Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sebivo

telbivudine

Procedure No.: EMEA/H/C/000713/R/0023

Note

Renewal Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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London, 16 February 2012
EMA/CHMP/295078/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on the renewal of the marketing authorisation for Sebivo

International non-proprietary name: telbivudine

Procedure No.: EMA/H/C/000713/R/23

Marketing authorisation holder (MAH): Novartis Europharm Ltd.

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1. Background information on the renewal

1.1. Marketing authorisation

The European Commission granted the Marketing Authorisation for Sebivo based on a favourable opinion adopted by the CHMP on 26 April 2007.

1.2. Steps taken after the granting of the marketing authorisation / first renewal

Subsequent to the granting of the Marketing Authorisation, the following changes were approved:

No	Scope	Opinion/ Notification issued on	Annexes affected[1]
IG/0088/G	This was an application for a group of variations. C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system, C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DDPS	11/07/2011	no
IA/0022/G	This was an application for a group of variations. B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing, A.7 - Administrative change - Deletion of manufacturing sites	05/07/2011	yes
IA/0021/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release), A.7 - Administrative change - Deletion of manufacturing sites, B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	09/06/2011	yes
II/0020/G	This was an application for a group of variations. • To change the synthesis of the active substance • To add the new specification parameters to the specification of the active substance with its corresponding test methods. • To delete some test procedures. • To add some manufacture sites for active substance testing. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place, B.I.a.1.b - Changes in the manufacturing process of the active substance - Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product, B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method, B.I.b.2.b - Change in test procedure for active substance or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	20/01/2011	no
II/0018	Update of section 5.1 of the SmPC to include information related to 4 year resistance of telbivudine further to the assessment of FUM 020. In addition section 4.8 is updated to be in line with the SmPC guideline. Annex II is updated to delete the reference to the DDPS version number and an editorial change is made to section 5.1.	16/12/2010	yes

[1] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

No	Scope	Opinion/ Notification issued on	Annexes affected[1]
	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH		
IG/0032/G	This was an application for a group of variations. C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system, C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DDPS, C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	21/12/2010	no
II/0013	Update of sections 4.3, 4.4 and 4.5 of the SmPC to include a contra-indication related to the combination of telbivudine with standard or pegylated interferon alfa-2a, due to an increased risk of developing peripheral neuropathy. The PL has been updated accordingly. The MAH has also incorporated some updates following the QRD template. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/10/2010	yes
IB/0019	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	21/09/2010	yes
IB/0017	B.I.b.2.e - Change in test procedure for active substance or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	15/07/2010	no
IB/0015	B.II.f.1.b.1 - Stability of FP – Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	13/07/2010	yes
IA/0016/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the active substance - Minor change in the manufacturing process of the active substance, B.I.b.2.a - Change in test procedure for active substance or starting material/reagent/intermediate - Minor changes to an approved test procedure, A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance, B.I.a.3.a - Change in batch size (including batch size ranges) of active substance or intermediate - Up to 10-fold increase compared to the currently approved batch size, B.I.a.3.b - Change in batch size (including batch size ranges) of active substance or intermediate - Downscaling	08/07/2010	no
IB/0014/G	This was an application for a group of variations. • To extend the shelf life from 24 months to 36 months for Sebivo 20mg/ml oral solution in glass bottle. • To tighten the release specifications for Thymine from nmt 0.5% to nmt 0.2%. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits, B.II.f.1.b.1 - Stability of FP – Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	18/06/2010	yes

No	Scope	Opinion/ Notification issued on	Annexes affected[1]
II/0011	• Update of the Detailed Description of the Pharmacovigilance system (DDPS). • Update of DDPS (Pharmacovigilance), • Changes to QPPV	18/02/2010	yes
II/0010	Update of sections 4.4 and 5.2 of the SmPC with regards to rhabdomyolysis in line with information already available in section 4.8 and with data from a PK substudy, following the CHMP's request having assessed follow-up measure 008.4, respectively. The PL is updated in accordance. The MAH also took this opportunity to update contact details of local representatives, to align Annex II with QRD 7.3 template wording and to correct a minor typographical error in the Labelling.	21/01/2010	yes
IB/0012	B.I.d.1.a.4 - Stability of AS – Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	11/03/2010	no
II/0009	Update of section 4.4 of the SPC with regards to switching lamivudine-experienced patients with lamivudine-resistance or experiencing virological failure after at least 24 weeks of treatment with lamivudine. This was requested by the CHMP in April 2009 following the assessment of FU2 011.2 related to the resistance analysis of study NV-02B-01.	17/12/2009	yes
II/0008	Update of sections 4.6 and 5.3 of the SPC further to the results of a toxicity study in juvenile rats.	24/09/2009	yes
II/0006	Update of section 4.8 of the SPC and section 4 of the PL to include rhabdomyolysis and lactic acidosis following post marketing reports.	23/07/2009	yes
IA/0007	The introduction of a polypropylene oral syringe with graduation as an additional dosing device for Sebivo Oral Solution 43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	03/03/2009	yes
X/0004	The MAH applied for the addition of a new pharmaceutical form (20 mg/ml oral solution), in addition to the currently approved pharmaceutical form (film-coated tablets). Annex I_2.(d) Change or addition of a new pharmaceutical form	20/11/2008	yes
II/0005	To update sections 4.2, 4.4, 4.8 and 5.1 of the SPC based on 104 weeks safety and efficacy data from the Phase III studies NV-02B-007 and NV-02B-015 and data from resistance studies. Furthermore, the MAH took the opportunity of this change to update section 4.5 of the SPC to reflect the lack of pharmacokinetic (PK) interaction with tenofovir as requested by the CHMP following evaluation of the PK study in May 2008. Section 4 of the PL was updated accordingly.	25/09/2008	yes
II/0003	To update sections 4.4, 4.5 and 4.8 of the SPC to include the adverse reaction peripheral neuropathy with frequency uncommon and to inform prescribers that an increased risk of peripheral neuropathy has been observed when telbivudine and pegylated interferon alfa-2a are co-administered. Sections 2 and 4 of the PL were updated accordingly. The MAH took the opportunity of this change to update the contact details for Slovenia, Slovakia and Latvia.	24/01/2008	yes
IB/0001	41_b_Change in pack size - change in fill weight/volume of non-parenteral multid. products	22/06/2007	yes
IA/0002	07_a_Replacement/add. of manufacturing site: Secondary packaging site	29/05/2007	no

1.3. Renewal application

Pursuant to Article 14 (1-3) of Regulation (EC) No. 726/2004, the Marketing Authorisation Holder Novartis Europharm Ltd., submitted to the Agency on 25 August 2011 an application for renewal of the Marketing Authorisation for Sebivo. The expiry date of the Marketing Authorisation is 26 April 2012.

Rapporteur: Philippe Lechat
Co-Rapporteur: Ian Hudson

1.4. Steps taken for the assessment of the renewal:

The Marketing Authorisation Holder submitted an application for renewal of the Marketing Authorisation on:	25 August 2011
The procedure started on:	18 September 2011
The Rapporteur's preliminary assessment report was circulated to all CHMP Members on:	28 October 2011
During the November 2011 CHMP meeting, the CHMP agreed on a List of Questions (LoQ) relating to clinical issues that was sent to the MAH on:	18 November 2011
The MAH submitted the responses to the CHMP List of Questions on:	29 and 30 November 2011
CHMP discussion and questions referred to HIV/viral CHMP Scientific Advisory Group	15 December 2011
The Rapporteur's and Co-Rapporteur's joint assessment report on the MAH's responses to the CHMP List of Outstanding issues was circulated to all CHMP members on:	3 January 2012
HIV/Viral CHMP Scientific Advisory Group discussion	9 January 2012
The Rapporteur's and Co-Rapporteur's updated joint assessment report on the MAH's responses to the CHMP List of Outstanding issues was circulated to all CHMP Members on:	12 January 2012
During the January 2012 CHMP meeting, the CHMP agreed on a List of Questions (LoQ) relating to non-clinical and clinical issues that was sent to the MAH on:	19 January 2012
The MAH submitted the responses to the CHMP List of Questions on:	24 January 2012
The Rapporteur's and Co-Rapporteur's joint assessment report on the MAH's responses to the CHMP List of Outstanding issues was circulated to all CHMP members on:	6 February 2012

The Rapporteur's and Co-Rapporteur's updated joint assessment report on the MAH's responses to the CHMP List of Outstanding issues was circulated to all CHMP Members on:	13 February 2012
The CHMP, during its January 2012 plenary meeting, issued a positive Opinion on the renewal of the Marketing Authorisation on:	16 February 2012

2. Scientific discussion

2.1. Introduction

Sebivo (INN: telbivudine; LDT) is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase. Telbivudine-5'-triphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5'-triphosphate, resulting in inhibition of HBV replication.

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

Sebivo was first registered in Ghana on 13 July 2006 and received market authorization in Switzerland on 21 August 2006 (the latter date is considered to be the international birth date of the product). It received market authorization in the EU on 24 April 2006. It is currently approved in 109 countries worldwide as a tablet formulation under the trademark Sebivo, except in Chile and the United States, where it is approved under the trademark Skebiv and Tyzeka, respectively. An oral solution formulation has also been developed and is currently registered in 24 countries and the EU.

In the setting of variation II-18 (opinion adopted in December 2010) dealing with the 4 years resistance data, it was stressed that the resistance to telbivudine had reached the worrying level of 40% in HbeAg positive and 20% in HbeAg negative patients at 4 years. The low genetic barrier of the Sebivo combined with a problematic safety profile (notably creatinine phosphokinase (CPK) elevation and muscle disorders) questioned the adequacy of this medicinal product in first line therapy. Therefore, the MAH was requested to discuss to what extend Sebivo is considered a treatment option in the current treatment landscape.

In response to this request (FUM 050), the MAH proposed to restrict the indication based on baseline HBV DNA/ALT levels and Week 24 on-treatment response in order to improve benefits beyond those observed in the overall pivotal study population while reducing the risk of resistance development. The CHMP noted the proposal and concluded that, with additional details and clinical data to substantiate the proposal, the final conclusion on the benefit/risk assessment of Sebivo will be performed within the forthcoming renewal procedure.

Consequently, this renewal application includes new and expanded information about the clinical benefit/risk profile of Sebivo accrued during the reporting period from 01 March 2007 to 30 June 2011 along with a proposal for narrowing the indications by describing the patient population most likely to achieve a better response to treatment with minimal resistance and to provide guidance to physicians to modify therapy if undetectable serum hepatitis B virus (HBV) DNA of viral load is not achieved after 24 weeks of treatment.

2.2. Quality

The Marketing Authorisation Holder has confirmed that the quality, with respect to the method of preparation and control, has been regularly updated by variations to take account of technical and scientific progress in accordance with article 16(1) of Regulation (EC) No 726/2004 and that the product conforms to current CHMP quality guidelines.

Concerning Module 3, the MAH has submitted the relevant documents required for the application for renewal such as quality expert statement, including currently authorised specifications for the active substance and the finished product and qualitative and quantitative composition in terms of the active substance and the excipients, statement of GMP compliance, list of variations granted since authorisation, chronological list of follow-up measures submitted and the proposed texts for SmPC, outer and inner labelling and package leaflet. There are no outstanding quality issues.

All the relevant sites of manufacture and testing are undergoing regular GMP inspections by an EEA competent authority or MRA partner authority and satisfactory GMP compliance of these sites has been confirmed by the MAH by submission of the appropriate documentation.

Appropriate declarations have been submitted concerning the GMP compliance status of the active substance manufacturer(s).

The quality of Sebivo continues to be considered acceptable.

2.3. Non-clinical

Non-clinical

In this renewal application, an update has been provided on non-clinical information of Sebivo based on data generated over the reporting period from 01 March 2007 to 30 June 2011 from internal preclinical studies and published literature.

The *in vivo* non-clinical studies in animals and *in vitro* studies with animal-derived or human-derived material performed by the MAH or its designees are summarised.

The literature published during the review period is also included, with literature searches conducted to identify any publications related to the pharmacology, pharmacokinetics, or toxicity of Sebivo or its active ingredient (telbivudine) during the reporting period.

2.3.1. Pharmacodynamics

Primary pharmacodynamics

During the reporting period (01 March 2007 until 30 June 2011), Seifer et al 2009 reported that telbivudine, a nucleoside analogue inhibitor polymerase, has a different cross-resistance profile than the nucleotide analogue inhibitors adefovir and tenofovir. The activity of telbivudine against A181V, a mutation in the HBV polymerase gene associated with resistance to adefovir was further assessed *in vitro* [(RD-2009-50084)]. Compared to the known telbivudine-resistant mutation, M204I, which reduced its activity by >1000-fold, A181V caused only a small increase (4.1-fold) of IC50 with telbivudine.

Secondary pharmacodynamics

Telbivudine has not been found active against any virus other than HBV-related hepadnaviruses as described in the original submission. During the reporting period (01-Mar-2007 until 30-Jun-2011), the activity of telbivudine was further investigated *in vitro* with temporally and geographically distinct wild-type and multidrug-resistant HIV-1 clinical isolates (Lin et al 2010). No inhibition was observed with up

to 600 µM of the drug, which supports further exploration of telbivudine as a therapeutic option for HBV in HIV-1 co-infected patients.

Pharmacodynamic drug interactions

As described in the original submission, there was no negative interaction in terms of anti-HIV or anti-HBV activities *in vitro* between telbivudine (LDT600) and seven FDA-approved nucleoside reverse transcriptase inhibitors (NRTIs), lamivudine (3TC, lam), abacavir (ABC), zidovudine (AZT), stavudine (D4T), 2', 3'-dideoxyinosine (DDI), emtricitabine (FTC) and tenofovir (TFV). No additional study was performed during the reporting period.

2.3.2. Pharmacokinetics

Drug interactions

In vitro assessment of liver microsomal cytochrome P450 (CYP450) induction potential of LDT600 (telbivudine) was conducted in primary cultures of human hepatocytes (Study 321007220-1800). Telbivudine (0.334, 3.34, and 33.4 µg/mL) and known CYP450 inducers, 3-methylcholanthrene (3-MC), phenobarbital (PB), and rifampicin (RIF) were incubated in cultures of human hepatocytes from three separate donors for three consecutive days. Microsomes were isolated and activities of CYP1A2, CYP2B6, CYP2C9, and CYP3A4 were determined using selective metabolite markers. For each of the three positive controls mentioned above, mean induction data were generated and from those means, the corresponding mean vehicle control values were subtracted to yield "adjusted positive control responses". Induction results from telbivudine assays were averaged from triplicate samples and compared to the corresponding adjusted positive controls. The percent positive control induction level is arbitrarily set at 100% for the positive control specific to a given enzyme.

Overall, the results of this study suggest that treatment of primary cultures of human hepatocytes with telbivudine is not associated with induction of liver microsomal CYP1A2, CYP2B6, CYP2C9, and CYP3A4 via assessment of enzyme activity under the concentrations examined. Therefore, these results indicate that there is low potential for drug-drug interactions with telbivudine due to enzyme induction of CYP1A2, CYP2B6, CYP2C9, and CYP3A4.

No other additional studies or relevant publications were issued during the reporting period on the pharmacokinetic aspects.

2.3.3. Toxicology

In vitro mechanistic studies to examine the effects of telbivudine (LDT600) on mitochondrial function demonstrated that treatment of rat and human hepatocytes, skeletal muscle, or neuron cells with telbivudine at concentrations that is relevant to, or largely exceed the therapeutically relevant levels in human plasma was not associated with mitochondrial toxicity. Additionally, model validation study demonstrated that telbivudine was extensively phosphorylated to its active triphosphate form (5'-triphosphate telbivudine) in all human cell models used in the *in vitro* studies. Additionally, results from the *in vitro* neuronal toxicity studies demonstrated that telbivudine at concentrations largely exceed the therapeutically relevant levels in human plasma did not cause either cytotoxicity or mitochondrial toxicity in SH-SY5Y cells.

The juvenile toxicity study and the follow up juvenile fertility study demonstrated reduced fertility when treated males were paired with treated females, but had no adverse effects on fertility on treated males when paired with untreated female, or treated female paired with untreated males. These results, although showing slightly different NOAELs for fertility effects in different studies, are still

consistent with the overall conclusion that telbivudine may cause reduced fertility in adult animals and in juvenile animals.

Discussion and conclusion on non-clinical data

The low potential for drug-drug interaction and the slightly reduced activity of telbivudine on A181V (one of the ADV resistance signature mutations) are appropriately reflected in the Sebivo SmPC. The possibility of reduced fertility as observed in adults and juvenile animals are also reflected. Additional activities have also been provided to provide further confidence on the absence of anti-HIV activity of telbivudine *in vitro* which were the starting point for *in vivo* exploration. A study in HIV-HBV co-infected patients is planned and should start Q1 2012.

Finally, a series of *in vitro* and *in vivo* studies in various experimental models have been carried out to clarify the mechanisms underlying the muscular and neuronal adverse events reported in patients treated with Sebivo. Despite being negative, the studies were judged insufficient to exclude a risk of mitochondrial toxicity in patients treated with Sebivo due notably to the fact that limited experience is available with the experimental model used in these studies. Going beyond these conclusions seemed difficult and given that the toxicity has already been identified *in vivo*, no further *in vitro* study was deemed necessary.

There are no outstanding non-clinical issues.

2.4. Clinical efficacy and safety

2.4.1. Clinical efficacy

Clinical Efficacy

Below are presented the clinical studies performed by the MAH during the review period, as well as other studies published in scientific journals in order to assess the overall efficacy of Sebivo in its approved indication, and new or expanded information about the clinical benefit.

Table 1. Overview of Novartis-sponsored Sebivo clinical trials completed within the review period

Protocol number / Reference(s)	Study description	Treatment(s) / No. of patients[1] / Duration	Main outcome(s)
NV-02B-007 (GLOBE)/NV-02B-015 Follow-on studies			
CLDT600A2303 / CLDT600A2303 CSR Jia et al 2010 Liaw et al 2011 Wursthorn et al 2011	Open-label 2-year extension study of LDT in patients with compensated CHB or decompensated CHB who were treated in a previous study (007/GLOBE, 015, 011, 010, 018, 019)	LDT 600 mg/day Off-treatment follow-up 1869 patients 104 weeks	Efficacy of LDT was maintained over 2 additional years of LDT treatment and over 2 years of follow-up in patients who discontinued treatment due to efficacy achieved in previous trial.
CLDT600A2303A1 / CLDT600A2303A1 CSR Wang et al 2011	Open-label sub-study of LDT and add-on ADV in Chinese patients previously treated in A2303 who failed to achieve and maintain non-detectable HBV DNA by PCR assay	LDT 600 mg/day + ADV 10 mg/day 40 patients 52 weeks	In patients who failed to achieve undetectable HBV DNA on previous therapy, LDT plus ADV was effective in reducing HBV DNA levels with good tolerability and minimum viral breakthrough.
CLDT600ACN04 / Jia et al 2011	Open-label extension study of LDT in Chinese patients with CHB who were treated in A2303 and who were PCR-negative at the end of 4-year LDT treatment	LDT 600 mg/day 104 patients 52 weeks	Anti-viral efficacy of LDT was maintained in the [illegible] year of continuous therapy with high rates of HBeAg loss and seroconversion.
CLDT600ACN04E1 / CLDT600ACN04E1 CSR Hou et al 2011	Open-label extension study of the effect of LDT treatment on liver histology in Chinese patients with CHB	LDT 600 mg /day 70 patients 52 weeks	In this largest cohort among all anti-HBV trials with paired biopsy data, LDT treatment for 5 years resulted in [illegible] of liver inflammation and fibrosis. Study also confirmed 6-year efficacy and safety of LDT.
Head-to-head comparison			
CLDT600A2407 / CLDT600A2407 CSR Suh et al 2010	Randomized, open-label exploratory study of LDT vs. ETV treatment for 12 weeks on viral kinetics in patients with HBeAg-positive CHB	LDT 600 mg/day ETV 0.5 mg/day 44 patients 12 weeks	Efficacy of LDT in HBV DNA suppression and other viral kinetics parameters was similar to ETV at 12 weeks.
CLDT600AHK01 / CLDT600AHK01 Viral Kinetics Report Leung et al 2011	Randomized, open-label trial of LDT + TDF combination vs. LDT or TDF monotherapy on viral kinetics in Chinese patients with HBeAg-positive compensated CHB	LDT 600 mg/day + TDF300 mg/day LDT 600 mg/day TDF300 mg/day 48 patients 12 weeks	LDT monotherapy has similar potency as TDF monotherapy in the reduction of HBV DNA levels over 12 weeks. Viral kinetics were more homogeneous and slightly improved in the combination therapy group vs. the monotherapy groups.
CLDT600A2402 (NV-02B-019) / CLDT600A2402 CSR Safadi et al 2011	Randomized study of switching from LAM to LDT vs. continued LAM treatment in CHB patients	LDT 600 mg/day LAM 100 mg/day 248 patients 52 weeks	LDT provided superior reduction of HBV DNA levels vs. LAM as early as 24 weeks (primary endpoint) and at 52 weeks. Results led to type II variation no. EMEA/H/C/713/II/009.

Protocol number / Reference(s)	Study description	Treatment(s) / No. of patients[1] / Duration	Main outcome(s)
Large patient population			
CLDT600ACN03 / CLDT600ACN03 CSR CLDT600ACN03 Addendum 1	Open-label phase IV study of LDT in Chinese patients with HBeAg-positive or HBeAg-negative CHB	LDT 600 mg/day 2211 patients 52 weeks	One-year treatment with LDT in a large CHB patient population demonstrated good safety and potent anti-viral efficacy, as observed in other LDT clinical trials.
Patients with decompensated CHB			
CLDT600A2301 (NV-02B-011) / CLDT600A2301 CSR Gane et al 2010 Chan et al 2011	Randomized double-blind trial of LDT vs. LAM in adults with decompensated CHB and evidence of cirrhosis	LDT 600 mg/day LAM 100 mg/day 232 patients 104 weeks	In the largest group of decompensated CHB patients, the primary endpoint was not achieved although LDT provided numerically higher efficacy with better survival compared with LAM. The study was underpowered to demonstrate statistical superiority for the primary efficacy endpoint (survival).
Combination therapy			
CLDT600A2304 [2] (NV-02B-027) / CLDT600A2304 CSR Ahn et al 2010	Randomized, open-label study of LDT+ADV or ADV monotherapy in CHB patients who were resistant to LAM	LDT 600 mg/day + ADV 10 mg/day ADV 10 mg/day 150 patients planned; 43 randomized 96 weeks planned; analysis at 48 weeks[2]	LDT and ADV combination was more effective in reducing HBV DNA levels after 48 weeks than ADV monotherapy, with similar tolerability/safety profile.
CLDT600A2406 [2] / CLDT600A2406 CSR Marcellin et al 2010	Open-label study of LDT + PegIFN vs. PegIFN or LDT monotherapy in treatment-naive patients with HBeAg-positive CHB	LDT600 mg/day + PegIFN 180 µg/week LDT 600 mg/day PegIFN 180 µg/week 250 patients planned; 156 randomized 48 weeks planned[2]	Due to early termination of the study, the primary efficacy endpoint could not be attained. Combination therapy provided better virologic outcomes than either monotherapy, but with increased risk of peripheral neuropathy. Results led to type II variations no. EMEA/H/C/713/II003 & 013.

[1] Number of patients represents the number of patients enrolled in the study or randomized to treatment, unless stated otherwise.
[2] Study was terminated early
ADV=adefovir; LAM=lamivudine, LDT=telbivudine; ETV=entecavir; PegIFN = pegylated interferon alpha-2a;

Table 2. Overview of on-going Sebivo clinical trials sponsored by Novartis

Protocol number / Reference	Study description	Treatment / No. patients / Duration	Preliminary data
CLDT600A2401	A randomized, open-label 104-week treatment study of LDT or TDF with the roadmap concept in patients with HBeAg-negative CHB across different European countries	LDT 600 mg/day with add-on TDF at Week 26* or continue LDT monotherapy TDF 300 mg/day with add-on LDT at Week 26* or continue TDF monotherapy 240 patients planned 104 weeks	None available at the time of this report. As of 28-Jun-2011, 128 patients were screened and 63 randomized to treatment.
CLDT600A2410 / CLDT600A2410 FIR Piratvisuth et al 2011a	Open-label, single-arm study of the efficacy and safety of lead-in LDT for 24 weeks with or without TDF intensification in patients with HBeAg-positive CHB	LDT 600 mg/day with add-on TDF at Week 24* or continue LDT monotherapy 105 patients (ITT population) 104 weeks	Primary efficacy analysis at year 1 confirmed the benefit of LDT treatment with Roadmap Concept of treatment intensification for patients with detectable HBV DNA at Week 24.

* add-on therapy for patients who show HBV DNA ≥300 copies/mL at Week 24
LDT=telbivudine; TDF=tenofovir

Table 3. Overview of efficacy data from non-Novartis sponsored studies

Reference	Study description	Treatment / No. patients / Duration	Main outcome(s)
Gerasimova et al 2011	Efficacy and safety of telbivudine in patients reinfected with HBV after orthotopic liver transplantation	LDT 600 mg/day 13 patients 12 months	LDT was effective and well-tolerated in patients re-infected with HBV after an orthotopic liver transplantation
Goyal et al 2011	LDT with or without add-on TDF therapy in 31 HBeAg-negative patients in India	LDT 600 mg/day TDF 300 mg/day for PCR-positive patients at Week 24 31 patients 52 weeks	Over 85% of patients achieved undetectable HBV DNA after 52 weeks. Of the 3 patients who received add-on TDF, 2 achieved undetectable HBV DNA and 1 had HBV DNA <1000 copies/mL at week 52.
Jiang et al 2011	Efficacy and safety of LDT treatment in a real-life cohort of Chinese patients with HBeAg-positive or HBeAg-negative CHB	LDT 600 mg/day 44 patients 1 year	LDT induced rapid and potent HBV DNA suppression after 1 year. Viral response at 3 months correlated with HBeAg loss and seroconversion.
Reference	**Study description**	**Treatment / No. patients / Duration**	**Main outcome(s)**
Jin et al 2011	Retrospective analysis of LDT treatment in patients with HBeAg-positive CHB and predictors of outcomes	LDT 600 mg/day LAM 100 mg/day 210 patients 52 weeks	LDT was more effective than LAM in HBV DNA suppression and HBeAg seroconversion. Week 4 PCR negativity was predictive of favorable outcomes at 52 weeks.
Lv et al 2010	Efficacy and safety of LDT treatment in patients with HBeAg-positive CHB who had high baseline ALT levels (10-20×ULN)	LDT 600 mg/day 80 patients (40 with ALT >10-20×ULN; 40 with ALT 2-10×ULN 52 weeks	Rates of HBV DNA non-detectability, HBeAg loss and seroconversion and HBsAg loss with LDT treatment were better in patients with high baseline ALT levels.
Maximov et al 2010	Efficacy and safety of LDT treatment in patients with CHB and HIV infection not receiving HAART	LDT 600 mg/day 12 patients 3-12 months	LDT showed good anti-HBV efficacy without an effect on HIV RNA dynamics.
Milazzo et al 2009	Molecular analysis of HBV DNA and HIV-1 RNA and DNA sequences in HIV/HBV co-infected patients	LDT 600 mg/day 3 patients 24 weeks	LDT had no direct anti-HIV activity and induced no genotypic mutation of resistance to anti-HIV drugs.
Petersen et al 2011	Efficacy and safety of LDT treatment in a real-life cohort of German patients with mainly HBeAg-negative CHB	LDT 600 mg/day 273 patients 48 weeks	Interim data at 48 weeks confirm the efficacy of LDT in HBV DNA suppression and HBeAg loss in German patients with mainly HBeAg-negative CHB.
Piratvisuth et al 2011b	Retrospective study of CHB patients treated in clinical practice in Thailand	LDT 600 mg/day Mean follow-up period of 17.6 months 307 patients	LDT demonstrated high rates of HBV DNA non-detectability and HBeAg seroconversion in patients treated in clinical practices in Thailand.
Seto et al 2010	Efficacy and safety of LDT treatment in of CHB patients in Hong Kong	LDT 600 mg/day 117 patients Up to 3 years	Continuous therapy with LDT provided improvements over time in virologic and biochemical outcomes.

LDT=telbivudine; TDF=tenofovir; LAM=lamivudine

In line with the clinical development of Sebivo, most of the studies performed with the medicinal product since its initial MA were conducted in Asian patients. One study, performed in fulfilment of the MAH's commitment made at the time of the MA, is on-going in European countries (study CLDT600A2409). Another study is planned in HIV-HBV co infected patients who do not require Highly Active Antiretroviral Therapy (HAART).

Combination therapy has been explored. Combined use of Sebivo with peginterferon led to an increased risk of peripheral neuropathy (a contra-indication has been added to the SmPC via the variation II-13, adopted in October 2010 – see also Clinical safety section below). Add-on adefovir was first investigated but the most recent studies now explore intensification strategy with the more potent drug tenofovir ('Roadmap concept').

The MAH has performed a study in decompensated patients comparing telbivudine to the outdated lamivudine.

- **Viral kinetics**

The efficacy of telbivudine in early viral suppression was demonstrated in the pivotal study NV-02B-007/GLOBE and was confirmed in 2 additional studies, CLDT600A2407 and CLDT600AHK01. These studies also demonstrated that telbivudine has similar anti-viral potency as entecavir and tenofovir over 12 weeks of treatment.

- **Efficacy in treatment-naive patients with compensated CHB**

Predictors of efficacy: baseline data and early on-treatment Week 24 response
Recent studies have identified the baseline characteristics and early on-treatment responses that correlate with long-term efficacy responses and lower resistance development. Outcomes of 2-year treatment with telbivudine in patients from the NV-02B-007/GLOBE trial were analyzed retrospectively according to serum HBV DNA and ALT levels at baseline and on-treatment responses after 24 weeks (Zeuzem et al 2009). For baseline predictors, it was observed that baseline HBV DNA <9 log10 copies/ml and ALT ≥2×ULN in HBeAg-positive patients and baseline HBV DNA <7 log10 copies/ml in HBeAg-negative patients were associated with favorable outcomes at year 2. After initiation of telbivudine treatment, undetectable serum HBV DNA at treatment Week 24 was the strongest predictor of favourable outcomes at year 2 in both HBeAg-positive and HBeAg-negative patients.

In addition, a survey of 2023 CHB patients seen in clinical practices in France, Germany, Italy and Spain (Berg et al 2010) reported that patients were predominately HBeAg-negative (64%). However, few patients presented with high viral load at treatment initiation (97% of HBeAg-positive patients had baseline HBV DNA ≤9 log10 copies/ml and 94% of HBeAg-negative patients had HBV DNA <7 log10 copies/ml), and a majority of patients had elevated baseline ALT ≥2×ULN (72% of HBeAg-positive and 66% of HBeAg-negative patients). These patient characteristics are in line with the results of NV-02B-007/GLOBE study described above (Zeuzem et al 2009), suggesting that the baseline predictors of optimal outcomes as identified in the NV-02B-007/GLOBE study are indeed relevant for the optimal management of CHB patients seen in European clinical practice.

On this basis and as proposed following the assessment of the variation II-18 (FUM 050), in order to improve benefits while minimizing risk of resistance development, the MAH proposed within this renewal application to narrow the Sebivo indication according to baseline HBV DNA/ALT levels and Week 24 on-treatment response with treatment intensification (Roadmap Concept) (see Discussion and Conclusion on Efficacy hereafter for further details and discussion on this proposal).

Long-term anti-viral efficacy
Anti-viral efficacy of telbivudine was maintained during the 3rd to 6th year of telbivudine treatment, as demonstrated in 2-year extension study CLDT600A2303 (3 and 4 year data), the 52-week follow-on study CLDT600ACN04 (5 year data) and the 52-week extension study CLDT600ACN04E1 (6 year data).

Study CLDT600A2303
Study CLDT600A2303 was an open-label extension study in patients with compensated CHB who were previously treated with telbivudine for 2 years in a prior feeder study (including NV-02B-007/GLOBE and NV-02B-015). These patients were treated with telbivudine for an additional 2 years in study CLDT600A2303 and provided cumulative efficacy and safety data after 3 and 4 years of continuous telbivudine therapy (CLDT600A2303 CSR).

Table 4. Patients with undetectable HBV DNA at Week 24 had better outcomes at 3 and 4 years.

	Week 52	Week 104	Week 156	Week 208
HBeAg-positive patients (n = 293*)				
Maintained undetectable HBV DNA (< 300 copies/ml)	70.3% (206/293)	77.3% (218/282)	75.0% (198/264)	76.2% (163/214)
Maintained undetectable HBV DNA (< 300 copies/ml) with undetectable HBV DNA at week 24	99.4% (161/162)	94.9% (150/158)	86.7% (130/150)	87.9% (109/124)
Cumulative HBeAg seroconversion rates (%)	27.6% (81/293)	41.6% (122/293)	48.5% (142/293)	53.2% (156/293)
Cumulative HBeAg seroconversion rates in patients with undetectable HBV DNA at week 24 (%)	40.1% (65/162)	52.5% (85/162)	59.3% (96/162)	65.4% (106/162)
Maintained ALT normalisation	81.4% (228/280)	87.5% (237/271)	82.9% (209/252)	86.4% (178/106)
HBeAg-negative patients (n = 209*)				
Maintained undetectable HBV DNA (< 300 copies/ml)	95.2% (199/209)	96.5% (195/202)	84.7% (160/189)	86.0% (141/164)
Maintained undetectable HBV DNA (< 300 copies/ml) with undetectable HBV DNA at week 24	97.8% (175/179)	96.5% (166/172)	86.7% (143/165)	87.5% (126/144)
Maintained ALT normalisation	80.3% (151/188)	89.0% (161/181)	83.5% (142/170)	89.6% (129/144)

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

Studies CLDT600ACN04 and CLDT600ACN04E1

Study CLDT600ACN04 was an open-label follow-on study of Chinese patients from study CLDT600A2303 who had undetectable HBV DNA at the end of the 4-year treatment with telbivudine. Patients were treated with telbivudine for an additional year in this study and provided cumulative efficacy and safety data after 5 years of continuous telbivudine therapy.

In the ITT population (N=97; 67 HBeAg-positive and 30 HBeAg-negative), 93.7% of HBeAg-positive patients and 96.4% of HBeAg-negative patients maintained undetectable HBV DNA at year 5 (Jia et al 2011). ALT normalization was achieved in 84.6% and 79.3%, respectively.

After study CLDT600ACN04, patients were allowed to continue telbivudine for an additional year (total of 6 years) in the extension study CLDT600ACN04E1. In the ITT population (N=66; 43 HBeAg-positive and 23 HBeAg-negative) of CLDT600ACN04E1, 90.7 % of HBeAg-positive patients and 87.0% of HBeAg-negative patients maintained undetectable HBV DNA at year 6 (overall 89.4%) (CLDT600ACN04E1 CSR).

HBeAg seroconversion

Study CLDT600A2303

Overall, results from NV-02B-007/GLOBE, NV-02B-015 and CLDT600A2303 studies show that HBeAg seroconversion rate increased with duration of treatment: 27.6% at year 1, 41.6% at year 2, 48.5% at year 3, and 53.2% at year 4 in 293 per-protocol HBeAg-positive patients without resistance at entry to CLDT600A2303 (Jia et al 2010).

Studies CLDT600ACN04 and CLDT600ACN04E1

In study CLDT600ACN04, the cumulative rate of HBeAg seroconversion over 5 years was 67.2% (Jia et

al 2011). In study CLDT600ACN04E1, 79.1% achieved HBeAg seroconversion cumulatively over 6 years.

HBsAg seroconversion

Study CLDT600A2303

For patients treated in NV-02B-007/GLOBE and CLDT600A2303 studies, telbivudine therapy reduced mean (± SD) serum HBsAg levels from 3.8 ± 0.6 log10 IU/ml at baseline to 3.0 ± 1.4 log10 IU/ml at year 3 ($p<0.0001$) in 162 HBeAg-positive patients who had undetectable HBV DNA at year 2 (Wursthorn et al 2010). A total of 9/162 (6%) patients achieved HBsAg loss at year 3.

Studies CLDT600ACN04 and CLDT600ACN04E1

In study CLDT600ACN04 (ITT population, N=97), 6 (6.2%) patients showed HBsAg clearance, with 3 (3.1%) of these patients also achieving HBsAg seroconversion after 5 years of treatment (Jia et al 2010).

At year 5, i.e. baseline of study CLDT600ACN04E1 (ITT population, N=66), the cumulative rate of HBsAg loss and HBsAg seroconversion was 6.1% (4 patients) and 4.5% (3 patients), respectively.

Study CLDT600A2410

In study CLDT600A2410, which has applied the roadmap concept of telbivudine therapy with add-on tenofovir at treatment week 24, the rate of HBsAg clearance after 1 year was 6% in the overall mITT population (N=101) and 11% in patients with treatment intensification (CLDT600A2410 FIR; Piratvisuth et al 2011a).

Sustained efficacy after discontinuation of treatment

Study CLDT600A2303 included patients with compensated CHB who had discontinued telbivudine treatment in NV-02B-007/GLOBE study because they had achieved an efficacy response (i.e. HBV DNA <5 log10 copies/mL and HBeAg loss for at least 24 consecutive weeks) that allowed for per-protocol treatment discontinuation and in line with recommendations in current practice guidelines. These patients were followed for a median time of 120 weeks in NV-02B-007/GLOBE, NV-02B-015 and CLDT600A2303 studies to evaluate off-treatment efficacy and safety outcomes.

At Week 104 of off-treatment observation in study CLDT600A2303, the majority of HBeAg-positive patients who had received telbivudine in study NV-02B-007/GLOBE or NV-02B-015 showed sustained HBeAg loss (83.3%, 25/30), sustained HBeAg seroconversion (79.2%, 19/24), sustained virologic response (58.5%) and sustained HBV DNA suppression (55.8%). 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 at Week 104 (CLDT600A2303 Sustainability Report).

The MAH proposes in this renewal application to update the section 5.1 of the Sebivo SmPC with these 208-week data on off-treatment sustained efficacy results (see also section 2.6 Changes to the Product Information hereafter).

Liver histology improvement

Limited data are available on the impact of long-term viral suppression on liver histology and patient outcome.

In study CLDT600ACN04E1, 70 patients with CHB (all Chinese, 47 HBeAg-positive, 23 HBeAg-negative) were evaluated for changes in liver histology and virologic parameters. This was an open-label, single-arm study that included patients who previously completed from 4 to 5 years of treatment.

A total of 57 patients (38 HBeAg-positive and 19 HBeAg-negative) had paired biopsies at baseline and year 5. The main findings (CLDT600ACN04E1 CSR) are as follows:

- Resolution of liver inflammation: mean change from baseline to year 5 in Knodell HAI score was −6.3 ± 2.8 and 98.2% (56/57) had absence of liver inflammation (Knodell score ≤ 3; no or minimal necroinflammation) at year 5 compared to 84.2% (48/57) with Knodell score ≥ 4 at baseline before treatment initiation.
- Fibrosis regression: mean change from baseline in Ishak fibrosis score was −1.3 ± 1.3 and 84.2% (48/57) had absence of liver fibrosis (Ishak score ≤ 1; no or minimal fibrosis) at year 5 compared to 75.4% (43/57) with Ishak score ≥ 2 at baseline.
- Among patients with baseline Ishak fibrosis score ≥ 2, 83.7% (36/43) achieved an Ishak fibrosis score of 0 or 1 (no or minimal fibrosis) after 5 years of treatment.
- In 6 (10.5%) patients who had advanced fibrosis or cirrhosis (Ishak score 4-6) at baseline, the Ishak score was reduced by a median of 3.0 (range 1-3) points at year 5.
- Virologic and biochemical responses at year 5 (at entry to study CLDT600ACN04E1) for the 57 patients with paired biopsies: HBV DNA was undetectable in 98.2% of patients, cumulative HBeAg loss/seroconversion in 86.8%/78.9%, cumulative HBsAg loss/seroconversion in 5.3%/3.5%, and ALT normalization in 79.6%.

Therefore, the profound and durable viral suppression with telbivudine over 5 years was associated with an improvement in liver histology, reaching the long-term goals of treatment in patients with CHB.

The MAH proposes in this renewal application to update the section 5.1 of the Sebivo SmPC with these liver histology study results (see also section 2.6 Changes to the Product Information hereafter).

- **<u>Efficacy in special populations</u>**

Decompensated CHB patients

Telbivudine is not currently indicated for use in patients with decompensated CHB. However, results from the 2-year double-blind, randomized study CLDT600A2301, the largest randomized controlled trial performed to date in patients with decompensated CHB (n=114 in LDT group and 114 in LAM group) shown the superior benefits of telbivudine vs. lamivudine in patients with decompensated CHB.

It was noted that neither of these medicinal products can be considered as an optimal option in patients with decompensated disease nowadays, especially when considering that virological breakthrough could be associated with a more pejorative evolution of the disease. Medicinal products with high genetic barrier for resistance are mandatory in this sensible population.

HIV/HBV co-infection

Telbivudine is not currently indicated for use in patients co-infected with HIV. Due to the high risk of HIV resistance, the monotherapy of antivirals with dual efficacy on HIV and HBV (e.g. emtricitabine, lamivudine, tenofovir, or entecavir) without a full combination antiretroviral regimen should be avoided in HIV/HBV co-infected patients (DHHS HIV Guidelines 2011).

The MAH has been requested to investigate whether telbivudine exhibits anti-HIV activity *in vitro* before initiating clinical trials in HIV co-infected patients.

Telbivudine did not exhibit anti-HIV activity in the *in vitro* investigations performed by the MAH. However extrapolation of the *in vitro* observations to *in vivo* situations requires caution, especially

when considering that the case-report of a patient who experienced significant suppression of HIV viral load under telbivudine had been reported (CROI 2009). Therefore, a pilot study with sequential inclusion of HIV-HBV co-infected patients has been requested to determine whether telbivudine had an activity on HIV *in vivo* before a larger study in HIV/HBV infected patients could be performed.

The study is planned with first inclusion scheduled for February 2012. The target population is patients with hepatitis B virus and HIV-1 who require treatment for chronic hepatitis B but are not yet eligible for HAART.

Whether telbivudine had no activity against HIV and could be regarded as a valid option in HIV-HBV co-infected patients not in need of HAART remains to be confirmed.

Treatment-experienced patients

The MAH referred to data from two clinical studies (CLDT600A2303 and CLDT600A2402) in order to demonstrate the efficacy of telbivudine in patients who switched from lamivudine to telbivudine treatment. In addition, studies CLDT600A2304 and CLDT600A2303A1 are provided as showing the efficacy of telbivudine in combination with adefovir in patients who previously failed on anti-viral monotherapy.

It noted that in the setting of the variation II-09 (adopted in December 2009) and as reflected in the SmPC, telbivudine monotherapy is not considered an option for patients with established lamivudine-resistant hepatitis B virus infection. Patients who failed to achieve virological response following treatment with lamivudine for more than 24 weeks are unlikely to benefit from telbivudine monotherapy.

Furthermore the CHMP consider that there is currently no clinical data to properly assess the benefit and risk of switching to telbivudine for lamivudine-treated patients who achieve complete viral suppression on lamivudine. When considering that lamivudine is a well-tolerated drug, there is no reason for switching from lamivudine to telbivudine a patient stable under lamivudine.

Study CLDT600A2304: Combination therapy

Study CLDT600A2304 was a randomized, open-label study of telbivudine in combination with adefovir (ADV) vs. ADV monotherapy in patients with HBeAg-positive CHB and confirmed resistance (YMDD mutation) to prior lamivudine treatment. The study was terminated early, with agreement from the EMA on 01 February 2008, primarily due to difficulties enrolling patients into the ADV monotherapy arm.

Study CLDT600A2303A1: Combination therapy

Study CLDT600A2303A1 was an open-label study of telbivudine and adefovir in patients with CHB who had failed to achieve or maintain undetectable HBV DNA after 8 months of LDT monotherapy in a previous qualifying study CLDT600A2303.

The CHMP considers that medicinal products with high potency and high genetic barrier to resistance should be preferred for the management of treatment-experienced patients. Due to its low genetic barrier and safety profile, telbivudine cannot be regarded as an interesting option for combination therapy.

Post-transplant patients

In a 12-month study of 13 patients (8 HBeAg-positive, 5 HBeAg-negative) infected with HBV after undergoing OLT, 3 patients had undetectable HBV DNA and 10 had HBV DNA $>10^4$ copies/mL at baseline (Gerasimova et al 2011). Following telbivudine treatment, HBV DNA was undetectable in 60% (6/10) at 6 months and 90% (9/10) at 12 months. HBeAg seroconversion was achieved in 2 of 8 HBeAg-positive patients at baseline and HBsAg loss in 23% (3/13). ALT normalization was achieved in 80% of patients after 3 months. Telbivudine was well-tolerated as evidenced by absence of serious

adverse events and discontinuations, neutropenia, creatine kinase elevations, ALT flares, renal impairment (GFR) and myopathy.

Paediatric patients
CLDT600A2414 is an ongoing, cross-sectional, global, non-interventional epidemiology survey of HBV infection in children and adolescents (2 to ≤18 years). (Kelly et al 2011).

This large global epidemiology survey showed that paediatric CHB infection is largely HBeAg positive and affects mostly patients aged >7 years, reflecting the impact of vaccination programs introduced worldwide. Most patients had slow disease progression over the last 12 months. These results highlight the difficulty of conducting paediatric studies in patients with decompensated CHB or in children aged <7 years due to low prevalence. Nonetheless, results from this study show that despite the advent of successful infant and adolescent immunization programs in many countries, the burden of hepatitis B in children and adolescents remains high worldwide and warrants further study to find safe and effective treatment options.

- **Resistance**

The MAH has undertaken an analysis of resistance development using the published mathematical model by Pawlotsky et al 2008. Resistance was analyzed for years 1 and 2 using data from the pivotal NV-02B-007/GLOBE trial, followed by analysis for years 3 and 4 using data from the open-label, 2-year extension study CLDT600A2303.

In the new analysis, applying the mathematical model by Pawlotsky et al 2008, the cumulative resistance rate over the 2-year, double-blind treatment period in the NV-02B-007/GLOBE trial is 13.7% for HBeAg-positive patients and 6.8% for HBeAg-negative patients. These year 2 rates recalculated as per the mathematical model by Pawlotsky et al are much lower than the rates (25.1% for HBeAg-positive patients and 10.8% for HBeAg-negative patients) reported in the currently approved Sebivo SmPC, which were based on a 2-year analysis of NV-02B-007/GLOBE data that included all 680 patients irrespective of the patient's PCR status at the beginning of year 2.

Table 5. Cumulative genotypic resistance at 1 and 2 years (confirmed by viral breakthrough) by HBeAg status using the mathematical model of Pawlotsky et al in patients from the NV-02B-007/GLOBE trial

	ITT Population (N=680)	
Time Interval	HBeAg status	Cumulative Genotypic Resistance
Year 1	Positive (n=458)	5.0%
	Negative (n=222)	2.3%
	Overall	4.1%
Year 2*	Positive (n=275)	13.7%
	Negative (n=195)	6.8%
	Overall	11.1 %

*Only patients who were PCR negative at the end of year 1 were counted for year 2.

Resistance rates at 1 and 2 years in defined patient subgroups

Table 6. Efficacy responses and resistance rates at years 1 and 2 stratified by baseline characteristics and early on-treatment response at Week 24

	HBeAg-positive[1]		HBeAg-negative[2]	
Year 1 / Week 52[3]				
Undetectable serum HBV DNA	96.5%		97.7%	
HBeAg seroconversion	39.6%		–	
Genotypic resistance	0%		0%	
	HBeAg-positive[1]		**HBeAg-negative[2]**	
	Subgroup analysis[3]	**Mathematical model[4]**	**Subgroup analysis[3]**	**Mathematical model[4]**
Year 2 / Week 104				
Undetectable serum HBV DNA	89%	90.9%	91%	92.9%
HBeAg seroconversion	52%	53.2%	–	–
Cumulative genotypic resistance[5]	1.8 %	1.8%	2.3%	2.4%

[1] Subgroup of HBeAg-positive patients with baseline HBV DNA <9 log_{10} copies/ml, baseline ALT ≥2×ULN, and undetectable HBV DNA at treatment Week 24 (as defined by Zeuzem et al 2009)
[2] Subgroup of HBeAg-negative patients with baseline HBV DNA <7 log_{10} copies/ml and undetectable HBV DNA at treatment Week 24 (as defined by Zeuzem et al 2009)
[3] All patients in the subgroups defined by Zeuzem et al 2009 who started at baseline are included in the analysis.
[4] Only patients in the subgroups who were PCR-negative at the beginning of year 2 are included in the analysis, as per the mathematical model by Pawlotsky et al 2008.
[5] Cumulative resistance rates for year 2 were calculated using the mathematical model of Pawlotsky et al 2008.

Cumulative resistance at 3 and 4 years

As per the mathematical model by Pawlotsky et al, the analysis at years 3 and 4 includes only those patients who were PCR-negative at the beginning of the respective year. Using this method, the cumulative resistance rate over 4 years of treatment in patients from the NV-02B-007/GLOBE trial is 20.0% overall, 22.3% for HBeAg-positive patients and 16.0% for HBeAg-negative patients.

Table 7. Genotypic resistance (confirmed by viral breakthrough): annual rate and cumulative rate (calculated using the mathematical model by Pawlotsky et al) in patients from NV-02B-007/GLOBE trial

		ITT Population (N=680)	
Time interval	**HBeAg status**	**Annual rate**	**Cumulative rate***
Year 1 / Week 52	Positive (n=458)	23 (5.0%)	5.0%
	Negative (n=222)	5 (2.3%)	2.3%
	Overall (n=680)	28 (4.1%)	4.1%
Year 2 / Week 104	Positive (n=275)*	25 (9.1%)	13.7%
(PCR-negative patients at the beginning of year 2)	Negative (n=195)*	9 (4.6%)	6.8%
	Overall (n=470)*	34 (7.2%)	11.1%
Year 3 / Week 156**	Positive (n=186)*	7 (3.8%)	16.9%
(PCR-negative patients at the beginning of year 3)	Negative (n=172)*	9 (5.2%)	11.6%
	Overall (n=358)*	16 (4.5%)	15.0%
Year 4 / Week 208	Positive (n=168)*	11 (6.5%)	22.3%
(PCR-negative patients at the beginning of year 4)	Negative (n=142)*	7 (4.9%)	16.0%
	Overall (n=310)*	18 (5.8%)	20.0%

*Cumulative resistance rate is calculated using the mathematical model by Pawlotsky et al 2008.
For all rate calculations, the resistance rate at year 1 is calculated considering all ITT patients. For rates at year 2 to year 4, only patients who were PCR negative at the beginning of the respective year are considered in the calculation of the resistance rate.
** Includes only patients enrolled for further treatment in CLDT600A2303 (ITT population).

The 4-year cumulative resistance rate of 22.3% for HBeAg-positive patients calculated using the published mathematical model by Pawlotsky et al is considerably lower than the 41% currently reflected in the SPC (Section 5.1 on Pharmacodynamic Properties). Also, the 4-year cumulative rate is

even lower for HBeAg-negative patients (16.0%) who constitute the majority of CHB patients in Europe.

The CHMP noted that, even though substantially decreased with the Pawlotsky method, the risk of resistance for telbivudine remains a concern and is likely to be approx 10-fold higher as compared to that with entecavir.

Discussion and Conclusion on Efficacy

Even though substantially decreased with the Pawlotsky method, the risk of antiviral resistance for telbivudine remains a concern.

In order to minimize this higher risk of resistance, the MAH is proposing in this renewal application to define patient subgroups at lower risk of developing resistance and for which a treatment initiation with telbivudine monotherapy would not represent a sub-optimal management as compared to tenofovir or entecavir.

Based on the clinical efficacy data described above (see efficacy in treatment-naïve patients with compensated CHB), the MAH suggests to restrict the use of telbivudine to patients with favourable baseline characteristics (i.e. baseline HBV DNA<9log10 copies/ml and ALT<2x ULN in HBeAg+ and HBV DNA<7log10 copies/ml in HBeAg- patients) and propose intensification (Roadmap concept) if viral suppression is not achieved after 24 weeks.

The CHMP agreed that in these patients subgroups, risk of resistance was lower (resistance rate 1.8% in HBeAg+ and 2.3% in HbeAg- patients at 2 years). However it noted that those rates are still higher than those reported with tenofovir or entecavir (no resistance found at 4 years for tenofovir, resistance found in 0.5% at year 2 and in 1.2% of patients at year 5 for entecavir). It was also noted that 30% of HBeAg+ and 5% of HBeAg- would not achieve undetectable HBV DNA at week 24 with telbivudine and therefore will require intensification. On the contrary, for tenofovir or entecavir, intensification is not needed for the majority of patients with partial virological response (as suggested in recent literature for entecavir: Zoutendijk R.. VIRGIL surveillance study group Hepatology 2011) or is only suggested by some experts at week 48.

In addition, it was noted that the patient population selected represents the vast majority of the patients who would be seen in clinical practice and would better benefit from treatment with tenofovir or entecavir. Also, the intensification strategy as proposed at week 24 if undetectable serum HBV DNA are not achieved is still under development.

Therefore, the CHMP did not consider the MAH proposal to delineate the population appropriate. It agreed that initiation of treatment with telbivudine can be regarded as a downgraded option for the management of HBV-infected patients comparing to other medicinal products with high potency and high genetic barrier such as tenofovir or entecavir.

In the view of this confirmed low genetic barrier to resistance, put into perspective of the newly approved medicinal products with a better resistance profile as well as the telbivudine safety concerns (see below Clinical Safety), the CHMP requested clarification from the HIV/viral CHMP Advisory Group (CAG) on the role of Sebivo in the treatment of HBV infected patients in Europe and the benefit/risk balance (see section 2.7 Overall conclusion and benefit risk balance hereafter)

2.4.2. Clinical safety

In this renewal application, the MAH has submitted:

- one summary bridging report (SBR) covering the period from 01 March 2007 to 30 June 2011,
- one addendum report covering the period from 01 Mar 2011 to 30 Jun 2011,
- a clinical overview for product license renewal,

In the period under the review the following PSURs were submitted and assessed by the CHMP:

- PSUR 2 covering the period from 01 Mar 2007 to 31 Aug 2007
- PSUR 3 covering the period from 01 Sep 2007 to 28 Feb 2008
- PSUR 4 covering the period from 01 Mar 2008 to 31 Aug 2008
- PSUR 5 covering the period from 01 Sep 2008 to 28 Feb 2009
- PSUR 6 covering the period from 01 Mar 2009 to 31 Aug 2009
- PSUR 7 covering the period from 01 Sep 2009 to 28 Feb 2010
- PSUR 8 covering the period from 01 Mar 2010 to 31 Aug 2010
- PSUR 9 covering the period from 01 Sep 2010 to 28 Feb 2011.

Patient exposure

During the period covered by this renewal, 256 010 patient treatment years have been exposed to telbivudine.

An estimate of the patient exposure was calculated by the MAH based on kg of active substance sold and the defined daily dose (600 mg/day). From 01 March 2007 to 30 June 2011 a total of 56 066 kg of active substance have been sold.

Period:	Patient treatment-years (PTY)
2: 01 Mar 2007 to 31 Aug 2007	4 428
3: 01 Sep 2007 to 28 Feb 2008	11 816
4: 01 Mar 2008 to 31 Aug 2008	19 290
5: 01 Sep 2008 to 28 Feb 2009	26 379
6: 01 Mar 2009 to 31 Aug 2009	33 140
7: 01 Sep 2009 to 28 Feb 2010	41 059
8: 01 Mar 2010 to 31 Aug 2010	39 990
9: 01 Sep 2010 to 28 Feb 2011	44 721
AR: 01 Mar 2011 to 30 Jun 2011	35 187
Total	**256 010**

The MAH did not provide a layout of the patient exposure by formulation (film coated tablet or oral solution) and by region. However, the data provided in the last PSUR (PSUR 9) showed that the patient exposure to film coated tablets remained low in European countries (2.2%, 984 PTY) while the exposure in China represented alone nearly 76% (34 270 PTY) of the total worldwide patient exposure to this product. In the European countries the exposure was the following (exposure in PTY): Austria: 68, Bulgaria: 21, Croatia: 12, France: 9, Germany: 156, Greece: 222, Italy: 405, Netherlands: 15, Norway: 2, Romania: 2, Slovenia: 1, Spain: 60, Sweden: 2, Turkey 4, and the UK: 5. The total patient exposure to oral formulation was 5.18 PTY and concerned Germany.

2.4.2.1. Cumulative experience from 01 March 2007 until 30 June 2011

Globally, the main safety concerns of telbivudine in HBV-infected patients are represented by the risk of myopathy, peripheral neuropathy and rhabdomyolysis (and lactic acidosis as secondary events). These safety issues are reflected in the SmPC of Sebivo and the MAH closely monitors these issues in the PSURs. Beside the above safety issues, hypersensitivity reactions, ALT flares, fertility disorders and cases suggesting lack of efficacy and/or drug resistance information are closely monitored by the MAH.

Period covered by the Summary Bridging Report from 01 March 2007 to 30 June 2011

The layout of the distribution of the ADRs reported from 01 March 2007 to 30 June 2011 is provided in the table below.

Table 8. Distribution of ADRs from 01 March 2007 – 30 June 2011

	Serious		**Non-serious**		**Grand Total**
Report type	**Unlisted**	**Listed**	**Unlisted**	**Listed**	
Spontaneous HCP	583	799	226	281	1889
Suspect Solicited HCP	120	301	35	32	488
HCP total	**703**	**1100**	**261**	**313**	**2377**
Spontaneous non-HCP	116	70	188	309	683
Non-HCP total	**116**	**70**	**188**	**309**	**683**
Grand Total	**819**	**1170**	**449**	**622**	**3060**

The MAH provided the layout of the number of AEs of special interest in the period covered by this renewal as follows.

Table 9. Summary of cases retrieved by PSUR/safety finding

Relevant safety finding	PSUR 2	PSUR 3	PSUR 4	PSUR 5	PSUR 6	PSUR 7	PSUR 8	PSUR 9	AR	Total
Identified risk*										
Creatine phosphokinase increased	4	25	20	33	15	28	43	28	9	205
Rhabdomyolysis	0	1	0	5	2	2	3	4	1	18
Myopathy / myositis	8	38	31	37	19	41	52	33	12	271
Peripheral neuropathy	2	24	33	21	9	23	27	19	12	170
Potential risk*										
Alanine aminotransferase flares	0	6	6	5	4	5	12	4	4	46

Relevant safety finding	PSUR 2	PSUR 3	PSUR 4	PSUR 5	PSUR 6	PSUR 7	PSUR 8	PSUR 9	AR	Total
Lack of efficacy	1	18	2	8	3	2	17	15	3	69
Lactic acidosis (with/without hepatic steatosis, class effect of nucleoside analogues)	0	0	3	3	2	4	11	7	2	[illegible]
Acute pancreatitis (class effect of nucleoside analogues)	0	11	0	2	0	0	1	0	1	15
Hypersensitivity reactions	0	0	1	2	4	7	11	[illegible]	7	46
Important missing information*										
Maternal and fetal/child outcomes**	19	30	45	29	37	25	17	[illegible]	22	247
Fertility disorders	-	-	-	2***	0	1	1	0	0	4

* Current classification as of RMP version 6

** In PSURs the Maternal and fetal/child outcomes is covered by the standard PSUR pregnancy search, which is more encompassing than the search specified in the RMP

*** This was a cumulative search, and includes one spontaneous report received during the review period for PSUR 4

Fatal cases

In total there were 26 reports with fatal outcome. According to the MAH, alternative causes (underlying condition, multiple confounding factors, accident etc) were present in the majority of cases. The remaining cases did not provide sufficient information to allow an assessment.

Creatine phosphokinase (CK) elevations

In the period covered by the renewal a total of 205 reports of CK elevations were received, including 9 cases reported during the period covered by the addendum report. Cumulatively, 35 cases reported by Health Care Professionals (HCPs) were classified into CK-only category.

CK elevations and muscle events

One-year data were pooled from 4 telbivudine studies: NV-02B-007/GLOBE (n=680), NV- 02B-015 (n=161), CLDT600ACN03 (n=2206) and CLDT600A2410 (n=59). From 1-year pooled data, grade 3 or 4 CK elevations occurred in 4.4 % (136/3112) and myopathy/myositis in 0.4% (11/3112). All 11 cases resolved, including 2 patients who recovered without interrupting telbivudine treatment. Ten of the 11 cases resolved within 14-120 days and the remaining case showed evidence of myopathic process in EMG and muscle biopsy.

Four-year data were pooled from patients (n=655) treated in NV-02B-007/GLOBE, NV-02B- 015 and CLDT600A2303 for up to 4 years with telbivudine. Over 4 years of continued therapy, 71% patients had grade 1-2 elevations and 15.9% (104/655) had grade 3 or 4 elevations. However, CK elevations were asymptomatic and transient (lasting 1-2 visits with a visit interval of 2-12 weeks for 97.5% of patients and most resolved spontaneously or returned to baseline levels (1.8% of patients had grade 3 or 4 elevations persisting ≥ 2 visits). On-treatment CK elevations were not predictive of muscle events.

A total of 0.46% (3/655) telbivudine-treated patients discontinued study drug due to CK elevation or muscle related adverse events during the 4 years follow-up in studies NV-02B-007 /GLOBE, NV-02B-015 and CLDT600A2303 (CLDT600A2303 CSR).

Taken together, there is no uniform pattern to the degree or timing of CK elevations. In addition, the predisposing factors for the infrequent development of muscle-related events in telbivudine-treated patients are not known but do not appear to involve CK elevations.

Table 10. CK toxicity Grade 3 or 4 adjusted for baseline covariates by logistic regression in study NV-02B-007 (GLOBE) at week 104 for telbivudine-treated group (Caucasian and Asian patients)

Variables included in the model [1]	Odds ratio	Odds Ratio 95% CI	p-value
ALT level	0.93	(0.57, 1.53)	0.7827
HBeAg status	1.01	(0.57, 1.79)	0.9666
Ethnicity (Caucasian vs. Asian)	1.47	(0.78, 2.76)	0.2349
Baseline Age			
>50 vs.<30	0.81	(0.35, 1.88)	0.6269
30-50 vs. <30	0.61	(0.35, 1.05)	0.0759
Gender	0.51	(0.24, 1.09)	0.0814
Baseline CK			
Tertile 3 vs.1	1.99	(0.99, 4.02)	0.0547
Tertile 2 vs.1	1.33	(0.65, 2.70)	0.4302

[1] Endpoint: CK toxicity Grade of 3 or 4 (12.2%, 76/623)
[2] Tertile: evaluated as three equal groups of the population based on ascending baseline CK values.
Source: Data on file available upon request.

Blood creatine phosphokinase increased is a common adverse reaction listed in the SmPC of Sebivo. Based on this new logistic regression analysis of grade 3 or 4 CK elevations by baseline covariates from study NV-02B-007/GLOBE, the MAH proposes in this renewal application to delete the SmPC statement that pre-treatment CK values and Caucasian race are predictive of CK elevations. The outcome was that neither baseline CK nor Caucasian race are predictive factors for grade 3 or 4 elevations by week 104 (both p>0.05) (see also section 2.6 Change to Product Information hereafter).

Rhabdomyolysis
A total of 18 cases containing the Preferred Term "Rhabdomyolysis" were received during the period under review including one case during the period covered by the addendum report. No reports of rhabdomyolysis were reported in the clinical program. The section 4.4 of the SmPC of Sebivo mentions that cases of rhabdomyolysis have been reported during post-marketing use of telbivudine. Additionally rhabdomyolysis is currently listed as an adverse reaction with an unknown frequency in section 4.8 of the SmPC.

Myopathy / myositis
A total of 271 cases of myopathy / myositis cases were retrieved during the review period including 12 cases reported during the period covered by the addendum report. These 271 cases included 46 cases of myopathy combined with peripheral neuropathy. Cumulatively, 145 cases reported by Health Care Professionals (HCP) were classified into Myo-only category and 46 cases in myopathy and peripheral neuropathy category.

The specific mechanisms underlying myopathy/myositis are unknown. CK elevations are not predictive of muscle events associated with telbivudine. Mitochondrial toxicity, another potential mechanism, has not been observed with telbivudine in preclinical studies.

Myopathy is listed as an uncommon adverse reaction in the SmPC of Sebivo.

Lactic acidosis

Thirty-two cases of lactic acidosis were identified during the review period including 2 cases reported during the period covered by the addendum report. Lactic acidosis as a secondary event often associated with serious conditions (e.g. multiorgan failure or sepsis) is currently listed in section 4.8 of the SmPC.

Peripheral neuropathy (PN)

During the period under review a total of 170 reports of peripheral neuropathy were received including 12 cases reported during the period covered by the addendum report. Cumulatively, 51 cases reported by HCP were classified into PN-only category. No new cases of peripheral neuropathy due to a combination use of Sebivo and pegylated interferon (or standard) were reported since PSUR 6.

The risk of peripheral neuropathy with telbivudine, even in monotherapy is mentioned in the SmPC Sebivo.

ALT flare

A total of 46 reports of increased ALT were received during the review period including 4 cases reported during the period covered by the addendum report. After review by a hepatologist, only 2 of the 46 cases were assessed as an ALT "flare".

Acute pancreatitis

A total of 15 cases of acute pancreatitis were retrieved by the search performed by the MAH during the period covered by the renewal. However, in PSUR 3, although the search retrieved 11 cases, upon review there were no cases of pancreatitis. In the addendum report, upon review, only 1 case involved the pancreas, and described a 50-year-old female patient who experienced an asymptomatic increase in lipase during treatment with Sebivo. There were 2 reports during PSUR 5 received from HCPs and one report was made during PSUR 8. In this case, the patient received combination treatment of interferon alfa-2b and Sebivo, which is now contra-indicated.

Hypersensitivity reactions

A total of 46 reports of hypersensitivity reactions were reported during the review period. The majority of the reports were related to various underlying conditions and did not reflect hypersensitivity in nature. There is no evidence that Sebivo is associated with severe hypersensitivity reaction.

Mitochondrial toxicity

As cases of myopathy, peripheral neuropathy and rhabdomyolysis have been reported with use of telbivudine, it was suggested that product could be associated to a risk of mitochondrial toxicity.

Preclinical studies of mitochondrial toxicity were performed to address requests to provide additional information on muscle events and peripheral neuropathy (described in the assessment report FU2 019.7).

Mitochondrial toxicity was not observed in preclinical studies.

Fertility disorders

A total of 4 reports of fertility disorders were received during the review period, none of them has been reported during the period covered by the addendum report. In all cases there was insufficient information to make a medical assessment.

Cardiac repolarization

A thorough QT/QTc Study of telbivudine has been carried out in healthy subjects. The results of the study were published by Poordad et al 2009 and are as follows:

- None of the changes in QTcF for either dose of telbivudine (600 and 1800mg) exceeded 5 msec, and none of the associated upper 1-sided 95% confidence intervals exceeded the limit of 10 msec.
- There was no increase in QTcF with increasing plasma telbivudine. The supratherapeutic dose of telbivudine was well tolerated with a safety profile similar to the clinical dose despite a 3-fold increase in plasma exposure.

This study met the criteria (ICH-E14) for a negative thorough QT study.

Renal function

Renal toxicity is neither an identified risk nor a potential risk of telbivudine treatment. No renal toxicity has been previously reported with telbivudine.

Glomerular Filtration Rate (GFR) was assessed at baseline and on treatment in 5 telbivudine clinical trials (NV-02B-007/GLOBE, CLDT600A2301, CLDT600A2303, CLDT600A2410 and CLDT600ACN03). GFR was calculated using the MDRD equation, which is considered to be an accurate index to evaluate GFR in patients with liver disease.

According to the MAH, results show that telbivudine treatment is associated with a consistent improvement of GFR from baseline in both compensated and decompensated CHB patients. This improvement was seen in patients receiving either telbivudine monotherapy (all 5 studies) or LDT + tenofovir (TDF) combination therapy (study CLDT600A2410) (Table 4.1.1). In contrast, worsening of GFR was seen in patients treated with lamivudine (LAM).

Table 11. Summary of calculated GFR (MDRD equation) at baseline and change from baseline in Sebivo clinical studies

			GFR change from baseline*		
Study	**Treatment**	**Mean baseline GFR**	**Week 52**	**Week 104**	**Week 208**
NV-02B-007 / GLOBE 2 years	LDT (N=680)	98.3	5.1[1]	6.7[1]	–
	LAM (N=687)	99.8	−1.0[1]	−1.8[1]	–
CLDT600A2303 4 years	LDT (N=655)	94.9	13.7	17.8	14.9
CLDT600A2301 2 years	LDT (N=114)	102.0	−1.1[2]	2.0[3]	–
	LAM (N=114)	100.8	−4.5[2]	−4.6[3]	–
CLDT600A2410 1 year	LDT (N=55)	93.4	6.9[4]	–	–
	LDT+TDF (N=[illegible])	93.3	7.4[5]	–	–
CLDT600ANC03 1 year	LDT (N=98)**	98.1	3.8[6]		

Source: LDT600A GFR Analysis Full Report; CLDT600A2301 GFR Analysis Full Report; CLDT600ACN03 Addendum 1

[1] LDT vs. LAM; p<0.0001 at week 52 and week 104
[2] LDT vs. LAM; p=0.0410
[3] LDT vs. LAM; p=0.0214
[4] Week 52 vs. baseline; p=0.0057
[5] Week 52 vs. baseline; p=0.0054
[6] Week 52 vs. baseline; p<0.0001
* LS mean change for NV-02B-007/GLOBE and CLDT600A2301; mean change for all other studies
** Only patients with GFR ≤120 mL/min/1.73m^2 at baseline or Week 52 were included in the GFR analysis

The results of GFR analysis confirmed the overall renal tolerance of telbivudine. According to the MAH, it may therefore be concluded that telbivudine is a safe renal drug. Renal function steadily improved in patients receiving telbivudine, with a significant improvement starting during the second year of treatment and largest improvement after 4 years. The apparent benefit of telbivudine in improving renal function could reflect both the recovery of liver synthetic dysfunction and lack of drug nephrotoxicity.

However, in agreement with the SAG advice, the CHMP is of the opinion that the proposed MAH's beneficial claim of Sebivo on the renal function, measured as an improvement of the GFR, lacks of

biological plausibility and would need to be better substantiate to considered and reflected in the Product Information.

In this view, the MAH noted that CHMP recommendations to consider additional non clinical investigation, with adequate methodology on the protective effect of telbivudine on the renal toxicity of tenofovir as well as the recommendation to clarify and show how to substantiate the question on whether the use of tenofovir with telbivudine might be of interest as compared to tenofovir alone.

Lack of Efficacy/Resistance:
As discussed above in section 2.4.1 Clinical Efficacy, new data on the analysis of resistance development showed that the risk of resistance for telbivudine remains a concern and is likely to be approx 10-fold higher as compared to that with entecavir.

Pregnancy and newborns

During the period covered by the addendum report there were 18 prospective reports of drug exposure during pregnancy.

Cumulatively there have been 196 prospective and 64 retrospective cases of pregnancy.

Table 12. Summary of pregnancy outcomes

Pregnancy outcome	Prospective cases (198)†						Retrospective cases (64) †					
	Timing of exposure in pregnancy (trimester)						Timing of exposure in pregnancy (trimester)					
	Before conception	1st	After 1st	All	Unk	Father‡	Before conception	1st	After 1st	All	Unk	Father‡
Spontaneous abortion	4	2	0	0	0	0	1	0	0	0	0	
Intra-uterine death *	0	0	0	0	0	0	1	0	0	0	0	
Elective termination (fetal defects) *	0	0	0	0	0	0	1	0	0	0	0	
Elective termination (no fetal defects or unknown)	1	13	2	0	0	2	12	0	0	3	1	
Live birth with congenital anomaly *	0	0	1	0	0	0	0	1	0	1	0	
Live birth without congenital anomaly	8	13	26	5	20	9	5	13	7	14	1	
Outcome unknown	7	25	20	0	35	4	0	0	0	2	0	
Total	20	53	49	5	56	15	20	14	7	20	2	

† Prospective and retrospective cases reflect the time when the pregnancy was reported to Novartis

The MAH performed an analysis of the telbivudine clinical safety database and post-authorization exposure data including spontaneous reports, unpublished and published reports to assess the outcomes of newborns exposed in utero to telbivudine (Trylesinski et al 2010). As of 31-Aug-2009, 176 pregnancies were identified (132 prospectively and 44 retrospectively). Information on outcomes was available for 62% of the pregnancies. Of the 109 pregnancies, 28% ended in abortion (8 spontaneous, 22 induced; 80% in the first trimester) and congenital abnormalities were detected in 2.5% of the remaining pregnancies that resulted in live births. This rate of birth defects (2.5%) in live newborns exposed to telbivudine in utero is similar to that reported by the Centre for Disease Control, USA for the general population (2.72 per 100 live births).

The CHMP noted that pregnancy outcomes remain unknown in a high number of cases, leading difficulties to draw reliable conclusion. As already mentioned in the SmPC, Sebivo should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

Actions taken for safety reasons

During the period covered by the PSUR 3 (01 Sept 2007 to 28 Feb 2008), an increased risk of developing peripheral neuropathy was observed in chronic hepatitis B patients treated with Sebivo and pegylated interferon alfa-2a in a well controlled pilot clinical trial. The combination arm of this trial was permanently discontinued during the period covered by this report due to this increased risk of peripheral neuropathy. The Product Information was updated (variation II-03 adopted in January 2008) and a global Dear Healthcare Professional Communication (DHPC) was prepared for distribution by the MAH to inform prescribing physicians of this event.

2.4.2.2. Report of post marketing experience from 01 March 2011 to 30 June 2011

In addition, the MAH submitted within the renewal dossier one addendum report covering the period from 01 March 2011 to 30 June 2011.

Overview of adverse reactions

A total number of 63 cases were reported during the period covered by the addendum report. Among them 7 were serious unlisted cases. Among the 63 cases, there were 33 reports received from HCPs and 30 reports received from non-HCPs. The layout of the 63 reports is summarized in the table below.

Table 13. Overview of reported cases by report type

	Serious		**Non-serious**		**Grand Total**
Report type	**Unlisted**	**Listed**	**Unlisted**	**Listed**	
Spontaneous HCP	4	4	7	8	**23**
Suspect Solicited HCP	0	10	-	-	**10**
HCP total	**4**	**14**	**7**	**8**	**33**
Spontaneous non-HCP	3	3	7	17	**30**
Non-HCP total	**3**	**3**	**7**	**17**	**30**
Grand Total	**7**	**17**	**14**	**25**	**63**

The distribution of adverse reactions reported with Sebivo by MedDRA System Organ Class in the addendum report is presented in the table below.

Table 14. Distribution of ADRs in the addendum report (01 March 2011 – 30 June 2011)

MedDRA SOC	HCP reports		Non-HCP reports	
	PTs Nb	PTs reported ≥ 2 times	PTs Nb	PTs reported ≥ 2 times
Cardiac disorders	2		0	
Gastrointestinal disorders	4		5	Dyspepsia (2)
General disorders and administration site conditions	17	Asthenia (3), Drug interaction (2), Fatigue (3), Feeling abnormal (2)	6	Asthenia (2), Pain(2)

Hepatobiliary disorders	1		0	
Infections and infestations	3	Hepatitis B (2)	0	
Injury, poisoning and procedural complications	7	Drug exposure during pregnancy (6)	15	Drug exposure during pregnancy (15)
Investigations	33	Alanine aminotransferase increased (2), Blood creatine phosphokinase increased (5), Blood lactic acid increased (2), Hepatitis B DNA, increased (6)	7	Blood creatine phosphokinase increased (4)
Metabolism and nutrition disorders	4		0	
Musculoskeletal and connective tissue disorders	17	Back pain (2), Muscular weakness (4), Myalgia (3), Pain in extremity (2)	5	Myalgia (3)
Nervous system disorders	12	Hypoaesthesia (3), Neuropathy peripheral (4)	7	Hypoaesthesia (4), Neuropathy peripheral (2)
Pregnancy, puerperium and perinatal conditions	2	Normal newborn (2)	2	
Psychiatric disorders	1		1	
Renal and urinary disorders	4		1	
Respiratory, thoracic and mediastinal disorders	3		2	Dyspnoea (2)
Skin and subcutaneous tissue disorders	2	Rash (2)	1	
Social circumstances	1		0	
Total number of events	**113**		**52**	

The most frequently adverse events concerned the SOC "Investigations" (n=40), followed by the SOC" General disorders and administration site conditions" (n=23) and the SOC "Musculoskeletal and connective tissue disorders" (n=22), and the SOC "Injury, poisoning and procedural complications" (n=22).

It is noteworthy that muscular related adverse events (CPK increases + muscular disorders) are the most commonly reported adverse events with telbivudine, illustrating that muscle is the main target for drug toxicity.

Although telbivudine and lamivudine are close on a virological point of view, CPK increases+ muscles disorders constitute a clear differential of risk between telbivudine and lamivudine.

Discussion and Conclusion on Safety

Beside the confirmed issue of increased resistance, the main safety concerns of telbivudine in HBV-infected patients are represented by the high risk of myopathy, myalgy, peripheral neuropathy and rhabdomyolysis (and lactic acidosis as secondary events). These issues are reflected in the SmPC of Sebivo and the MAH should continue to closely monitor these issues in the next PSURs. In addition, hypersensitivity reactions, ALT flares, fertility disorders and cases suggesting lack of efficacy and/or drug resistance information should continue to be closely monitored.

The CHMP agrees that the safety profile of telbivudine, mainly characterized by occurrence of muscular disorders, needs to be kept under close monitoring and that the MAH should carry on submitting PSUR every 6 months.

2.5. Risk management plan

During the renewal procedure, the MAH submitted an updated risk management plan, which included a risk minimisation plan as follows.

In particular, following the CHMP concern (see hereafter section 2.7 Overall Conclusion and benefit risk balance), the commitment to provide additional data in pregnancy, with data collection report from post-marketing surveys in women exposed to telbivudine during pregnancy, has been reflected in the updated RMP.

Table 15. Summary of the risk management plan

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Blood creatine phosphokinase (CK) elevation	Routine pharmacovigilance activities including cumulative analysis in PSUR Investigators of all Novartissponsored trials and third-party sponsored trials are provided with guidance on suggested management of symptomatic CK elevation contained in the "Muscle Symptom Algorithm".	[SPC section 4.8 (Undesirable effects)] Educational material has been requested for European countries and approved by CHMP. Educational material is distributed upon approval by local HAs to prescribers in Europe.
Rhabdomyolysis	Routine Pharmacovigilance activities including cumulative analysis in PSUR Investigators of all Novartissponsored trials and third-party sponsored trials are requested to follow the "Muscle Symptom Algorithm" when evaluating and managing patients with muscular events. All myopathy-like SAEs from clinical Novartis-sponsored trials and all myopathy-like SRs are being followed-up using a "Targeted Follow-up Questionnaire".	[SPC section 4.4 (Special warnings and precautions for use)] [SPC section 4.8 (Undesirable effects)] Subjects in telbivudine clinical trials (including Novartis sponsored and third-party sponsored) with complaints of muscle weakness, muscle pain or achiness, or unexplained fatigue should be managed according to the Muscle Symptom Algorithm. Subjects being followed with this algorithm should have a physical exam with muscle strength testing and muscle symptom questionnaire administered at each visit. A muscle symptom questionnaire is administered to clinical trial subjects who complain of new or worsening muscle weakness, muscle pain or achiness, or unexplained fatigue. Educational material to emphasize the wording from the current CDS in Section 4.8 and Section 4.4 and in line with the material developed in EU, addressing CK elevation and muscle events, have been developed for distribution to prescribers and patients in China, in order to further inform about these risks. Since the first Educational program launch in China, local activities are ongoing and continue to implement the actions planned in the current RMP. In line with these activities, a Patient Support Program (PSP) called HOPEs, a website based program in China, in which the goal is to improve compliance of Hepatitis B patients. This is a nation-wide public benefit program initiated and owned by China Foundation of Hepatitis Prevention and Control. Novartis China supports this program in order to ensure all Hep B patients receive a follow-up by their physician and receive a medical advice in case of changes in concurrent medications or new treatments.
Myopathy / myositis	Routine Pharmacovigilance activities including cumulative analysis in PSUR. Investigators of all Novartis- sponsored trials and third-party sponsored trials are requested to follow the "Muscle Symptom Algorithm" when evaluating and managing patients with muscular events. All myopathy-like SAEs from clinical Novartis-sponsored trials and third-party sponsored trials and all myopathy-like SRs are being followed-up using a "Targeted Follow-up Questionnaire".	[SPC section 4.4 (Special warnings and precautions for use)] [SPC section 4.8 (Undesirable effects)] Educational material addressing CK elevation and myopathy has been requested and approved by CHMP and is distributed in the EU upon approval by local HAs to prescribers in Europe. Physicians are informed how to minimize these risks in patients receiving telbivudine as described in the CDS. Educational material to emphasize the wording from the current CDS in Section 4.8 and Section 4.4 and in line with the material developed in EU, addressing CK elevation and muscle events, have been developed for distribution to prescribers

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		and patients in China, in order to further inform about these risks. Since the first Educational program launch in China, local activities are ongoing and continue to implement the actions planned in the current RMP. In line with these activities, a Patient Support Program (PSP) called HOPEs, a website based program in China, in which the goal is to improve compliance of Hepatitis B patients. This is a nation-wide public benefit program initiated and owned by China Foundation of Hepatitis Prevention and Control. Novartis China supports this program in order to ensure all Hep B patients receive follow-up by their physician and receive a medical advice in case of changes in concurrent medications or new treatments
Peripheral neuropathy (PN)	Routine pharmacovigilance activities including cumulative analysis in PSUR. PN-like SAEs from clinical Novartis-sponsored trials and PN-like SRs are being followedup using a targeted follow-up questionnaire.	[SPC section 4.3 (Contraindication)] [SPC section 4.4 (Special warnings and precautions for use)] [SPC section 4.8 (Undesirable effects)] The pilot trial CLDT600A2406 was terminated and all patients, specifically those who developed PN were followedup. A DHCP letter was agreed with CHMP and dispatched to prescribing physicians in all countries where telbivudine was launched depending on local regulatory requirements. All investigators participating in trials with telbivudine were informed by Investigator Notifications. The Investigator's Brochure was updated to include this risk. US FDA requested a REMS composed of a patient Medication Guide for the US.
Alanine aminotransferase (ALT) flares	Routine Pharmacovigilance activities including cumulative analysis in PSUR.	[SPC section 4.4 (Special warnings and precautions for use)] [SPC section 4.8 (Undesirable effects)]
Lack of efficacy (with/ without antiviral resistance development)	Routine Pharmacovigilance activities including cumulative analysis in PSUR. Reporting of resistance data from ongoing trials: CLDT600A2303 CLDT600A2410 CLDT600A2409	[SPC section 4.4 (Special warnings and precautions for use)] [SPC section 5.1 (Pharmacodynamic properties)]
Peripheral neuropathy for the combination of telbivudine with other interferon (than pegylated interferon alfa-2a)	Routine Pharmacovigilance activities including cumulative analysis in PSUR. SAEs from clinical Novartissponsored trials and SRs are being followed-up using a targeted follow-up questionnaire checklist. Pilot Drug Utilization Study	SPC section 4.3 (Contraindication) [SPC section 4.4 (special warnings and precautions for use)] [SPC section 4.5 (interactions with other medicinal products and other forms of interaction)].
Lactic acidosis with/ without hepatic steatosis (Class effects of nucleoside analogs)	Routine Pharmacovigilance activities including cumulative analysis in PSUR	[SPC section 4.4 (Special warnings and precautions for use)] [SPC section 4.8 (Undesirable effects)] [SPC section 5.1 (Pharmacodynamic properties)]
Acute pancreatitis (Class effects of nucleoside analogs)	Routine Pharmacovigilance activities including cumulative analysis in PSUR	[SPC section 4.4 (Special warnings and precautions for use)]
Hypersensitivity reactions	Routine Pharmacovigilance activities including cumulative analysis in PSUR	[SPC section 4.8 (Undesirable effects)]
Maternal and fetal/ child outcomes	Routine Pharmacovigilance activities including cumulative analysis in PSUR Novartis has joined the APR: all pregnancies occurring in clinical trials or post-marketing (retro- or prospective) including outcome follow-up reports are reported to the APR	[SPC section 4.6 (Pregnancy and lactation)] All pregnancy cases and outcomes are reported to the Anti-retroviral pregnancy Registry (APR)
Fertility disorders	Routine pharmacovigilance activities including cumulative analysis in PSUR	[SPC section 4.6 (Pregnancy and lactation)] [SPC section 5.3 (Preclinical

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		safety data)]
Drug-drug interaction between telbivudine and pegylated interferon alfa-2a HIV/HBV co-infected patients	Routine pharmacovigilance activities including cumulative analysis in PSUR Routine pharmacovigilance activities including cumulative analysis in PSUR	[SPC section 4.5 (Interaction with other medicinal products and other forms of interaction)] [SPC section 4.4 (Special warnings and precautions for use)] Study CLDT600A2202 to be conducted in HBV/HIV coinfected patients

The CHMP, having considered the data submitted, was of the opinion that the proposed pharmacovigilance activities were adequate to monitor the safety of the product.

2.6. Changes to the product information

As presented above, in this renewal application, the MAH proposed changes to the Product Information (PI), which were reviewed during the assessment of this renewal application.

In particular, as per the conclusion of the post-authorisation measure 050 and in order to improve benefits while minimizing risk of resistance development, the MAH proposed to narrow the Sebivo indication according to baseline HBV DNA/ALT levels and Week 24 on-treatment response with treatment intensification.

In line with the SAG minutes & answers (meeting of 9 January 2012) and as discussed above in 'Conclusion and discussion on efficacy', the CHMP did not consider this proposal appropriate but considered that Sebivo has a role in clinical practice for patients who are unable to tolerate entecavir and tenofovir due to side effects and that it should be a therapeutic option when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.

Accordingly, it was agreed to amend the section 4.1 Therapeutic indications as follows:

4.1 Therapeutic indications

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

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

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

It was agreed that, in ***section 5.1 Pharmacodynamic properties,*** the initial proposed statement on the improvement of the GFR should not endorsed as lacking of biological plausibility and not sufficiently demonstrated.

In addition, also in ***section 5.1 Pharmacodynamic properties***, in line with the refusal of the initial MAH proposal of baseline criteria to define a population with lower resistance risk, a proposal to reflect the resistance data according to restricted baseline criteria and week 24 responses (based on retrospective analysis in NV-02B-007/GLOBE study) was not accepted as not informative and potentially misleading.

Other SmPC updates, based on the reviewed efficacy and safety data over the reporting renewal period, were proposed, reviewed and agreed by the CHMP, including inclusion of the 208-week data on off-treatment sustained efficacy results (section 5.1), liver histology results (section 5.1) or deletion of the statement that pre-treatment CK values and Caucasian race are predictive of CK elevation (section 4.8).

In addition, changes were made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were reviewed by QRD and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Poland and Romania.

2.7. Overall conclusions and benefit risk balance

Sebivo has been approved in Europe for the treatment of HBV infection in April 2007. Already at the time of the initial MA, the benefit/risk of the drug was considered as borderline positive since telbivudine was considered to be a "lamivudine-like" antiviral that was not deprived of adverse effects (signal on muscular disorders was identified).

Since the initial MA, long-term data were gained from follow-up studies. These data confirm the low genetic barrier of the drug with follow-up studies showing that resistance developed at high rate over time in patients that received telbivudine (40% in HbeAg positive and 20% in HbeAg negative patients at 4 years). Even though the resistance rate is less than that of lamivudine, antiviral resistance remains a major limitation of telbivudine treatment. In addition, these data highlight that another important limitation of telbivudine is its safety profile, mainly characterized by occurrence of muscular disorders. Whereas CPK elevations mostly asymptomatic had been reported during the clinical development, clinical cases of myalgia, myopathy, as well as rhabdomyolysis have now emerged. Cases of peripheral neuropathy have also been reported.

Moreover, since the MA of Sebivo was granted, the standard of care has evolved. Two medicinal products with both high potency and high genetic barrier to resistance have become the "gold standard" for the treatment of chronic hepatitis B infection in Europe. They are recommended as first-line monotherapy in EASL guidelines and have become the medicinal products of choice for initiation of treatment.

Given these updated data and therapeutic evolution, the CHMP considered the input of the Scientific Advisory Group (SAG) was necessary during the renewal procedure in order to determine the role of telbivudine in the treatment of HBV patients in Europe and whether it is possible to delineate a patient population (if any) where the benefit/risk of telbivudine could be considered as favourable.

In this context the following questions were put to the SAG:

- Is there still a role for telbivudine in the treatment of HBV infected patients in Europe? If so, for which patients groups would telbivudine still be a proper treatment.
- Given the low genetic barrier to resistance of telbivudine and the safety profile, it is under consideration whether the risks related to the use of this compound do not outweigh the benefits of its use. What is, from a clinical practice perspective, the view from the HIV / AV SAG on this point.

On 9 January 2012, the SAG reviewed the available data concerning Sebivo.

The SAG agreed that, due to the low genetic barrier to resistance of Sebivo, the benefit risk balance could only be considered positive when the use of an alternative antiviral agent with a higher genetic barrier is not available or appropriate.

The SAG also commented that the effect of telbivudine on GFR, for which the MAH has initially proposed a beneficial effect claim, should be further and robustly demonstrated

In addition, it was noted that Sebivo may be used for treatment of women of child-bearing age who are not compliant with contraception and as such who may not be able to take entecavir or for pregnant women with renal insufficiency for which tenofovir is not an option. However, so far, safety data in pregnancy only consist in pre-clinical data and one investigator lead study not yet fully assessed. In the view of the public health need for HBV treatment option in pregnant women in Europe, the SAG recommended that the MAH should provide more data to substantiate the safety of telbivudine in pregnancy. Accordingly, the Sebivo RMP has been updated to include data collection report from post-marketing surveys in women exposed to telbivudine during pregnancy.

Overall, CHMP endorsed the outcome of the SAG and, and in line with the recommendations, did not agree with the MAH's initial proposed indication restriction (baseline criteria of HBV DNA $\leq$9 log10 copies/ml and ALT$\geq$2x ULN in HBe Ag pos and $\leq$7 log10 copies/ml in HBe neg with intensification at week 24) as a way to overcome the acknowledged low genetic barrier of this drug. Indeed, even under these proposed restricted conditions, the resistance rates observed with telbivudine are higher than those with tenofovir and entecavir. In addition, resistance data are only available for 2 years for the restricted population while quite reassuring 5 years data are available for tenofovir and entecavir.

It is also noted that, according to an epidemiological survey in EU, these population criteria are not so restrictive since the vast majority of EU patients (more than 80%) match these criteria.

In conclusion, the CHMP agreed that telbivudine has a role in clinical practice for patients for whom an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate. It was agreed to amend the Sebivo indication to recommend the initiation of Sebivo treatment only when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.

The CHMP also endorsed the SAG concern regarding the lack of data for the use of telbivudine during pregnancy since there is a public health need for treatment options in pregnant women. It noted that the MAH updated accordingly the Sebivo RMP to include data collection report from post-marketing surveys in women exposed to telbivudine during pregnancy.

Regarding safety, the CHMP agreed that Sebivo needs to be kept under close monitoring, mainly due to the risk of resistance/lack of efficacy and the occurrence of muscular disorders. The MAH will continue to submit 6 monthly PSUR's and an additional 5 year renewal based on these Pharmacovigilance concerns is warranted.

3. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considers by consensus that the risk-benefit balance of Sebivo in the treatment of chronic hepatitis B in adult patients remains favourable and therefore recommends the renewal of the marketing authorisation

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk management system (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the European Medicines Agency

PSUR

The PSUR cycle for Sebivo should follow a half-yearly cycle until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

The CHMP recommends that one additional five-year renewal be required. This is based on the following pharmacovigilance grounds:

Grounds for one additional renewal

Based on the review of the available information, the CHMP was of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently

demonstrated within the restricted indication and therefore considered that the benefit/risk balance of Sebivo remains favourable.

However specific issues related to pharmacovigilance remain, notably the resistance of this drug of low genetic barrier as well as the growing evidence of muscular toxicity during the first 5 years period justify keeping the Marketing Authorisation of this medicinal product under close scrutiny.

Based upon the above defined pharmacovigilance issues of Sebivo, the CHMP decided that the MAH should continue to submit 6 monthly PSURs and that the MAH should submit one additional renewal application in 5 years time.

Amendments to the marketing authorisation

In view of new data submitted as part of the renewal application, the CHMP recommends amendments to the Annexes I, II, IIIA and IIIB. The CHMP requested the above mentioned changes on safety grounds and in order to maintain the positive risk-benefit balance of the product.