocellular cancer, hepatic cirrhosis or decompensated liver disease.[7,8] However, HBeAg-negative disease often presents at a more advanced stage[5] and is less likely to achieve a permanent antiviral response[1] than HBeAg-positive disease. Among the most important risk factors for developing hepatocellular carcinoma is an elevated HBV viral load (serum HBV DNA ≥3 $\log_{10}$ copies/mL).[8,9]

The immediate treatment goal in patients with chronic hepatitis B is to reduce the viral load and arrest or reverse hepatic damage, including hepatic fibrosis; the ultimate aim is to prevent the development of cirrhosis, hepatic decompensation and hepatocellular cancer.[1,6,7] This is best achieved by sustained suppression of HBV replication and induction of HBeAg seroconversion.[6,7]

Currently approved therapies for adult patients with compensated chronic hepatitis B in Europe include recombinant interferon-α[5,7] and more recent therapies, such as peginterferon-α-2a (40kD),[10] lamivudine,[11] adefovir dipivoxil (the prodrug of adefovir)[12] and entecavir.[4] Although these agents significantly reduce or inhibit viral replication during therapy in patients with chronic hepatitis B, relapse after treatment cessation is common (especially in patients with HBeAg-negative disease) and may occur months or years later.[1,5] In addition, the emergence of viral resistance during prolonged monotherapy may prevent longer-term control of the infection.[1,5] Consequently, the search for new therapies is ongoing.

Telbivudine (Sebivo®, Tyzeka®)[1] is a recently developed synthetic thymidine nucleoside analogue that inhibits hepadnavirus DNA replication. This article reviews the pharmacological properties, clinical efficacy and tolerability of oral telbivudine in adult patients with compensated chronic HBeAg-positive or HBeAg-negative hepatitis B.

1. Pharmacodynamic Profile

Mechanism of Action

- Telbivudine, the unmodified L-enantiomer of the naturally occurring nucleoside D-thymidine,[13,14] is a synthetic nucleoside analogue that prevents HBV DNA synthesis by competitively inhibiting HBV DNA polymerase activity (HBV polymerase inhibitor).[15]
- Within hepatocytes, telbivudine is phosphorylated by host cell kinases to telbivudine-5′-

1 The use of trade names is for product identification purposes only and does not imply endorsement. Telbivudine is registered as Sebivo® globally and as Tyzeka® in the US.

triphosphate; once incorporated into HBV DNA, telbivudine-5′-triphosphate causes DNA chain termination, thus inhibiting HBV replication.[14,15]

Antiviral Activity

- Telbivudine is a potent, specific inhibitor of HBV replication *in vitro*, and preferentially inhibits HBV second strand (DNA-dependent) compared with first strand (RNA-dependent) DNA synthesis[16] (mean 50% effective concentration [EC_{50}] 0.12–0.24 vs 0.4–1.3 μmol/L[15]). By contrast, lamivudine and torcitabine (deoxycytidine nucleoside analogues) showed greater inhibition of first strand than second strand DNA synthesis (reported as an abstract).[16]
- The relationship between these mechanistic differences and the clinical antiviral potency of the agents is not clear,[16] and no additive or synergistic effect was evident when telbivudine and lamivudine were coadministered in a clinical trial.[17]
- Unlike lamivudine and adefovir, telbivudine is active only against hepadnaviruses and has no activity against HIV or other viruses.[14,15]
- In a woodchuck hepatitis virus model, the mean telbivudine concentration required to inhibit ≥50% of viral DNA replication *in vitro* was 0.24 μmol/L,[3,18] and in the HBV-expressing human hepatoma cell line HepG2 2.2.15, telbivudine inhibited HBV DNA replication with an EC_{50} of 0.19 μmol/L.[13-15]
- In a stable transfected hepatocyte cell line that expresses high levels of HBV (HepG2 49-29), the combination of telbivudine and adefovir resulted in additive antiviral activity *in vitro* compared with the antiviral activity of either drug alone.[19]
- Telbivudine effectively inhibited HBV replication in a phase II clinical trial in HBeAg-positive patients with compensated hepatitis B.[17] In this trial, 104 patients were randomised to one of five treatment arms: once-daily telbivudine 400mg, telbivudine 600mg or lamivudine 100mg, or either dosage of telbivudine in combination with lamivudine. Median reductions from baseline in serum HBV DNA after 52 weeks' treatment with telbivudine 400 or 600 mg/day were not significantly different and, as a consequence, protocol-defined pooling of data was permitted.
- Telbivudine induced a greater mean reduction from baseline in serum HBV DNA than lamivudine at 52 weeks (6.01 vs 4.57 $\log_{10}$ copies/mL; $p < 0.05$).[17] In addition, more telbivudine than lamivudine recipients had HBV DNA undetectable by COBAS® Amplicor polymerase chain reaction (PCR) assay (lower limit of detection 200 copies/mL) [61% vs 32%] and normalised serum ALT levels (86% vs 63%) [both $p < 0.05$].[17]
- HBeAg seroconversion was evident in 31% of telbivudine and 22% of lamivudine recipients at study end, and 4.5% and 15.8% of patients receiving the respective treatments experienced virological breakthrough at week 48.[17] The efficacy of telbivudine in combination with lamivudine was not superior to that of telbivudine alone.[17]
- In a 1-year follow-on of the phase II study (n = 90; reported as an abstract),[20] mean 2-year serum HBV DNA reductions from baseline were 5.2 $\log_{10}$ copies/mL with telbivudine versus 3.9 $\log_{10}$ copies/mL with lamivudine. Significantly more telbivudine than lamivudine recipients were PCR-negative (71% vs 32%; $p < 0.05$) or maintained normalised serum ALT levels (81% vs 47%; $p < 0.05$).[20]
- HBeAg seroconversion was achieved in 38% of telbivudine and 21% of lamivudine recipients, and significantly fewer telbivudine than lamivudine recipients had evidence of treatment failure (virological breakthrough with elevated serum ALT levels) [4.5% vs 21.1%; $p < 0.05$].[20]
- Irrespective of treatment arm, an undetectable or low serum HBV DNA load (≤3 $\log_{10}$ copies/mL; assessed by PCR) at 24 weeks in the phase II study was associated with positive clinical and virological efficacy responses at week 52 (i.e. HBeAg loss, HBV DNA undetectable by PCR, normalised serum ALT levels, no virological breakthrough). Conversely, a viral load >3 $\log_{10}$ copies/mL was associated with a poor response.[17]

Resistance

- Based on results of *in vitro* studies (reported as abstracts and/or posters)[21,22] and a phase II study in patients with chronic hepatitis B,[17] the M204I mutation in the YMDD motif is considered the key determinant of telbivudine resistance.[3]
- In patients with virological breakthrough resulting from genotypic resistance in the phase III GLOBE trial[22] (see section 3), the M204I mutation was detected in 27 of 28 telbivudine recipients. By contrast, the dominant mutation patterns in lamivudine recipients were the M204I and L180M/M204V mutations (59 of 75 patients). L180M/M204V-based resistance was not associated with telbivudine therapy.[22] Virological breakthrough was defined as ≥1 $\log_{10}$ copies/mL rebound above nadir in serum HBV DNA after a reduction of ≥1 $\log_{10}$ copies/mL during therapy.
- Telbivudine was active or had slightly reduced activity *in vitro* against adefovir-resistant HBV strains (N236T and A181V mutants).[22,23]
- *In vitro* studies using HepG2 cell lines expressing HBV encoding the four most frequent lamivudine resistance mutations showed that lamivudine-resistant HBV had a high degree of cross-resistance to telbivudine (>300-fold resistance) and other L-nucleosides (including emtricitabine, clevudine and torcitabine; >180- to >2000-fold) and reduced susceptibility to entecavir (37- to 471-fold resistance, but some viral load suppression), but remained susceptible to adefovir, tenofovir or alamifovir.[24]

Toxicity

- In *in vitro* studies, telbivudine-5′-triphosphate had no inhibitory effect on host cell DNA polymerases α, β or γ at concentrations up to 100 μmol/L.[13,15] In addition, the drug had a minimal toxic effect on host cell mitochondrial structure, function and DNA content at concentrations up to 10 μmol/L, did not increase lactic acid production[13,15] and was not cytotoxic to human hepatoma cell lines (50% cytotoxic concentration [CC_{50}] >2000 μmol/L) or human peripheral blood mononuclear cells (CC_{50} >200 μmol/L).[3,13]
- No evidence of genotoxicity was shown with telbivudine *in vitro* or *in vivo*, and there was no evidence of teratogenicity or embryofoetal toxicities in preclinical studies;[3] in the US, telbivudine has been granted US FDA pregnancy category B (no adverse findings in animal studies, no human studies performed).[25]
- It is not known whether the risk of telbivudine-related myopathy (see section 4) is increased when the drug is coadministered with other agents associated with myopathy, such as ciclosporin (cyclosporine), HMG-CoA reductase inhibitors or fibric acid derivatives. The potential benefits and risks should be considered if these drugs are coadministered and patients should be monitored closely for signs and symptoms of myopathy (section 4).[15]
- No dose-related or dose-limiting toxicities were evident in phase I and phase I/II dose-escalation studies in healthy volunteers[26] or patients with chronic hepatitis B.[27]

2. Pharmacokinetic Profile

The single- and multiple-dose pharmacokinetics of oral telbivudine have been investigated in healthy volunteers (n = 16–42),[26,28-31] in patients with chronic hepatitis B (n = 35)[27,32] and in individuals with normal or impaired renal or hepatic function (n = 36[33] and 24[34]). The recommended dosage of telbivudine (600mg once daily) was not evaluated in patients with chronic hepatitis B;[15,27] however, the pharmacokinetics of telbivudine at other dosages in these patients did not differ from those in healthy volunteers.[15] Data reported in clinical studies[26-34] (some available only as abstracts[29,31,33]) are supplemented by those from the manufacturer's prescribing information[15] and the European Medicines Agency (EMEA) scientific discussion document.[3]

Absorption and Distribution

- Telbivudine is rapidly absorbed after oral administration, and pharmacokinetics are dose-proportional in the dose range 25–1800mg in healthy volunteers or patients with chronic hepatitis B.[15,26,32]

● After a single dose of telbivudine 600mg in healthy volunteers, the mean peak plasma concentration (C_{max}) of 3.2 μg/mL was achieved after a median of 3.0 hours (t_{max}) and the mean area under the plasma concentration-time curve from time zero to infinity (AUC_∞) was 28 μg • h/mL.[15] Moderate (≈30%) inter-individual variability in C_{max} and AUC_∞ values was evident.

● Steady-state plasma concentrations were achieved after 5–7 days' administration of once-daily telbivudine 600mg in healthy volunteers.[15] Mean steady-state C_{max} and AUC_∞ values were 1.2- and 1.5-fold higher than after a single dose of telbivudine,[26,30,32] indicating slight accumulation of the drug (effective accumulation half-life ≈15 hours).[15] Mean steady-state trough plasma concentrations were ≈0.2–0.3 μg/mL.[15] Telbivudine is minimally bound to plasma proteins *in vitro* (3.3%).[15]

● The pharmacokinetics of a single oral dose of telbivudine 600mg did not alter when the drug was administered under fed or fasting conditions.[28] Consequently, the drug can be administered without regard to food intake.[15]

Metabolism and Elimination

● Apart from intracellular conversion into the active form of the drug (see section 1), telbivudine does not appear to be metabolised (no metabolites were detected following administration of ^{14}C-telbivudine).[15]

● Telbivudine elimination is bi-exponential, with a mean terminal elimination half-life of ≈40 hours. It is excreted as the unchanged active substance, primarily via the kidneys, and the rate of renal clearance indicates that renal filtration predominates.[15] A mass balance study showed that after a single dose of telbivudine 600mg, 42% of the dose was recovered from urine over 7 days.[15]

Special Populations

● Systemic exposure to telbivudine is increased in patients with impaired renal function.[33] C_{max} and AUC_∞ values in patients with mild renal impairment (creatinine clearance [CL_{CR}] 50–80 mL/min) did not differ from those in individuals with normal renal function after a single oral dose of telbivudine 600mg.

● However, telbivudine dose reductions to 200–400mg were required to achieve this outcome in patients with CL_{CR} <50 mL/min or end-stage renal disease requiring haemodialysis.[33] Until an oral solution is available, dose-interval adjustments are currently recommended in these patients,[35] although the effectiveness of such adjustments has not been clinically evaluated.[15]

● Hepatic impairment had no effect on the pharmacokinetics of a single dose of telbivudine 600mg in a study in individuals with normal hepatic function or mild, moderate or severe hepatic impairment (Child-Pugh categories A, B and C).[34] Dosage adjustments are not required in hepatic impairment.[15]

● The pharmacokinetics of telbivudine are not affected by race or gender, and have not been studied in paediatric or geriatric populations.[15]

Drug Interactions

● Telbivudine is neither a substrate for nor an inducer or inhibitor of the cytochrome P450 enzyme system; consequently, pharmacokinetic drug-drug interactions with agents metabolised by these enzymes are unlikely.[15]

● As telbivudine is predominantly eliminated by renal excretion, coadministration of the drug with agents that affect renal function (e.g. aminoglycosides, loop diuretics, platinum compounds, vancomycin, amphotericin B) may alter plasma concentrations of telbivudine or the coadministered drug and caution is required.[15]

● In healthy volunteers,[29,30] no clinically significant pharmacokinetic interactions were evident at steady state between telbivudine 600mg and ciclosporin,[29] adefovir[30] or tenofovir,[31] and between telbivudine 200mg and lamivudine[30] when these agents were administered concomitantly. Likewise, the pharmacokinetics of telbivudine 600mg were not affected by coadministration with peginterferon α-2a (40kD);[29] however, no firm conclusions could be drawn about the effects of

telbivudine on the pharmacokinetics of peginterferon α-2a (40kD) because of higher inter-individual variability of peginterferon α-2a (40kD) concentrations.[15]

3. Therapeutic Efficacy

The efficacy of telbivudine in patients with chronic hepatitis B infection has been investigated in several phase III randomised studies, including the large, double-blind international 2-year GLOBE trial comparing telbivudine with lamivudine (n = 1367),[36-41] a 2-year double-blind trial comparing telbivudine with lamivudine in Chinese patients (n = 332)[42,43] and two 1-year switching trials.[44,45] One of these trials, which was open-label, compared telbivudine with adefovir administered for either the full study period or for 24 weeks followed by a switch to telbivudine for 28 weeks (n = 135).[45] Limited data from a 24-week extension phase are also reported.[45,46] The other was a double-blind trial in patients who were already receiving lamivudine and either continued with lamivudine for a further year or switched to telbivudine (n = 246).[44] Apart from 1-year results from the Chinese study, which are fully published,[42] data are available only as abstracts and/or posters.

GLOBE Trial

Patients eligible for the GLOBE trial were HBsAg-positive and either HBeAg-positive or -negative, had pretreatment serum HBV DNA >6 $\log_{10}$ copies/mL by COBAS® Amplicor PCR assay (lower limit of detection 300 copies/mL), serum ALT levels ≥1.3 to ≤10 × the upper limit of normal (ULN) and compensated liver disease.[36] Patients were stratified according to HBeAg status and were then randomised to receive telbivudine 600mg (n = 680) or lamivudine 100mg (n = 687) once daily for 104 weeks.[36] Two-thirds of patients (921 of 1367 patients) were HBeAg-positive.[36] Approximately 80% of HBeAg-positive and ≈65% of HBeAg-negative patients were Asian (mainly Chinese).[37]

The primary efficacy endpoint was therapeutic response (serum HBV DNA ≤5 $\log_{10}$ copies/mL and serum ALT normalised or HBeAg loss) at 52 weeks.[37] The key secondary endpoint was histological response at 52 weeks; other secondary endpoints included serum HBV DNA reduction from baseline, HBV DNA clearance to undetectable PCR and serum ALT normalisation (level ≤1 × ULN) at 52 and 104 weeks and therapeutic response at 104 weeks.[37,40] An additional, prospectively defined analysis in the GLOBE trial considered whether efficacy and resistance outcomes at 52 and 104 weeks could be predicted from week 24 viral load (patients were categorised as PCR-undetectable, quantifiable level –3 $\log_{10}$ copies/mL, 3–4 $\log_{10}$ copies/mL and >4 $\log_{10}$ copies/mL).[36,37]

At baseline, mean serum HBV DNA levels were 9.5 $\log_{10}$ copies/mL (HBeAg-positive patients) or ≈7.5 $\log_{10}$ copies/mL (HBeAg-negative) and mean serum ALT levels were 137–159 IU/L.[40]

Hepatitis B e Antigen (HBeAg)-Positive Patients

- Telbivudine showed greater efficacy than lamivudine in HBeAg-positive patients with chronic hepatitis B in the GLOBE trial (figure 1). A therapeutic response (primary endpoint) was evident in more telbivudine than lamivudine recipients after 52 weeks' treatment (75% vs 67%; $p < 0.01$) [reported as an abstract and oral presentation].[37]
- In addition, telbivudine was superior to lamivudine at week 52 for a histological response and generally superior for other secondary endpoints, including mean reductions from baseline in serum HBV DNA levels (6.5 vs 5.5 $\log_{10}$ copies/mL; $p < 0.01$) and the proportions of patients with undetectable serum HBV by PCR (figure 1).[37] Moreover, fewer HBeAg-positive telbivudine than lamivudine recipients had evidence of resistance or primary treatment failure (figure 1).[37]
- At 104 weeks,[40] telbivudine continued to show greater efficacy than lamivudine in HBeAg-positive patients with chronic hepatitis B in terms of therapeutic response (64% vs 48%; $p < 0.0001$), mean reductions in serum HBV DNA levels from baseline (5.7 vs 4.4 $\log_{10}$ copies/mL; $p < 0.0001$) HBV DNA undetectable by PCR ($p < 0.0001$) and serum ALT normalisation ($p = 0.014$). Similar proportions of telbivudine or lamivudine recipients achieved

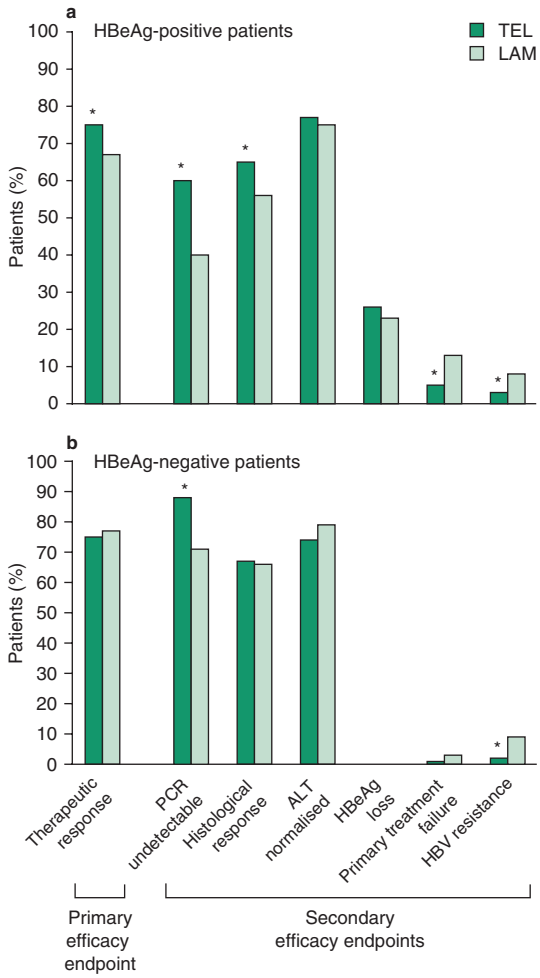


Fig. 1. Efficacy of telbivudine (TEL) in patients with chronic hepatitis B.[37] Results at 52 weeks from the GLOBE trial in (**a**) 921 hepatitis B e antigen (HBeAg)-positive patients or (**b**) 446 HBeAg-negative patients who received oral TEL 600 mg once daily or oral lamivudine (LAM) 100mg once daily for 2 years. Patients with hepatitis B virus (HBV) DNA undetectable by polymerase chain reaction (PCR) assay (lower limit of detection 300 copies/mL) were considered PCR negative. HBeAg loss was assessed only in HBeAg-positive patients. * $p < 0.01$ vs LAM.

HBeAg loss or HBeAg seroconversion (reported as an abstract and poster).[40]

- In a subgroup of 588 HBeAg-positive patients with baseline serum ALT levels ≥2 × ULN (i.e. those eligible for treatment based on international guidelines), more telbivudine than lamivudine recipients achieved HBeAg seroconversion (37% vs 27%; $p < 0.05$) or HBeAg loss (42% vs 32%; $p < 0.05$) [reported as an abstract and poster].[38]
- Telbivudine was also superior to lamivudine at 104 weeks for therapeutic response, mean reductions from baseline in serum HBV DNA levels, normalised serum ALT levels and HBV DNA undetectable by PCR in this patient group (all $p < 0.05$). In addition, treatment failure was less frequent with telbivudine than lamivudine ($p < 0.05$).[38]
- As part of the GLOBE trial design, HBeAg-positive patients who had received telbivudine or lamivudine for 52 weeks could cease treatment, provided they had evidence of serum HBV DNA <5 $\log_{10}$ copies/mL at that time and HBeAg loss for >24 weeks.[39] Of the 59 patients who discontinued treatment at the investigator's discretion, >80% demonstrated sustained HBeAg loss and HBeAg seroconversion at week 104 (reported as an abstract).[39]

HBeAg-Negative Patients

- In HBeAg-negative patients, a therapeutic response at 52 weeks occurred in similar proportions of telbivudine or lamivudine recipients (75% vs 77%; figure 1). However, mean reductions from baseline in serum HBV DNA levels (5.2 vs 4.4 $\log_{10}$ copies/mL; $p < 0.01$) and the proportions of patients who had HBV DNA undetectable by PCR at 52 weeks were greater with telbivudine than lamivudine (figure 1), and fewer telbivudine than lamivudine recipients showed resistance to treatment (figure 1).[37]
- After 104 weeks' of treatment, a therapeutic response was achieved in more HBeAg-negative telbivudine than lamivudine recipients (78% vs 66%; $p = 0.007$).[40] In addition, the superior outcomes seen at 52 weeks with telbivudine versus lamivudine for mean reductions from baseline in serum HBV DNA levels and HBV DNA undetectable by PCR were maintained at 104 weeks (both $p < 0.001$) [reported as an abstract and poster].[40]

Predictors of Efficacy Outcomes

- Response to therapy at week 24 was a strongly positive predictor of good virological and clinical outcomes, and less resistance at 52 weeks in both

HBeAg-positive and HBeAg-negative patients, irrespective of treatment [reported as an abstract and oral presentation].[36]

- HBV DNA was undetectable by PCR at 24 weeks in 45% of telbivudine and 32% of lamivudine recipients who were HBeAg-positive and 80% and 71% of those who were HBeAg-negative.[37] Regardless of treatment, 95% and 96% of HBeAg-positive or HBeAg-negative patients with HBV DNA undetectable by PCR at 24 weeks continued to have HBV DNA undetectable by PCR at 52 weeks. In addition, 90% and 79% achieved ALT normalisation, and HBeAg seroconversion was evident in 39% of HBeAg-positive patients.[15]
- At 48 weeks, resistance was seen in 0.5% of HBeAg-positive and 0% of HBeAg-negative patients with HBV DNA undetectable by PCR at 24 weeks.[15]
- In HBeAg-positive patients, the odds of achieving HBeAg loss, normal serum ALT and HBV DNA undetectable by PCR were 5- to 33-fold greater in patients with mean serum HBV DNA <3 $\log_{10}$ copies/mL at 24 weeks than in those with mean serum HBV DNA ≥3 $\log_{10}$ copies/mL and virological breakthrough was 8 times less likely (all $p < 0.0001$).[36]
- HBeAg-negative patients with HBV DNA undetectable by PCR at 24 weeks were 3- and 23-fold more likely to achieve normal serum ALT and HBV DNA undetectable by PCR at 52 weeks and 61 times less likely to have virological breakthrough than those who were not PCR negative at 24 weeks (all $p < 0.0001$).[36]
- The positive predictive value of virological response at 24 weeks for efficacy outcomes was also evident after 2 years' therapy in both HBeAg-positive and HBeAg-negative patients.[38,40]

Resistance

- Resistance to telbivudine or lamivudine at 2 years in the GLOBE trial was uncommon in patients with a viral load below the quantifiable limit at 24 weeks, irrespective of HBeAg status at baseline (4% vs 9% in HBeAg-positive patients and 2% vs 5% in HBeAg-negative patients), in the overall study population[40] and in the subgroup of patients eligible for treatment based on international guidelines.[38]
- During the GLOBE trial, 21 telbivudine recipients who had experienced virological breakthrough and had evidence of the M2041 mutation, then received ≥16 weeks' treatment with adefovir as monotherapy (n = 16) or in addition to telbivudine (n = 5). A switch to or addition of adefovir therapy resulted in a mean reduction in serum HBV DNA of 4.1 $\log_{10}$ copies/mL and a mean reduction in serum ALT levels of 93 IU/L (reported as an abstract and poster).[41]

Chinese Trial

In the trial in Chinese patients,[42,43] the key eligibility criteria were similar to those in the GLOBE trial; patients were HBeAg-positive or -negative, with pretreatment serum HBV DNA >6 $\log_{10}$ copies/mL by COBAS® Amplicor PCR assay (lower limit of detection 300 copies/mL), serum ALT levels ≥1.3 to ≤10 × ULN and compensated liver disease. Patients were stratified according to HBeAg status and ALT levels (<2.5 or ≥2.5 × ULN) and were randomised to receive either telbivudine 600 mg/day or lamivudine 100 mg/day for 104 weeks. The majority of patients were HBeAg-positive (87%; 290 of 332 patients).[42,43]

The primary endpoint in this trial was the mean reduction from baseline in serum HBV DNA at 52 weeks. Key secondary endpoints assessed at 52 weeks included therapeutic response, virological response, proportion of patients who were HBeAg-negative or had HBeAg seroconversion, and proportion of patients with serum ALT normalisation. The remaining secondary endpoint was primary treatment failure.[42,43] The trial also considered whether efficacy and resistance outcomes at 1[42] and 2[43] years could be predicted from week 24 viral load using the same 24-week response criteria as the GLOBE trial.

At baseline,[43] mean HBV DNA levels were 9.7 $\log_{10}$ copies/mL (HBeAg-positive patients) or ≈7.3 $\log_{10}$ copies/mL (HBeAg-negative) and mean serum ALT levels were 156–177 IU/L.

• The superior efficacy of telbivudine over lamivudine in patients with compensated chronic hepatitis B was confirmed in a trial in Chinese patients.[42,43] After 52 weeks' treatment, telbivudine recipients achieved greater mean reductions from baseline in serum HBV DNA than lamivudine recipients (6.2 vs 5.4 $\log_{10}$ copies/mL; $p < 0.01$).[42]

• At 52 weeks, more telbivudine than lamivudine recipients showed a treatment response (87% vs 64%), virological response (31% vs 18%), had HBV DNA undetectable by PCR (70% vs 43%), HBeAg loss (31% vs 20%) or normalised serum ALT levels (89% vs 75%) [all $p < 0.05$].[42] In addition, primary treatment failure occurred in fewer telbivudine than lamivudine recipients (4% vs 16%; $p < 0.01$). Similar proportions of patients in either treatment group achieved HBeAg seroconversion (25% vs 18%).[42]

• At 104 weeks, telbivudine achieved greater mean reductions from baseline in serum HBV DNA than lamivudine in the overall patient population (reported as an abstract and poster).[43] Additionally, more telbivudine than lamivudine recipients achieved HBV DNA undetectable by PCR, a therapeutic response, ALT normalisation and primary treatment failure was five times lower with telbivudine than lamivudine (all $p < 0.05$).

• In the subgroup of HBeAg-positive patients, HBeAg loss was greater with telbivudine than lamivudine ($p < 0.05$), and HBeAg seroconversion occurred in 29% of telbivudine and 20% of lamivudine recipients.[43]

• HBV DNA undetectable by PCR at week 24 with either telbivudine or lamivudine therapy was a strong predictor of improved efficacy at weeks 52[42] and 104,[43] and reduced virological resistance at week 48.[42]

Switching Trials

The adefovir switching trial[45] only enrolled patients with chronic hepatitis B who were both HBsAg-positive and HBeAg-positive. Other key eligibility criteria included baseline serum HBV DNA >6 $\log_{10}$ copies/mL by COBAS® Amplicor PCR assay (lower limit of detection 300 copies/mL), serum ALT levels ≥1.3 to ≤10 × ULN and compensated liver disease. Patients were randomised to receive either telbivudine 600mg (n = 45) or adefovir 100mg (n = 44) once daily for 52 weeks, or adefovir for 24 weeks, followed by telbivudine for 28 weeks (n = 46).[45]

The lamivudine switching trial[44] enrolled HBsAg-positive, HBeAg-positive or -negative patients who had received lamivudine therapy for 3–12 months prior to screening. The trial was designed to compare the efficacy of switching to telbivudine 600mg once daily (n = 122) versus continuing with lamivudine 100mg once daily (n = 124) for 52 weeks. Prior to randomisation, patients were stratified by HBeAg status (66% of patients in either treatment arm were HBeAg-positive) and duration of previous lamivudine therapy. Other eligibility criteria included serum HBV DNA >3 $\log_{10}$ copies/mL and compensated liver disease.[44]

The primary endpoint in both switching studies was mean reduction from baseline in serum HBV DNA at week 24;[44,45] secondary endpoints in the adefovir switching trial included clearance of HBV DNA to undetectable by PCR at weeks 24 and 52.[45] Analyses were in the intent-to-treat population.

At baseline in the adefovir switching trial,[45] mean serum HBV DNA levels were 9.5–10 $\log_{10}$ copies/mL and mean serum ALT levels were 138–199 IU/L. In the lamivudine switching trial,[44] baseline mean serum HBV DNA levels were ≈6 $\log_{10}$ copies/mL in either treatment group and mean serum ALT levels were <70 IU/L.

• Telbivudine showed greater antiviral efficacy than adefovir in patients with chronic hepatitis B in the adefovir switching trial.[45,46] Greater reductions in serum HBV DNA from baseline at 24 weeks (primary efficacy endpoint) were seen with telbivudine than adefovir (6.3 vs 4.97 $\log_{10}$ copies/mL; $p < 0.01$) [reported as abstracts and posters].[45,46] In addition, more telbivudine than adefovir recipients had serum HBV DNA <3 $\log_{10}$ copies/mL (49% vs 22%; $p < 0.01$).[45]

• At 52 weeks, mean serum HBV DNA levels were significantly lower in patients who received telbivudine throughout the study or who switched from adefovir to telbivudine compared with those who

received adefovir throughout (3.03 and 3.02 vs 4.26 $\log_{10}$ copies/mL; both $p < 0.01$).[45,46]

- A suboptimal response (serum HBV DNA levels ≥3 $\log_{10}$ copies/mL) was seen in 78% (36 of 46) of patients in the adefovir/telbivudine arm and 77% (34 of 44) of those in the adefovir arm after 24 weeks' treatment with adefovir.

- Between 24 and 52 weeks, the 36 suboptimal responders who switched to telbivudine achieved a further 2.1 $\log_{10}$ copies/mL reduction in serum HBV DNA, whereas the 34 adefovir recipients with a suboptimal response achieved a further 0.8 $\log_{10}$ copies/mL reduction.[45,46]

- In an extension phase of the adefovir switching trial, adefovir recipients who continued to show a suboptimal response after 52 weeks' treatment could also switch to telbivudine. Those who switched (n = 20) achieved a mean 2.1 $\log_{10}$ copies/mL reduction in serum HBV DNA between weeks 52 and 76.[45]

- Patients who received telbivudine throughout the switching trial and the extension phase (n = 40) achieved mean serum HBV DNA reductions from baseline of 6.8 and 7.2 $\log_{10}$ copies/mL at 52 and 76 weeks.[45] In addition, serum HBV DNA was undetectable by PCR in 39% of telbivudine recipients at 24 weeks, 60% at 52 weeks and 72% at 76 weeks.[46]

- Telbivudine demonstrated antiviral efficacy in patients with chronic hepatitis B and a suboptimal response to lamivudine (serum HBV DNA of >3 $\log_{10}$ copies/mL, despite lamivudine therapy for 3–12 months).[44] Patients randomised to receive telbivudine achieved greater mean reductions from baseline in serum HBV DNA at 24 weeks compared with those randomised to continue lamivudine therapy (1.9 vs 0.9 $\log_{10}$ copies/mL; $p = 0.002$) [reported as an abstract and poster].[44]

- Moreover, serum HBV DNA levels were reduced to <5 $\log_{10}$ copies/mL in significantly more telbivudine than lamivudine recipients (80% vs 56%; $p < 0.001$), and HBV DNA became undetectable by PCR in 40% of telbivudine and 31% of lamivudine recipients.[44]

4. Tolerability

The tolerability of telbivudine was evaluated in all clinical trials discussed in section 3. Discussion in this section focuses primarily on results from the GLOBE trial because it was the largest study. Data presented are from the manufacturer's prescribing information,[15] the EMEA scientific discussion document,[3] and several abstracts and posters.[40,44,45]

- Telbivudine was generally well tolerated in the GLOBE trial and most adverse events were mild or moderate in severity.[15] Few telbivudine or lamivudine recipients in the GLOBE trial discontinued treatment because of adverse events (2.8% vs 2.8%).[3]

- The incidence of adverse events of any severity or of severe adverse events with telbivudine did not differ from that with lamivudine in the GLOBE trial.[3] Dizziness, headache, cough, gastrointestinal disorders, rash, elevated blood creatine kinase (CK) levels, fatigue and elevated serum ALT levels were the most commonly reported adverse events of any severity reported with telbivudine in the first 52 weeks of treatment.[15]

- Elevated blood CK levels were the most frequent adverse event possibly or probably related to telbivudine in the first year of treatment, followed by fatigue, headache, nausea, dizziness and diarrhoea (figure 2).[3]

- The adverse event profile reported with telbivudine during the second year of the GLOBE study was consistent with that seen in the first year of treatment,[40] and in the switching trials, the tolerability profile of telbivudine did not differ from that of lamivudine[44] or adefovir.[45]

- Myopathy has been reported with the use of some nucleoside analogues,[25,47] including lamivudine,[48] and cases of myopathy during telbivudine therapy have been identified; however, these did not correlate with the magnitude or timing of CK elevations.[15,25] Persistent, unexplained muscle-related symptoms in telbivudine recipients should be investigated and treatment discontinued in the event of myopathy.[15,25]

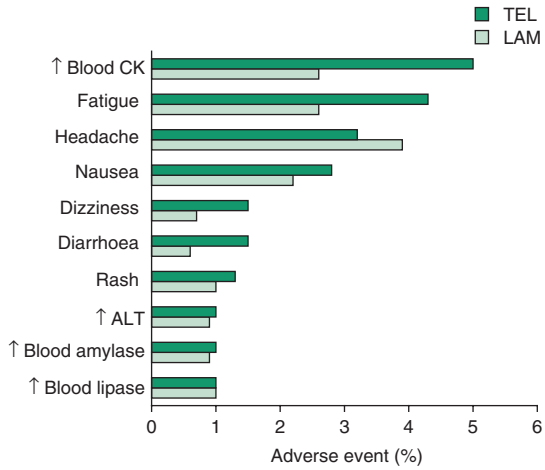


Fig. 2. Tolerability of telbivudine (TEL) in chronic hepatitis B. Incidence of adverse events possibly or probably related to treatment reported at 52wk in ≥1% of telbivudine recipients in the GLOBE trial, a 2-year randomised, double-blind study comparing oral TEL 600 mg/day (n = 680) with oral lamivudine (LAM) 100 mg/day (n = 687).[3] **CK** = creatine kinase; ↑ indicates increased.

ALT Flares

- In the first year of treatment in the GLOBE study, ALT flares of any severity were reported in 10.3% of telbivudine and 13.1% of lamivudine recipients,[3] while severe (grade 3–4) ALT flares occurred in 2.6% of telbivudine and 4.6% of lamivudine recipients.[15] When the total 104-week study period was considered, on-treatment ALT flares of any severity were reported in approximately half as many telbivudine recipients compared with lamivudine recipients (4.1% vs 7.4%).[40]
- ALT flares were more likely in the first 24 weeks of treatment and were more frequent in HBeAg-positive than HBeAg-negative patients.[3,15] From baseline to 24 weeks, ALT flares in HBeAg-positive patients were reported in 13.9% of telbivudine and 12.5% of lamivudine recipients compared with 2.1% and 2.2% of HBeAg-negative telbivudine or lamivudine recipients.[3]
- Between weeks 24 and 52, <1% of HBeAg-positive and no HBeAg-negative telbivudine recipients, and ≈5% of lamivudine recipients in either HBeAg group had evidence of ALT flares.[3] Patients experiencing ALT flares should be closely monitored for hepatic decompensation.[15,25]

Creatine Kinase Elevations

- The incidence of severe (grade 3–4 [>7 × ULN]) CK elevations with telbivudine, irrespective of cause, was 2.4-fold higher than that seen with lamivudine during the first year of treatment[15] and 3-fold higher over the total 2-year study period (statistical analysis not reported).[40] Caucasian race and elevated pre-treatment CK levels were predictive of severe CK elevations in the first 52 weeks of treatment.[15]
- CK elevations were generally asymptomatic[15,40] and once noted, generally decreased by the next assessment in the first 52 weeks of the study, even with continuing treatment.[15] Nevertheless, mean recovery time was longer with telbivudine than lamivudine over the 2-year treatment period.[40] CK elevations have also been noted with other antiviral therapies used in the management of chronic hepatitis B, including lamivudine[48] and adefovir.[49]

5. Dosage and Administration

Telbivudine is approved for the treatment of adult patients with HBeAg-positive or HBeAg-negative chronic hepatitis B who have compensated liver disease and evidence of viral replication, persistent elevation of serum ALT levels and[15]/or[25] histological evidence of active hepatic inflammation/fibrosis. The recommended dosage of telbivudine is 600mg administered orally once daily with or without food. The optimal duration of treatment is unknown.[15,25]

Local prescribing information should be consulted for other warnings, precautions and contraindications and the dose interval adjustments recommended in patients with renal impairment (CL_{CR} <50 mL/min). Telbivudine is not recommended for use in children and adolescents aged <16 years because of a lack of efficacy and tolerability data.[15,25]

6. Telbivudine: Current Status

Telbivudine is approved in Europe, the US and numerous other countries worldwide for the treatment of adult patients with chronic hepatitis B and

compensated liver disease who have elevated serum ALT levels and evidence of viral activity. In two phase III clinical trials in ≈1700 patients with chronic hepatitis B, telbivudine showed greater efficacy than lamivudine and was generally well tolerated. In addition, the drug was effective in patients who switched to telbivudine after treatment with lamivudine or adefovir.

Acknowledgements

The manuscript was reviewed by: **E. Gane**, NZ Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand; **J.-D. Jia**, Liver Research Center, Beijing Friendship Hospital, Beijing, China; **C.-L. Lai**, University of Hong Kong, Hong Kong, PR China. During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article. Changes based on any comments received were made on the basis of scientific and editorial merit.

References

1. Farrell GC, Teoh NC. Management of chronic hepatitis B virus infection: a new era of disease control. Intern Med J 2006 Feb; 36 (2): 100-13
2. Perz JF, Armstrong GL, Farrington LA, et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006 Oct; 45 (4): 529-38
3. European Medicines Agency. Sebivo: scientific discussion. [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/sebivo/H-713-en6.pdf [Accessed 2007 May 19]
4. Robinson DM, Scott LJ, Plosker GL. Entecavir: a review of its use in chronic hepatitis B. Drugs 2006; 66 (12): 1605-22; discussion 1623-4
5. Buti M, Esteban R. Drugs in development for hepatitis B. Drugs 2005; 65 (11): 1451-60
6. Ganem D, Prince AM. Hepatitis B virus infection: natural history and clinical consequences. N Engl J Med 2004 Mar 11; 350 (11): 1118-29
7. Liaw YF. Prevention and surveillance of hepatitis B virus-related hepatocellular carcinoma. Semin Liver Dis 2005; 25 Suppl. 1: 40-7
8. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006 Jan 4; 295 (1): 65-73
9. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006 Mar; 130 (3): 678-86
10. Robins GW, Scott LJ, Keating GM. Peginterferon-α-2a (40kD): a review of its use in the management of patients with chronic hepatitis B. Drugs 2005; 65 (6): 809-25
11. Jarvis B, Faulds D. Lamivudine: a review of its therapeutic potential in chronic hepatitis B [published erratum appears in Drugs 1999; 58: 587]. Drugs 1999 Jul; 58 (1): 101-41
12. Dando T, Plosker G. Adefovir dipivoxil: a review of its use in chronic hepatitis B. Drugs 2003; 63 (20): 2215-34
13. Bryant ML, Bridges EG, Placidi L, et al. Antiviral L-nucleosides specific for hepatitis B virus infection. Antimicrob Agents Chemother 2001 Jan; 45 (1): 229-35
14. Standring DN, Bridges EG, Placidi L, et al. Antiviral β-L-nucleosides specific for hepatitis B virus infection. Antivir Chem Chemother 2001; 12 Suppl. 1: 119-29
15. European Medicines Agency. Sebivo 600mg film-coated tablets: summary of prescribing information [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/sebivo/H-713-PI-en.pdf [Accessed 2007 May 19]
16. Seifer M, Patty A, Dukhan D et al. Telbivudine (LDT) preferentially inhibits second (+) strand HBV DNA synthesis [abstract no. M935]. Gastroenterology 2005 May 16; 128 (4 Suppl. 2): 742-43. Plus poster presented at Digestive Disease Week; 2005 May 14-19; Chicago (IL)
17. Lai CL, Leung N, Teo EK, et al. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology 2005 Aug; 129 (2): 528-36
18. Bridges EG, Juodawlkis A, Faraj A, et al. Antiviral activity of β-L-thymidine and β-L-2′deoxycytidine in the woodchuck model of chronic hepatitis B infection [abstract no. 91]. Antiviral Res 2000 Jan; 46 (1): 62
19. Delaney WEIV, Yang H, Miller MD, et al. Combinations of adefovir with nucleoside analogs produce additive antiviral effects against hepatitis B virus in vitro. Antimicrob Agents Chemother 2004 Oct; 48 (10): 3702-10
20. Lai CL, Leung NW, Teo EK, et al. Phase IIb extended-treatment trial of telbivudine vs lamivudine vs combination treatment in hepatitis B patients: two-year results [abstract no 320]. Gastroenterology 2005 Apr; 128 (4 Suppl. 2): A692
21. Seifer M, Patty A, Chapron C, et al. Genotypic analysis of patients with evaluable HBV DNA after 1 year of telbivudine therapy in the GLOBE Registration Trial [abstract no. 93]. Digestive Disease Week; 2007 May 19-24; Washington DC
22. Standring DN, Patty A, Chapron C, et al. Resistance determination in patients experiencing virologic breakthrough following telbivudine or lamivudine therapy in the international GLOBE trial [abstract no. S1781 plus poster]. Digestive Disease Week; 2007 May 19-24; Washington DC
23. Standring DN, Seifer M, Patty A, et al. HBV resistance determination from the telbivudine GLOBE registration trial [abstract no. 514]. J Hepatol 2006; 44 (2 Suppl.): S191
24. Yang H, Qi X, Sabogal A, et al. Cross-resistance testing of next-generation nucleoside and nucleotide analogues against lamivudine-resistant HBV. Antivir Ther 2005; 10 (5): 625-33
25. Idenix Pharmaceuticals Inc. Tyzeka (telbivudine) tablets. US prescribing information [online]. Available from URL: https://www.tyzeka.com/pdf/TYZEKA_PI_11-3-06_TYZ_MPI_02_001.pdf [Accessed 2007 Jul 29]
26. Hu P, Jiang J, Wang H, et al. Single-dose and multiple-dose pharmacokinetics and safety of telbivudine after oral administration in healthy Chinese subjects. J Clin Pharmacol 2006 Sep; 46 (9): 999-1007
27. Lai CL, Lim SG, Brown NA, et al. A dose-finding study of once-daily oral telbivudine in HBeAg-positive patients with chronic hepatitis B virus infection. Hepatology 2004 Sep; 40 (3): 719-26
28. Zhou XJ, Lloyd DM, Chao GC, et al. Absence of food effect on the pharmacokinetics of telbivudine following oral administra-

tion in healthy subjects. J Clin Pharmacol 2006 Mar; 46 (3): 275-81

29. Zhou XJ, Fielman B, Dubuc-Patrick G, et al. Absence of pharmacokinetic drug-drug interaction between telbivudine and peginterferon alpha-2a or cyclosporine in healthy subjects [abstract no. 522]. J Hepatol 2006; 44 Suppl. 2: S194
30. Zhou XJ, Fielman BA, Lloyd DM, et al. Pharmacokinetics of telbivudine in healthy subjects and absence of drug interaction with lamivudine or adefovir dipivoxil. Antimicrob Agents Chemother 2006 Jul; 50 (7): 2309-15
31. Zhou X, Pietropaolo K, Becker M, et al. Absence of pharmacokinetic drug-drug interaction between telbivudine and tenofovir [abstract no. 1782 plus poster]. Digestive Disease Week; 2007 May 19-24; Washington DC
32. Zhou XJ, Lim SG, Lloyd DM, et al. Pharmacokinetics of telbivudine following oral administration of escalating single and multiple doses in patients with chronic hepatitis B virus infection: pharmacodynamic implications. Antimicrob Agents Chemother 2006 Mar; 50 (3): 874-9
33. Zhou XJ, Myers M, Chao G, et al. Clinical pharmacokinetics of telbivudine, a potent antiviral for hepatitis B, in subjects with impaired hepatic or renal function [abstract no. 1166]. Hepatology 2004 Oct; 40 (4 Suppl. 1): 672
34. Zhou XJ, Marbury TC, Alcorn HW, et al. Pharmacokinetics of telbivudine in subjects with various degrees of hepatic impairment. Antimicrob Agents Chemother 2006 May; 50 (5): 1721-6
35. Data on file. Novartis Pharmaceuticals Corporation, 2007
36. Lai C-L, Gane E, Liaw Y-F, et al. Maximal early HBV suppression is predictive of optimal virologic and clinical efficacy in nucleoside-treated hepatitis B patients: scientific observations from a large multinational trial (the GLOBE study) [abstract no. 92]. Hepatology 2005 Oct; 42 (4 Suppl. 1): 232A-3A. Plus oral presentation at The Liver Meeting; 2005 Nov 11-15; San Francisco (CA)
37. Bzowej N, Lai C, Gane E, et al. Phase III comparison of telbivudine vs lamivudine in patients with chronic hepatitis B: efficacy, safety, and predictors of response at 1 year [abstract no. 482]. Gastroenterology 2006 Apr; 130 (4 Suppl. 2): A765-A766. Plus oral presentation at Digestive Disease Week; 2006 May 20-25; Los Angeles (CA)
38. Rasenack J, Poynard T, Lai C-L, et al. Efficacy of telbivudine vs lamivudine at 2 years in patients with HBeAg-positive chronic hepatitis B who are eligible for treatment based on guidelines [abstract plus poster]. 42nd Annual Meeting of the European Association for the Study of the Liver; 2007 Apr 11-15; Barcelona
39. Poynard T, Chutaputti A, Hwang SG, et al. Sustained off-treatment HBeAg response in telbivudine and lamivudine treated HBeAg-positive patients from the GLOBE study [abstract]. 42nd Annual Meeting of the European Association for the Study of the Liver; 2007 Apr 11-15; Barcelona
40. Han S, Lai C, Gane E, et al. Telbivudine GLOBE trial at year two: efficacy, safety, and predictors of outcome in patients with chronic hepatitis B [abstract no. S1777 plus poster]. Digestive Disease Week; 2007 May 19-24; Washington DC
41. Gane E, Lai C-L, Min A, et al. Adefovir salvage therapy for virologic breakthrough in telbivudine-treated patients from the GLOBE study [abstract and poster]. 42nd Annual Meeting of the European Association for the Study of the Liver; 2007 Apr 11-15; Barcelona
42. Jia JD, Hou JL, Yin YK, et al. The degree of HBV suppression with 24 week telbivudine- or lamivudine-treatment in hepatitis B patients predicts the efficacy of the treatment at week 52 [in Chinese]. Zhonghua Gan Zang Bing Za Zhi 2007 May; 15 (5): 342-5
43. Wang Y, Jia J, Hou J, et al. A phase III comparative trial of telbivudine vs lamivudine in Chinese patients with chronic hepatitis B: two-year results [abstract no. S1768 plus poster]. Digestive Disease Week; 2007 May 19-24; Washington DC
44. Safadi R, Xie Q, Chen Y, et al. A randomized trial of switching to telbivudine versus continued lamivudine in adults with chronic hepatitis B: results of the primary analysis at week 24 [abstract plus poster]. 42nd Annual Meeting of the European Association for the Study of the Liver; 2007 Apr 11-15; Barcelona
45. Bzowej N, Marcellin P, Chan H, et al. A randomized trial of telbivudine vs adefovir for HBeAg-positive chronic hepatitis B: efficacy through week 76, predictors of response and effects of switching to telbivudine [abstract no. S1774 plus poster]. Digestive Disease Week; 2007 May 19-24; Washington DC
46. Marcellin P, Chan HLY, Lai C-L, et al. 76 week follow up of HBeAg-positive chronic hepatitis B patients treated with telbivudine, adefovir or switched from adefovir to telbivudine [abstract]. 42nd Annual Meeting of the European Association for the Study of the Liver; 2007 Apr 11-15; Barcelona
47. Moyle G. Toxicity of antiretroviral nucleoside and nucleotide analogues: is mitochondrial toxicity the only mechanism? Drug Saf 2000 Dec; 23 (6): 467-81
48. GlaxoSmithKline Research. Epivir-HBV® (lamivudine). US prescribing information [online]. Available from URL: http://us.gsk.com/products/assets/us_epivir_hbv.pdf [Accessed 2007 Jul 29]
49. Gilead Sciences Inc. Hepsera® (adefovir dipivoxil). US prescribing information [online]. Available from URL: http://www.hepsera.com/pdf/GIL214-07_Hepsera_PDF.8.pdf [Accessed 2007 Jul 29]

Correspondence: *Susan J. Keam*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@adis.co.nz