Telbivudine (Sebivo) in patients with hepatitis B virus (HBV) chronic infection

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BRIEF DRUG PROFILE

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INTRODUCTION

Hepatitis B is the most common serious liver infection in the world, with about 350 million people who are infected with the hepatitis B virus (HBV) and about 1 million deaths annually. Hepatitis B is characterized by an acute and a chronic phase, if the subject fails to produce adequate immune response.

About 5-10% of adults infected with HBV go on to develop chronic infection and become chronic carriers (CHB); moreover, the liver damage, if not stopped, continues until cirrhosis or hepatocellular carcinoma. In the natural history of HBV infection, the most important event is HBeAg seroconversion, characterized by loss of HBeAg (a specific antigen of the virus) and development of anti-HBe antibodies (HBeAg-positive patients). If the seroconversion has occurred early (when liver damage is not already significant) and is maintained, long-term prognosis is excellent. The disease can follow a more aggressive course if active viral replication persists despite anti-HBe positivity. This state, characterized by continuing viral replication, has been termed as HBeAg-negative CHB, and is the most prevalent form in Italy. At the moment, there are 4 approved antiviral drug classes, with different antiviral efficacy, for the treatment of chronic hepatitis B: interferons, nucleoside analogues, nucleotide analogues, and cyclopents. The primary target of the treatment is a prolonged suppression of viral replication, in order to avoid long term complications and increase survival.

INDICATIONS AND DOSING

Telbivudine is a new synthetic thymidine nucleoside analogue with selective activity against HBV; it is the unmodified beta-L enantiomer of the naturally occurring nucleoside thymidine. The drug is indicated for the treatment of chronic hepatitis B in adults with compensated liver disease, evidence of active viral replication and signs of liver damage. Telbuvidine is orally administred at a once daily dose of 600 mg. Telbuvidine is currently included by AIFA (*Agenzia Italiana del Farmaco*) in a drug efficacy and safety monitoring program.

PHARMACOKINETICS

Telbuvidine pharmacokinetics data are similar in healthy subjects and CHB patients; there are not significant gender- or race-related differences. Dose adjustment is recommended in patients with moderate to severe renal dysfunction and in those undergoing hemodialysis, seen the prevalently renal excretion of this substance.

Absorption			
Bioavailability	**Cmax**	**Tmax**	**Binding to plasma proteins**
About 42%	3.2 ± 1.1 µg/l	3 h (1-6)	3.3 (2-5)%
Metabolism and distribution			
Volume of distribution	**Metabolism**	**Metabolites**	**Biological activity of metabolites**
8.2 ± 4.1 l/kg	-	No metabolites	-
Elimination			
Clearance	**Plasma terminal half-life**	**Elimination**	**Interactions**
130 ml/min	40-49 h	Primarily urinary	Drugs that alter renal function

Table I

Absorption, distribution, metabolism and elimination of telbivudine after oral administration

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PHARMACODYNAMICS

Telbuvidine is a synthetic thymidine analogue who must be activated by phosphorylation by cellular kinases; after activation, it selectively inhibits HBV polymerase (reverse transcriptase) by competing with one of its natural substrates, thymidine 5'-triphosphate.

EFFICACY AND SAFETY

Telbivudine efficacy and safety have been tested in three phase III trials, two of them using lamivudine as comparator, and one using adefovir dipivoxil. For the main study GLOBE, the vast majority of the population enrolled was asian; only 98 caucasian patients included in the study received telbivudine. Results showed the non-inferiority of telbuvidine over lamuvidine for both HBeAg-positive and negative patients; superiority of the telbuvidine treatment is showed only in the HBeAg-positive group. Generally, telbuvidine treatment provides greater antiviral and clinical efficacy than lamuvidine, with less development of resistance. Preliminary 2-year results show that telbivudine-treated patients exhibit higher rates of maintained responses on all key efficacy measures examined in both HBeAg-positive and HBeAg-negative patients populations. Two safety events of special interest have been identified in the GLOBAL trial: ALT flares and CK elevations. The first ones are globally more frequently reported in lamivudine than in telbivudine-treated patients (13.1% vs 10.0%). CK elevations were reported with higher incidence in telbivudine treated patients: because the rise of this enzyme is related to muscular toxicity, telbivudine treatment needs a close monitoring program for muscle-related side effects.

ECONOMIC EVALUATIONS

Costs of currently approved products for the treatment of chronic hepatitis B can vary widely: factors affecting costs include the direct cost of the drug, length of treatment, and complication associated with continued therapy, like development of resistance or intolerable adverse events.

Study	Design	Comparator	Efficacy (telbivudine vs lamivudine)	Safety
GLOBE study, 2007	1,367 chronic hepatitis B patients distinguished in HBeAg-positive and negative. Double blind, randomized 70-30%, multicenter, international phase III trial	Telbivudine 600 mg daily Lamivudine 100 mg daily	**HBeAg-positive patients (n = 921)** Therapeutic response*: 75.3% vs 67.0% p = 0.0049 Histologic response**: 64.7% vs 56.3% p = 0.0105 Showed superiority to lamivudine (52 weeks) **HBeAg-negative patients (n = 446)** Therapeutic response*: 75.2% vs 77.2% p = 0.6187 Histologic response**: 66.6% vs 66.0% p = 0.8994 Showed non-inferiority to lamivudine (52 weeks)	Incidence of adverse events was comparable between the two groups; AEs most commonly reported for telbivudine are infection and infestations, gastrointestinal disorders, general disorders and administration site conditions
Hou J et al., 2008	332 chronic hepatitis B patients distinguished in HBeAg-positive and negative. Double blind, randomized, multicenter, international phase III trial	Telbivudine 600 mg daily Lamivudine 100 mg daily	**HBeAg-positive patients (n = 290)** Reduction of serum HBV DNA: 6.3 $\log_{10}$ vs 5.5 $\log_{10}$, $p < 0.001$ HBV DNA polymerase chain-reaction negative: 67% vs 38%, $p < 0.001$ ALT normalization: 87% vs 75%, p = 0.007 Therapeutic response: 85% vs 62%, $p < 0.001$ HBeAg loss: 31% vs 20%, p = 0.047 HBeAg-negative patients (n = 42) Treatment effects showed similar pattern	Clinical adverse events were similar in the two treatment groups
Chan HL et al., 2007	135 treatment-naïve, chronic hepatitis B HBeAg-positive patients. Open-label, randomized, controlled, phase III trial	(1) Telbivudine daily (52 weeks) (2) Adefovir daily (52 weeks) (3) Adefovir (24 weeks) + Telbivudine (28 weeks)	**HBeAg-positive patients (n = 131)** Reduction of serum HBV DNA: (1) 6.30 $\log_{10}$ vs (2)+(3) 4.97 $\log_{10}$, $p < 0.001$ HBV DNA polymerase chain-reaction negative: (1) 39% vs (2)+(3) 12%, p = 0.001 Mean residual HBV DNA level: (1) 3.01 $\log_{10}$ vs (2) 4.00 $\log_{10}$ vs (3) 3.02 $\log_{10}$, p = 0.004	AEs were similar across groups; the most common were upper respiratory symtoms, headache, back pain, diarrhea

Table II

Summary of main studies investigating efficacy and safety of telbivudine in hepatitis B chronic patients

AEs = adverse events.

* primary endpoint, defined as serum HBV DNA < 5 $\log_{10}$ copies/ml associated with either HBeAg loss or ALT normalization at week 52

** secondary endpoint, defined as at least 2-point reduction in the Knodell necroinflammatory score with no worsening in the fibrosis score

	RS		Frequency	Package	Price	Ex-factory price	Monthly price**
Self-injectable drugs							
Interferon alpha-2b (HBeAg+ pts)	PHT	10 MIU	3 times a week	1 vial	88.46	53.60	611.03
Interferon alpha-2b (HBeAg+ pts)	PHT	18 MIU	3 times a week	1 vial	147.46	89.35	565.87
Interferon alpha-2b (HBeAg+ pts)	PHT	25 MIU	3 times a week	1 vial	203.69	123.42	562.78
Interferon alpha-2b (HBeAg- pts)	PHT	10 MIU	4 times a week	1 vial	88.46	88.46	353.75
Interferon alpha-2b (HBeAg- pts)	PHT	18 MIU	5 times a week	1 vial	147.46	147.46	327.61
Interferon alpha-2b (HBeAg- pts)	PHT	25 MIU	6 times a week	1 vial	203.69	203.69	325.82
Peginterferon alpha-2a*	PHT	180 mcg	3 times a week	1 vial	321.41	194.75	778.98
Oral drugs							
Adefovir dipivoxil*	H	10 mg	Daily	30 tablets	705.55	427.50	399.00
Entecavir*	H	0.5 mg	Daily	30 tablets	670.28	406.13	379.05
Entecavir*	H	1 mg	Daily	30 tablets	670.28	406.13	379.05
Lamivudine	PHT	100 mg	Daily	28 tablets	89.57	54.27	54.27
Lamivudine	PHT	5 mg	Daily	Oral solution (240 ml)	38.43	23.29	54.33
Telbivudine*	H	600 mg	Daily	28 tablets	625.58	379.04	379.04

Table III

Monthly pharmaceutical costs of different available therapies for chronic hepatitis B treatments

* Price neglects further negotiated discounts on supplies for NHS

** Four weeks

H = hospital prontuary; PHT = hospital-territorial prontuary; pts = patients; RS = reimbursement status; MIU = million international unit

Currently there are six approved drugs for hepatitis B therapy: interferon alpha-2b, pegylated interferon alpha-2a, and four oral monotherapeutic agents (adefovir dipivoxil, entecavir, lamivudine and telbivudine). Injectable interferons and oral drugs represent two different pharmacological approaches, one based on host immunity stimulation, and the other on direct antiviral action. Furthermore, polymerase inhibitors need to be indefinitely administered since they are unable to induce a sustained response even after years of continuous administration.
Costs of treatment with oral drugs represent a drastic reduction compared to subcutaneous therapy, and these treatments are also associated with a good response rate and excellent safety profile, making the overall treatment with oral drugs cost effective. The main limitation of these drugs is the emergence of resistance during the treatment: in particular patients treated with lamivudine, which is effective and not expensive, reported high resistance rates, ranging from 14-32% after 1 year of therapy to 58% with 2-3 years.
In Table III we calculated the monthly pharmaceutical cost of available hepatitis B treatments in Italy: this is not to be intended as a cost-minimization analysis, but as a simple overlook of currently available treatments. Considered dosages are those derived from reference trials or from the SPCs of the products. For interferon alpha-2b, we considered a dosing of 9-10 MIU/3 times a week for HBeAg+ patients and of 5-6 MIU/3 times a week for HBeAg-, as seen in a national treatment protocol. Prices of the drugs are deduced from Informatore Farmaceutico 2008: we always considered ex-factory price.
Globally, the monthly cost of telbivudine is nearly the same of entecavir (379 €), and similar to the one of adefovir; the cost of peginterferon is almost twice, and the less costly drug results lamivudine, with a monthly cost of about 54 €.

Name of the Medicinal Product	Sebivo
Marketing Authorisation Holder	Novartis Europharm LTD
Active Substance	Telbivudine
Pharmaco-therapeutic Group	Antiviral for systemic use
ATC Code	J05AF11
Date of issue of Marketing Authorisation valid throughout the European Union	24 April 2006

REFERENCES

- AIFA – Agenzia Italiana del Farmaco – Elenco dei farmaci sottoposti a monitoraggio intensivo. Available on http://www.agenziafarmaco.it/REGISTRAZIONE_FARMACO/sectionb998.html?target=&area_tematica=REGISTRAZIONE_FARMACO§ion_code=AIFA_FARMACOV_MONIT_INT&cache_session=false
- Amarapurkar DN. Telbivudine: a new treatment for chronic hepatitis B. *World J Gastroenterol* 2007; 13: 6150-5
- Chan HL, Heathcote EJ, Marcellin P, Lai CL, Cho M, Moon YM et al.; 018 Study Group. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial. *Ann Intern Med* 2007; 147: 745-54
- Gazzetta Ufficiale della Repubblica Italiana – GU 28 – 03/02/2007
- Gazzetta Ufficiale della Repubblica Italiana – GU 135 – 13/06/2003
- Gazzetta Ufficiale della Repubblica Italiana – GU 271 – 21/11/2007
- Gazzetta Ufficiale della Repubblica Italiana – GU 278 – 26/11/2003
- Holbrook ML. Cost-effective pharmacologic therapies to treat chronic hepatitis B: how far have we really come? *J Manag Care Pharm* 2008; 14: 65-9
- Hou J, Yin YK, Xu D, Tan D, Niu J, Zhou X et al. Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: Results at 1 year of a randomized, double-blind trial. *Hepatology* 2008; 47: 447-54
- Informatore Farmaceutico 2008, Ed. Elsevier Masson, updated to June, 2008
- Jones R, Nelson M. Novel anti-hepatitis B agents: A focus on telbivudine. *Int J Clin Pract* 2006; 60: 1295-9
- Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y et al.; Globe Study Group. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007; 357: 2576-88
- Massari M, UO Malattie Infettive, ASMN di Reggio Emilia. Protocollo per il trattamento delle epatiti croniche CCV, HBV, HDV. Reviewed December 2004
- Sebivo – EPAR summary for the public
- Sebivo Scientific Discussion – European Medicines Agency (EMEA), 2006. Available on http://www.emea.europa.eu/humandocs/PDFs/EPAR/sebivo/H-713-en6.pdf
- Smith VE, Bruno CJ. The search for cost-effective treatment of chronic hepatitis B. *J Manag Care Pharm* 2008; 14: 61-4
- Tyzeka official FDA information, side effects and uses – Professional information. Available on http://www.drugs.com/pro/tyzeka.html

