Sebivo

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
T/0050	Transfer of Marketing Authorisation	26/03/2018	12/04/2018	SmPC, Labelling and PL	
II/0048	Submission of RMP version 11.0 in order to upgrade the risk of lactic acidosis from an important potential to an important identified risk and to include a targeted questionnaire for fatal cases as additional risk minimisation measure as requested by the PRAC	08/03/2018	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	as part of the assessment of PSUSA/00002880/201608. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IB/0049/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in	11/01/2018	n/a		

	the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
PSUSA/2880/ 201608	Periodic Safety Update EU Single assessment - telbivudine	21/04/2017	23/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2880/201608.
R/0045	Renewal of the marketing authorisation.	13/10/2016	16/12/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Sebivo in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. In addition section 5.1 'Pharmacodynamic properties' of the SmPC was updated to add that transient reductions in HIV-1 RNA have been reported in a small number of patients treated with telbivudine in the absence of antiretroviral therapy but that the significance of these reductions has not been determined.
IA/0044	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	24/06/2016	n/a		
IA/0043/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter	13/04/2016	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0042/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/01/2016	n/a		
IB/0041	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	10/07/2015	n/a		
IG/0484/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/11/2014	n/a		

II/0039/G	This was an application for a group of variations. - Type IA (A.1): To update the address of the marketing authorisation holder, Novartis Europharm Limited, from Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom, to Frimley Business Park, Camberley GU16 7SR, United Kingdom. - Type II (C.I.4): To update section 4.6 of the SmPC with information on pregnancy outcomes and recommendations related to treatment in second and third trimester. The package leaflet is amended accordingly. In addition, the product information is amended according to the latest QRD template and MedDRA system organ class terminology. The side effect “Hepatomegaly” in section 2 of package leaflet is further clarified with the inclusion of symptoms “abdominal swelling and/or discomfort” for better understanding. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data A.1 - Administrative change - Change in the name and/or address of the MAH	23/10/2014	18/09/2015	SmPC, Annex II, Labelling and PL	The MAH provided a review of information on telbivudine usage in pregnant women with HBV infection from the published literature, APR and their own safety database to support an update of the Product information for Sebivo with regards to pregnancy. Section 4.6 of the SmPC and the corresponding section in the Package Leaflet were updated and now instruct as follows: Do not use Sebivo during pregnancy unless your doctor recommends it. If you are pregnant or think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you the potential risks of taking Sebivo during pregnancy. If you have hepatitis B and become pregnant, talk to your doctor about how you can best protect your baby. Sebivo may reduce the risk of passing your hepatitis B virus on to your unborn baby if taken in combination with Hepatitis B immune globulin and Hepatitis B vaccine.
IB/0038	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	15/07/2014	n/a		

IA/0037/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	27/06/2014	n/a		
PSUV/0036	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/11/2013	18/09/2015	PL	Inclusion of additional local representative of the MAH for the new member state Croatia. Furthermore, the MAH took this opportunity to update the details of the local representatives in Malta.
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IA/0032/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	26/10/2012	n/a		
IA/0033	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding	24/10/2012	n/a		

	manufacturer for batch release)				
IA/0031/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/09/2012	n/a		
IG/0209/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV 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	17/08/2012	n/a		
IA/0029	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	14/08/2012	n/a		
IA/0028	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 AS -replacement or addition of a site where batch control/testing takes place	13/07/2012	n/a		

R/0023	Renewal of the marketing authorisation.	16/02/2012	20/04/2012	SmPC, Annex II, Labelling and PL	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 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 as a second line option.
IG/0148/G	This was an application for a group of variations. 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 DD 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	22/02/2012	n/a		
IG/0088/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the	11/07/2011	n/a		

	major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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				
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	n/a	Annex II and PL	
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	n/a	Annex II and PL	
IG/0065	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	17/05/2011	n/a		

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.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product 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 AS -replacement or addition of a site where batch control/testing takes place 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 AS -replacement or addition of a site where batch control/testing takes place 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 AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a	20/01/2011	31/01/2011		

	starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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.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 AS 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				
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. 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 Article 45/46, or amendments to reflect a Core SPC -	16/12/2010	27/01/2011	SmPC and Annex II	The Marketing Authorisation for SEBIVO was supported by one pivotal clinical trial, the NV-02B-007 GLOBE study which is a randomised, double-blind, multinational phase III study of telbivudine compared to lamivudine for a treatment period of 104 weeks in 1,367 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative patients. At the end of GLOBE study (that included 680 LdT and 687 LAM patients), patients were offered the opportunity to continue LdT treatment in the subsequent CLDT600A2303 trial. Following the CHMP recommendation the MAH has now included a wording derived from the data in the GLOBE extension study (CLDT600A2303 trial) to reflect resistance data in the 3rd

	Change(s) with new additional data submitted by the MAH				and 4th year of telbivudine treatment
IG/0032/G	This was an application for a group of variations. To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest wording as per October 2010 CHMP procedural announcement. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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 DD 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	21/12/2010	n/a		

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 Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/10/2010	29/11/2010	SmPC, Annex II and PL	The efficacy and the safety of telbivudine in combination with 180 µg pegylated interferon alfa-2a (Pegasys) once weekly was investigated in the Phase IIIb study CLDT600A2406. However a total of nine serious cases of peripheral neuropathy (PN) involving the combination arm were described in the final clinical study report. Based on the final results of this study, the CHMP recommended that the current labelling regarding the co-administration of telbivudine and (peg)interferon alfa be strengthened by the addition of a contra-indication in order to discourage this combination. In addition even though only the combination of pegylated interferon alfa 2a and telbivudine have been clinically investigated so far, the potential increased risk may be extrapolated to other interferon alfa containing products indicated in the treatment of hepatitis C infection. Of note spontaneous case reports of peripheral neuropathy with telbivudine in combination with interferons other than peginterferon alfa2a were reported in PSURs of Sebivo. Furthermore, for the time being, the mechanism behind these events has not been elucidated but the most likely hypothesis is an overlapping toxicity of both drugs. It is likely that such overlapping toxicities can be observed with all interferon alfa.
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	21/09/2010	n/a	SmPC	To update the annexes with information related to sensitivty of the A181V mutation to telbivudine.

	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				
IB/0017	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	15/07/2010	n/a		
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	n/a	SmPC	
IA/0016/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.I.a.3.a - Change in batch size (including batch size ranges) of AS 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 AS or intermediate - Downscaling B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of	08/07/2010	n/a		

	the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
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	n/a	SmPC	
II/0011	Update of the Detailed Description of the Pharmacovigilance system (DDPS). Changes to QPPV Update of DDPS (Pharmacovigilance)	18/02/2010	15/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 8.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. Consequently, Annex II has been updated with the new version numb er of the agreed DDPS.
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	21/01/2010	15/03/2010	SmPC, Annex II, Labelling and PL	The steady-state pharmacokinetics of telbivudine in 9 patients with decompensated CHB and evidence of cirrhosis was evaluated in a PK sub-study of a larger ongoing phase III trial. The results of this sub-study confirmed both theoretical considerations as well as results in compensated CHB

	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. Update of Summary of Product Characteristics, Labelling and Package Leaflet				patients, i.e. that no dose adjustment of telbivudine for patients with underlying liver disease is necessary. The results in these 9 patients were added to section 5.2 of the SmPC to further underline the validity of this dosing recommendation. In addition, based on the potential gravity of the recently added (see variation II/06) adverse drug reaction "rhabdomyolysis" (breakdown of the muscle), it was added as a warning in section 4.4 of the SmPC as well as in section 2 of the PL.
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	n/a		
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. Update of Summary of Product Characteristics	17/12/2009	25/01/2010	SmPC	Data submitted for Study NV-02B-019 (A randomized trial of switching antiviral therapy from Lamivudine to Telbivudine versus continued Lamivudine treatment in adults with chronic hepatitis B) and other data presented from the GLOBE study and enrolled into the extension study CLDT600A2303 (A2303) do not support the broad terminology of "lamivudine- experienced patients", as this includes different populations. For patients with established resistance to lamivudine, switching these patients to telbivudine does not provide any further virologic benefit. Furthermore, switching to telbivudine for those patients virologically failing lamivudine (without evidence of LAM- R) after exposure > 24 weeks does not provide clear benefit either and guidelines recommend the use of a more potent medicinal product that does not share cross-resistance with

					lamivudine. In relation to the other patients with prior lamivudine therapy (i.e. those who achieve complete viral suppression on lamivudine and those who show virological failure without established LAM-R after exposure to <24 weeks of lamivudine), there is currently no clinical data to properly assess the benefit/risk of switching to telbivudine. However, taken into account the safety and known resistance profile of telbivudine, patients who failed to achieve virological response following treatment with lamivudine within 24 weeks are unlikely to benefit from telbivudine monotherapy.
II/0008	Update of sections 4.6 and 5.3 of the SPC further to the results of a toxicity study in juvenile rats. Update of Summary of Product Characteristics	24/09/2009	29/10/2009	SmPC	A recently completed toxicity study in juvenile rats showed an effect on fertility, similar to the modest effect observed in one of the original fertility studies submitted at the time of the initial marketing authorisation (see EPAR Module 6 "Scientific Discussion"). Consequently the effect of telbivudine on fertility was re-evaluated. The current available data on fertility is limited due to the variability of study protocols and sites and not allowing a conclusion on the possible mechanism of decreased fertility observed in adults and juvenile rats treated with telbivudine. To further investigate this issue, a new toxicity study has been agreed and will be completed by December 2010. Section 4.6 and 5.3 were updated to reflect the current available data.
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. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	07/09/2009	SmPC and PL	Following the assessment of safety data on telbivudine reported during the period of 1 March 2008 to 31 August 2008 (PSUR 4) which included a cumulative review of musculoskeletal disorders (including rhabdomyolysis/myopathy), the product information for Sebivo was amended to list rhabdomyolysis and lactic

					acidosis as adverse reaction to telbivudine treatment. Six cases of rhabdomyolysis were identified of which in 3 the causality with Sebivo treatment was suspected. As regards lactic acidosis, a total of 8 cases were identified. Based on these data, section 4.8 and section 4 of the PL were updated to list these reactions. In addition, since the data available is solely based in spontaneous report cases and as no further data is currently available, the frequency of occurrence of these reactions could not be estimated. Therefore, the frequency category attributed is "not known".
IA/0007	The introduction of a polypropylene oral syringe with graduation as an additional dosing device for Sebivo Oral Solution IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	03/03/2009	n/a	SmPC, Labelling and PL	
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	20/01/2009	SmPC, Annex II, Labelling and PL	The goal of the MAH was to apply for the addition of a new pharmaceutical form (oral solution, in addition to the currently approved pharmaceutical form (film-coated tablets). This particular the oral solution was developed to further optimize the treatment of patients with renal impairments by dose adjustment instead of dose interval adjustment and help patients with difficulties to swallow the 600 mg film-coated tablets. In order to support the commercialisation of the pharmaceutical form of telbivudine (Sebivo oral solution 20 mg/ml) the Applicant has provided quality and clinical information that were evaluated. It is important to underline that the active substances manufacture and control is essentially the same as that reviewed for the already authorised film-coated tablets.

					Information on development, manufacture, and control of the finished product (Oral solution) have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines.
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. Update of Summary of Product Characteristics and Package Leaflet	25/09/2008	31/10/2008	SmPC and PL	The Marketing Authorisation for Sebivo 600 mg film-coated tablets was based on 52 weeks of efficacy and safety phase III data of GLOBE study. With this variation the MAH submitted 104 week results from the GLOBE study together with 104 week results of the confirmatory phase III study NV-02B-015. Overall, in GLOBE study, clinical results at week 104 in telbivudine-treated patients were consistent with those at week 52, demonstrating durability of efficacy responses for telbivudine-treated patients with continued treatment. The supportive data from study NV-02B-015 confirm the results derived from the GLOBE study. An analysis provided demonstrates the predictive value of the 24 weeks on-treatment response on serologic, virologic and biochemical endpoints as well as on the rate of emergence of resistance. This information is useful for prescribers to optimize the therapeutic management of patients treated with telbivudine. Furthermore, a statement was included in section 4.2 to warn the prescribers on the reduced likelihood of achieving favourable outcome with continued monotherapy in patients without undetectable HBV DNA at week 24. The current data shows high levels of maintained durability of seroconversion after consolidation treatment. Furthermore, there is growing evidence of the beneficial value of a treatment consolidation after HBeAg seroconversion is achieved in term of durability. Therefore

					section 4.2 of the SPC was revised to wait at least 6-12 months after HBeAg seroconversion (providing HBV DNA is undetectable) before stopping treatment and to recommend a close monitoring of patients to detect relapse. The 104-week analysis further confirms the role of the M204I mutation as the signature mutation associated with telbivudine resistance. With the exception of the occurrence of the first M204V variant (that occurred as a M204V-L180M double mutant), no other primary mutation was identified in telbivudine breakthrough patients. No major concern emerge
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. Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	28/02/2008	SmPC and PL	Results from a double-blind trial of telbivudine versus lamivudine in adults with compensated chronic hepatitis B show an incidence of peripheral neuropathy of 0.3 % in telbivudine-treated patients. Furthermore, to date 8 cases of peripheral neuropathy (including 5 serious) have been reported in an ongoing clinical study with telbivudine in combination with pegylated interferon alfa-2a (i.e in 16.6% of patients in the study) and one case with telbivudine monotherapy. On the basis of this information the CHMP concluded that peripheral neuropathy has been uncommonly reported in telbivudine-treated patients when used as monotherapy and that the risk of peripheral neuropathy is increased when telbivudine and pegylated interferon alfa-2a are combined. Such increased risk cannot be excluded for other interferons alfa (pegylated or standard). The CHMP recommends that treatment with telbivudine

					should be reconsidered if peripheral neuropathy is suspected. The benefit of telbivudine in combination with interferon alfa (pegylated or standard) is not currently established. The CHMP endorsed a Direct Health Care Professional Communication with this information to be sent to prescribers.
IB/0001	IB_41_b_Change in pack size - change in fill weight/volume of non-parenteral multid. products	22/06/2007	22/06/2007	SmPC, Labelling and PL	
IA/0002	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	29/05/2007	n/a		