EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Hepsera

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
IB/0086	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/04/2021		SmPC, Annex II, Labelling and PL	
IA/0085/G	This was an application for a group of variations.	30/03/2020	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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

	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) 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)				
IAIN/0084	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	29/07/2019	n/a		
PSUSA/60/201809	Periodic Safety Update EU Single assessment - adefovir	29/05/2019	25/07/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/60/201809.
IB/0083	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)	27/06/2019	15/09/2020	SmPC	
II/0081	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	17/01/2019	n/a		
N/0080	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/07/2018	25/07/2019	Labelling and PL	

T/0078	Transfer of Marketing Authorisation	25/04/2018	28/05/2018	SmPC, Labelling and PL	
IA/0079	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	24/05/2018	n/a		
N/0077	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/08/2017	28/05/2018	Labelling and PL	
IA/0076	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)	10/05/2017	n/a		
IB/0075	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/10/2016	n/a		
IA/0074	A.7 - Administrative change - Deletion of manufacturing sites	24/06/2016	n/a		
PSUSA/60/201509	Periodic Safety Update EU Single assessment - adefovir	13/05/2016	n/a		PRAC Recommendation - maintenance
IG/0624	A.7 - Administrative change - Deletion of manufacturing sites	11/01/2016	n/a		

IG/0595	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	04/08/2015	n/a		
IA/0070	A.7 - Administrative change - Deletion of manufacturing sites	10/07/2015	n/a		
IA/0069	B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)	15/04/2015	n/a		
IG/0521	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	26/02/2015	08/02/2016	Annex II and PL	
IG/0469	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	07/08/2014	n/a		
IG/0422	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	28/03/2014	n/a		
II/0065	Submission of the final study report of a paediatric clinical study GS-US-103-0518 including additional analysis of the presence of basal core promoter (BCP) and pre-core (PC) mutations at baseline among	20/03/2014	n/a		The analyses provided show that both BCP and PC mutations were found to pre-exist in HBeAg+ disease, with 23% of subjects harbouring either BCP or PC mutations at baseline. The incidences of BCP or PC mutations at baseline were not

	hepatitis B e antigen positive (HBeAg+) paediatric patients. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				significantly associated with HBeAg seroconversion nor were the mutations sufficient to predict treatment-induced HBeAg seroconversion. The majority of subjects (n=35/47, 74%) remained wild-type before and after confirmed HBeAg seroconversion. In conclusion, the analyses show that BCP or PC mutations are not predictive of treatment response and therefore no changes to the product information are required.
II/0064	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) to inform prescribers that long term treatment with Hepsera may increase the risk of renal impairment and to strengthen the monitoring of the renal function, as requested by the CHMP, following the evaluation of the last PSUR and to address a post-authorisation measure on this topic also requested following evaluation of the PSUR. Additionally, the MAH proposed to update the PI to reflect QRD version 9 and to update the PL with the details of the local representatives for Croatia and the Czech Republic. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and Annex A. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	20/03/2014	11/02/2015	SmPC, Annex II, Labelling and PL	The safety data included in the last Hepsera PSUR showed a significant increase in the reporting of renal proximal tubulopathy. Furthermore, published literature concerning long term renal impact of Hepsera and time to onset for renal events suggested a possible progressive alteration of the renal function in patients receiving long–term adefovir dipivoxil therapy. Based on these data the CHMP recommended the strengthening of the recommendations on renal monitoring. Sections 4.4 and 4.8 of the SmPC were updated to mention the negative long term impact of ADV therapy on renal function and to revise the recommendations for the renal monitoring in line with Viread SmPC. This included the addition of the monitoring of serum phosphate and more frequent monitoring of the renal function during the first year (every 4 weeks).

IAIN/0063/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	31/07/2013	n/a		
IA/0062	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	28/06/2013	n/a		
IB/0061	Update of sections 4.1 and 4.2 to reflect the evolving standard of care for HBV patients, namely that Hepsera treatment should only be initiated when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate, and the need for combination therapy in patients with decompensated liver disease. This follows from assessment of FUM 062. Moreover, the obligation to conduct post-authorisation measures "Submission of 5-year long-term data from Study GS-00-494 (an NIH study) evaluating the safety, antiviral activity and clinical benefit of the combination of adefovir 10 mg and lamivudine 100 mg once daily in adefovir treatment-naive patients with chronic hepatitis B" was fulfilled with submission of FUM 062 and therefore deleted from Annex II.	19/04/2013	14/05/2013	SmPC and Annex II	Implementation of wording changes agreed by the CHMP in follow-up measure FUM 062. Please refer to assessment report: EMA/H/C000485/FUM/062

	In addition the MAH took this opportunity to update to the latest QRD version 8.3. 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				
IG/0290	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2013	n/a		
II/0059	Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) to add information relevant to the paediatric study GS-US-103-0518. The requested variation procedure proposed amendments to the Update of Summary of Product Characteristics. 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	19/07/2012	23/08/2012	SmPC	Study GS US-103-0518 was designed to evaluate the efficacy and safety of adefovir dipivoxil (ADV) in paediatric subjects with chronic hepatitis B who were 2 to < 18 years old at the time of the first dose of study treatment. The effects of open-label long term therapy with ADV in this patient population were assessed in this 5 year study. Overall, the long-term (Week 240) data from Study GS-US-103-0518 are consistent with and further confirm the findings observed at 48 weeks and the final results are reflected in the relevant section of the product Information.
IB/0057	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/06/2012	n/a		
IG/0166	C.I.9.h - Changes to an existing pharmacovigilance	13/04/2012	n/a		

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0052/G	This was an application for a group of variations. Update to clarify an existing ADR in section 4.8 of the SmPC and to remove Gilead Sciences Limited, Dublin as a site responsible for secondary packaging. The product information was revised to be in line with the QRD template and the Guideline on the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data A.7 - Administrative change - Deletion of manufacturing sites	20/10/2011	19/12/2011	SmPC, Annex II, Labelling and PL	Osteomalacia is listed in the SmPC of Hepsera with an unknown frequency. Based on the cumulative review of cases of fractures in patients treated with Hepsera it was observed that bone abnormalities (osteomalacia) associated with proximal renal tubulopathy can infrequently contribute to fractures. The product information was updated accordingly.
IG/0114/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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	17/10/2011	n/a		
IG/0078	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	14/07/2011	n/a		

	pharmacovigilance system				
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2011	19/12/2011	PL	
IG/0047/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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	10/03/2011	n/a	Annex II	
IA/0050	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	12/07/2010	n/a	Annex II	
IA/0049	Addition of a supplier of packaging components B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	17/03/2010	n/a		

IA/0048	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	08/07/2009	n/a		
II/0047	Update of section 4.5 of the SPC to reflect available data on the co-administration of adefovir dipivoxil and pegylated interferon and of section 4.2 to align the recommendations for treatment discontinuation with those for tenofovir disoproxil fumarate. These changes were requested by the CHMP further to the assessment of the respective follow-up measures. Furthermore, minor amendments to the Czech, Finnish, German and Latvian version of the annexes are being made. Update of Summary of Product Characteristics	29/05/2009	30/06/2009	SmPC	A pharmacokinetic interaction study between adefovir and pegylated interferon showed that the pharmacokinetics for adefovir remained unchanged. However, increased serum concentrations of pegylated interferon were observed. Due to the high variability of the data, the lack of other relevant available information and considering that significant interactions between these two agents are unlikely given their different metabolic pathways, it was not possible to reach a conclusion on the issue. Caution is however recommended when adefovir and pegylated interferon are given concomitantly. The recommendation for treatment discontinuation with Hepsera were updated in section 4.2 of the SPC in line with the ones for tenofovir i.e treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed.
IA/0046	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	17/03/2009	n/a		
II/0043	Update section 4.4 of the SPC and section 2 of the PL to emphasise the need to monitor renal function prior to starting treatment with adefovir dipivoxil, as agreed with CHMP in August 2008. Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	27/01/2009	SmPC and PL	A cumulative review of renal events covering a total of 149 renal cases associated with adefovir therapy up to 15 March 2008 was assessed by the CHMP in August 2008. It was concluded that no new renal issues were identified, and that the existing SPC recommendations for monitoring renal function were appropriate. However, the CHMP agreed with the MAH proposal to add a new statement to the warning section of the SPC to emphasize the need to monitor renal

					function prior to starting treatment with Hepsera. The PL is amended accordingly.
II/0039	Update sections 4.2 and 5.1 of the SPC to reflect the impact of the rtA181T mutation on the clinical response to adefovir dipivoxil. This change was agreed by the CHMP in July 2008. The PL is updated on section 6 to better describe the possible presentations of the silica gel desiccant. The MAH took this opportunity to make minor linguistic amendments to German version of the Annexes, as relevant. Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	27/01/2009	SmPC and PL	Lamivudine-refractory patients and patients harbouring HBV with evidence of resistance to lamivudine (mutations at rtL180M, rtA181T and/or rtM204I/V) should not be treated with adefovir dipivoxil monotherapy in order to reduce the risk of resistance to adefovir. Adefovir may be used in combination with lamivudine in lamivudine-refractory patients and in patients harbouring HBV with mutations at rtL180M and/or rtM204I/V. However, for patients harbouring HBV that contains the rtA181T mutation, consideration should be given to alternative treatment regimens due to the risk of reduced susceptibility to adefovir.
II/0040	Update of section 5.1 of the SPC to reflect the paediatric weight and Body Mass Index (BMI) Z score data, exactly as requested by the CHMP in July 2008. Update of Summary of Product Characteristics	20/11/2008	17/12/2008	SmPC	Further to the assessment of additional analyses of Body Mass Index (BMI) Z scores as well as Z-score data on weight, height and BMI for up to 96 weeks of treatment for all patients in study 518 (paediatric study) in July 2008 it was concluded that amendments to section 5.1 of the SPC were needed. The fact that at week 48 and 96, mean changes from baseline in weight and BMI Z scores tended to decrease in adefovir dipivoxil-treated patients is now reflected in the SPC for Hepsera, as requested by the CHMP.
IB/0042	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	20/11/2008	n/a		
IB/0041	IB_38_c_Change in test procedure of finished product - other changes	20/11/2008	n/a		

IA/0044	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	06/11/2008	n/a	Annex II and PL	
II/0037	Update sections 4.4, 4.5, 4.7 and 4.8 of the SPC in line with the SPC guideline, as agreed at the time of the renewal of the Marketing Authorisation. The contact details of the local representatives in Austria, Belgium, Cyprus, Denmark, Finland, Greece, Iceland, Luxembourg, Netherlands, Norway and Sweden are updated in section 6 of the PL. In addition, minor linguistic amendments are introduced in some EU languages versions of the Annexes, as relevant. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	13/08/2008	SmPC and PL	Further to the renewal of the marketing authorization of Hepsera, the MAH was requested to submit a type II variation to update the interactions section, the effects on the ability to drive and the undesirable effects sections of the SPC to be in line with the SPC guideline. The lack of interactions between adefovir and paracetamol, ibuprofen and trimethoprime/sulfamethoxazole have been removed from the SPC as well as interaction data on the use of adefovir at higher doses than the recommended 10 mg dose. Consequently, the warnings section (4.4) was updated to reflect theses changes. Section 4.7 is amended to include a specific statement that adefovir is expected to have no or negligible influence on the ability to drive and operate machines. The undesirable effects section includes now a single table listing the adverse drug reactions reported for adefovir during clinical studies, post-marketing studies and spontaneous reporting. A general description of the most serious and/or most frequently adverse reactions reported in patients with compensated disease and in patients with decompensated disease is included in section 4.8 of the SPC.
IA/0038	IA_05_Change in the name and/or address of a manufacturer of the finished product	17/07/2008	n/a		
II/0034	Update of Summary of Product Characteristics Update sections 4.4, 4.8 and 5.1 of the SPC to reflect long term safety and resistance data from study GS-98-437, a double-blind, randomised,	19/03/2008	21/04/2008	SmPC	Based on the final results from study GS-98-437, which included the long-term safety and efficacy data up to 235 weeks of treatment with adefovir dipivoxil, was judged necessary to reflect the resistance and safety findings in the SPC. Of the 65 patients who received treatment with adefovir

	placebo-controlled study in HBeAg(+) chronic HBV patients with compensated liver function, as requested by the CHMP. Update of Summary of Product Characteristics				10mg daily during the first 48 weeks of this study and were enrolled in the long term open-label phase, 6 had confirmed increases in serum creatinine of at least 0.5 mg/dl from baseline. Furthermore, patients with a confirmed increase of ? 0.3 mg/dl by week 48 were at a significant higher risk of a subsequent confirmed increase in creatinine of ? 0.5 mg/dl. Consequently, the warnings on the monitoring of renal function in patients at risk of renal were amended. Finally, hypophosphatemia and decrease in carnitine concentrations reported in these patients were also included in the SPC.
IB/0035	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	08/04/2008	n/a		
II/0033	Update of sections 4.2 , 4.4 and 5.1 of the SPC with resistance information including in lamivudine-resistant patients and of section 4.8 to add renal failure, proximal tubulopathies and associated muscular and bone disorders to the list of adverse drug reactions to adefovir. These amendements were requested by the CHMP in September 2007 following the assessments of FU2 045.1 and PSUR 6 (covering the period from 21.9.05 to 20.9.06). The PL is updated under sections 2 and 4 in line with the SPC amendments. Update of Summary of Product Characteristics and Package Leaflet	21/02/2008	01/04/2008	SmPC and PL	Further to a cumulative safety review of renal events associated with adefovir dipivoxil (ADV), the CHMP requested for the adverse events renal failure, proximal renal tubulopathy, Fanconi syndrome, hypophosphatemia, myopathy and osteomalacia to be added in section 4.8 of the SPC, with a frequency not known. The package leaflet has been updated accordingly. Cases of hepatic decompensation involving resistance to adefovir dipivoxil were reviewed: All 8 cases reviewed involved lamivudine-resistant HBV and in 6 of the 8 cases, the patient had a history or evidence of diminished hepatic reserve at baseline. Based on this review, a warning entitled 'Resistance' has been added in Section 4.4 of the SPC with that respect. Further to a literature search of reports describing HBV resistance to ADV and/or lamivudine (LAM), it was

					considered appropriate to recommend the combination of ADV+LAM as the optimal therapeutic management (as compared to the switch from LAM to ADV monotherapy) in patients with LAM-resistance. Also, based on the available data, it was considered appropriate to add in section 4.2 of the SPC a sentence to consider modification of treatment in patients if serum HBV DNA remains above 1000 copies/mL at or beyond 1 year of treatment.
IA/0036	IA_09_Deletion of manufacturing site	31/03/2008	n/a		
R/0031	Renewal of the marketing authorisation.	24/01/2008	18/03/2008	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of Hepsera continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk balance of Hepsera continues to be favorable. The CHMP is therefore of the opinion that the renewal can be granted with unlimited validity. However in the context of the evolving therapeutic management of hepatitis b, and given the increased risk of resistance (25% at 5 years) the benefit of Hepsera is tending to decrease over time. There are also remaining uncertainties pertaining to the long term safety data in particular renal events and impact on the bone due to progressive loss of phosphate. The CHMP therefore considers that the MAH should continue to submit PSUR on a yearly basis, and in particular to closely monitor the renal safety and the emergence of resistance.
II/0030	Update of sections 4.2, 5.1 and 5.2 of the SPC to include data from the clinical development programme	24/01/2008	28/02/2008	SmPC	The CHMP variation Assessment Report will be published as part of the EPAR after deletion of confidential information.

	of adefovir in the paediatric population (age 2-17 years). Update of Summary of Product Characteristics				
II/0027	Update of sections 4.2, 4.4 and 5.2 of the SPC with regards to patients with renal impairment and of section 5.1 with regards to HIV/HBV coinfected patients, as requested by the CHMP following the assessment of available data from clinical studies. PL was updated in accordance and in line with the readability testing results. Furthermore the SPC, Labelling and PL, as relevant were amended to reflect the MAH new post code, EMEA website address, and minor linguistic changes including adaptation with latest version of the EMEA/QRD templates for all EU languages except English and Maltese. Update of Summary of Product Characteristics, Labelling and Package Leaflet	20/09/2007	23/10/2007	SmPC, Annex II, Labelling and PL	Based on the clinical data available in renal impaired patients the recommended dosing interval adjustments in the varies degrees of impairment were reviewed and amended. Adefovir dipivoxil should not be use in patients with a creatinine clearance lower than 30 ml/min or in patients on dialysis. However, if the treatment is judged strictly necessary in these patients, the dosing should be adjusted as mentioned in section 4.2 of the SPC. This dosing guidance is based on very limited data and a closely monitoring of these patients is required. Furthermore, the definition of the moderate renal impairment was reviewed and the lower cut-off changed to 30 ml/min. Therefore, patients with creatinine clearance between 30 and 49 ml/min should take 1 tablet of Hepsera every 48 hours. This information is reflected in section 4.2, 4.4 and 5.2 of the SPC. As regards HBV/HIV coinfected patients with lamivudine-resistance, further available data from a clinical study is now reflected in section 5.1 of the SPC. Although the data is very limited for a formal conclusion to be drawn, this study can be regarded as complementary to substantiate the efficacy and safety of adefovir in HBV/HIV coinfected patients. The PL is amended in accordance and in line with the results of the readability testing conducted with target patients groups.
IA/0032	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	22/10/2007	n/a		

IB/0028	IB_38_c_Change in test procedure of finished product - other changes	23/04/2007	n/a		
IA/0029	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	17/04/2007	n/a		
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/01/2007	n/a	PL	
IB/0025	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	21/09/2006	21/09/2006	SmPC, Labelling and PL	
II/0023	Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	28/08/2006	SmPC and PL	
II/0022	Update of Summary of Product Characteristics	27/07/2006	28/08/2006	SmPC	
II/0021	Update of section 4.8 and section 5.1 of the SPC in view of the efficacy, safety and resistance data from a study evaluating adefovir dipivoxil for the treatment of patients with presumed precore mutant chronic hepatitis B virus infection with open label long term follow up. Furthermore, resistance data in section 5.1 is organised to accommodate the status of patients (e.g. lamivudine resistant, nucleoside naive patients). The PL has been updated accordingly. The MAH has also taken this opportunity to amend the SPC, Annex II, labelling and the PL in line with the	28/06/2006	04/08/2006	SmPC, Annex II, Labelling and PL	One hundred and twenty five HBeAg negative patients who had completed the first 96 weeks of study and had received adefovir treatment during weeks 49-96 were included in the open label treatment phase with adefovir for up to 240 weeks. Efficacy, safety and resistance data from 96 weeks of the study treatment were included in the SPC/PL for Hepsera in 2004 (see below summary for II/002). The final results including data for up to 240 weeks of adefovir treatment showed that the long-term treatment results in sustained reduction in serum HBV DNA and ALT levels as well as continued histological improvement. The cumulative probabilities of developing adefovir-associated resistance

	latest QRD templates and to introduce minor linguistic changes to the some EU languages, as relevant. In addition, the local representatives in some EU Member States were updated in section 6 of the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet				mutations are 0%, 3%, 11%, 18% and 29% after 48, 96, 144, 192 and 240 weeks, respectively. Section 5.1 of the SPC was updated to reflect these results. No new safety concerns were identified during this extension of the study. However, hypophosphatemia and a decrease in carnitine concentrations were reported in 4% and 6% respectively of the 125 patients. These results were included in section 4.8 of the SPC. The PL was updated accordingly.
IB/0020	IB_10_Minor change in the manufacturing process of the active substance	18/04/2006	n/a		
IB/0019	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	18/04/2006	n/a		
IB/0018	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	18/04/2006	n/a		
II/0016	Update of sections 4.8, 4.9 and 5.1 of the SPC, to reflect efficacy and safety results of a study evaluating adefovir dipivoxil, 10 mg once daily, in the treatment of pre- and post-liver transplantation patients with chronic hepatitis B and lamivudine-resistant hepatitis B virus infection. Section 4.4 is also updated to substantiate the existing warnings regarding treatment cessation in decompensated patients, as requested by the CHMP following the assessment of the 4th PSUR (21.03.04 - 20.09.04) in September 2005. Relevant sections of the PL are updated in accordance.Minor linguistic changes were introduced in the SPC and/or PL for some of the EU languages, as	23/02/2006	29/03/2006	SmPC and PL	The final results of a study evaluating the efficacy and safety of adefovir dipivoxil, 10 mg once daily, in the treatment of pre- and post-liver transplantation patients with chronic hepatitis B and lamivudine-resistant hepatitis B virus infection included data from 241 patients who were post-transplantation at baseline (with median treatment duration of 99 weeks) and from 226 patients pre-liver transplantation at baseline (with median treatment duration of 51 weeks).Efficacy results confirmed the antiviral and clinical benefit of adefovir dipivoxil 10 mg in pre- and post-liver transplantation patients resistant to lamivudine and at high risk for morbidity and mortality. Section 5.1 of the SPC was updated to reflect these results. Safety results

	relevant. Update of Summary of Product Characteristics and Package Leaflet				from this study and from a safety review of hepatic events associated with discontinuation of adefovir dipivoxil due to renal disorders, in patients with decompensated liver function were the basis for the re-organisation and substantiation of the existing warnings regarding treatment cessation in decompensated patients, in section 4.4. Section 4.8 was updated in line with the MedDRA terminology and frequency. Hypophosphataemia and vomiting were included in section 4.8 as common adverse drug reactions associated with adefovir dipivoxil. Vomiting has been moved from section 4.9 to 4.8. Section 4 of the PL is updated in accordance.
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/01/2006	n/a	PL	
II/0011	Update section 5.1 of the SPC, to reflect the results of an integrated resistance summary from several clinical studies which includes patients treated with Hepsera, for up to 192 weeks. Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/07/2005	15/09/2005	SmPC, Labelling and PL	The resistance surveillance results (12 patients genotyped out of 67 patients included for assessment by week 192), confirmed that both mutations rtN236T and rtA181V could be defined as adefovir associated resistance mutations. The rtN236T mutation demonstrated a phenotypic resistance in vitro and also in patients with a serum HBV DNA rebound. The in vitro and in vivo data suggests that the rtN236T mutant HBV remains susceptible to lamivudine. The rtA181V mutation is associated with adefovir resistance in clinics but the in vitro phenotypic resistance is moderate. Preliminary data, both in vitro and in patients, suggests that the rtA181V mutant HBV may confer a reduced susceptibility to lamivudine. Further surveillance data will be submitted to

					substantiate the cross resistance to lamivudine. Overall, the cumulative probabilities of developing adefovir resistance mutations rtN236T or rtA181V are 0%, 2%, 7%, and 14.5% after 48, 96, 144 and 192 weeks of adefovir dipivoxil therapy, respectively.
II/0013	Update section 4.4 of the SPC, to clearly state that in patients with decompensated liver disease or cirrhosis treatment cessation is not recommended and to add "rash" and "pruritus" in section 4.8 as requested by the CHMP following the assessment of the 4th PSUR covering the period 21.03.04 to 20.09.04. Relevant sections of the PL are updated in accordance. Minor linguistic changes were introduced in the SPC, Annex II, Labelling and PL for some of the EU languages, as relevant. Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/07/2005	13/09/2005	SmPC, Labelling and PL	Although the relationship is currently unknown, post-treatment exacerbations of hepatitis have occurred especially within 12 weeks after discontinuation of treatment with adefovir dipivoxil 10 mg. The SPC adequately reflects the hepatic adverse events associated with adefovir dipivoxil on-treatment or following discontinuation in patients with compensated liver disease. However, patients with decompensated liver disease remain a cause of concern as severe, or even fatal, hepatitis events were almost exclusively reported in this population. Even though no new major safety concern arose from the assessment of a cumulative review of hepatic events reported up to 20 September 2004, the CHMP agreed that the warnings in section 4.4 of the SPC could be strengthened by highlighting the fact that treatment cessation is not recommended in patients with decompensated liver disease or cirrhosis as already mentioned in section 4.2. In addition, and based on the safety data provided in the 4th PSUR namely the cumulative cutaneous adverse reactions reported during the treatment with adefovir dipivoxil, the CHMP concluded that "rash" and "pruritus" should be included in section 4.8 of the SPC as adverse reactions associated with the adefovir dipivoxil treatment. Sections 2 and 4 of the PL have been updated accordingly.

IA/0015	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	08/08/2005	n/a		
IA/0014	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	08/08/2005	n/a		
IA/0012	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	26/04/2005	n/a		
N/0010	To update the contact details of the Local Representatives for Estonia, Latvia, Lithuania, Iceland and Cyprus in the Package Leaflet. In addition, the MAH took this opportunity to introduce minor corrections to the existing contact details and to be in line with the latest EMEA/QRD templates." Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/04/2005	n/a	PL	
IA/0009	IA_05_Change in the name and/or address of a manufacturer of the finished product	28/10/2004	n/a		
IA/0008	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	25/10/2004	n/a		
IB/0006	IB_33_Minor change in the manufacture of the finished product IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	09/09/2004	n/a		
IA/0007	IA_32_a_Change in batch size of the finished product	31/08/2004	n/a		

	- up to 10-fold				
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/08/2004	n/a	PL	
II/0004	Update of section 4.4 and 4.5 of the SPC, , to implement the results of the pharmacokinetic drug-interaction study that investigates the potential interactions of adefovir dipivoxil with tenofovir disoproxil fumarate. The list of the local representatives in the PL is being completed with the contacts of the new European Member Strates. Update of Summary of Product Characteristics and Package Leaflet	24/03/2004	25/05/2004	SmPC and PL	This was an open-label, fixed sequence, drug-drug interaction study of multiple doses of tenofovir disoproxil fumarate (tenofovoir DF) and single doses of adefovir dipivoxil. Tenofovir DF was provided as one 300 mg tablet for oral administration with food once daily (QD) on study days 2 through 8, whilst adefovir dipivoxil was given as one 10 mg tablet for oral administration with food QD on study days 1 and 8 only. Regular blood samples were collected to measure adefovir, tenofovir and tenofovir prodrug species. Results showed that the co-administration of single dose of ADV with multiple doses of TDF did not lead to clinically relevant drug-drug interaction with regard to pharmacokinetics. No conclusion in term of safe use for the adefovir/tenofovir co-administration could be derived from the present study. Additional clinical data would be required to recommend concomitant use of both medicinal products through a long period in clinical practice.
II/0002	Update of the section 5.1 of the SPC to implement the results of the 96 weeks analysis of a clinical study in naïve HbeAg negative patients and the results of the 144 weeks analysis of another study performed in HIV/HBV co-infected patients resistant to lamivudine. This SPC update addresses clinical/safety follow up measures agreed at the initial CPMP opinion. In addition, proposed amendments are made to	21/01/2004	02/03/2004	SmPC	In this study, HBeAg negative study patients on adefovir dipivoxil (0-48 weeks) were re-randomised in a blinded-manner to continue on adefovir dipivoxil or receive placebo for an additional 48 weeks. At week 96, patients continuing on adefovir dipivoxil 10 mg had sustained suppression of serum HBV with maintenance of the reduction seen at week 48. In over two thirds of patients suppression of serum HBV DNA was associated with normalisation of ALT levels. In most patients who stopped treatment with

	section 5.1 of the SPC with regard to an integrated resistance summary, which includes genotypic and phenotypic analysis of serum HBV DNA from several clinical studies, and to include details of the rtN236T mutation as requested by the CPMP following the assessment of the 1st Periodic Safety Update Report (PSUR), covering the period of 20.09.02 to 20.03.03. Section 5.1 is amended to describe all mutations in the HBV polymerase using the international consensus nomenclature.Two typographical errors have been corrected in section 5.2.. The MAH has also taken this opportunity to include in section 5.1, the full ATC code for Hepsera, as assigned by World Health Organisation Collaboration Centre for Drug Statistics Methodology.The MAH is also proposing to amend the current text in section 5.1 to describe all mutations in the HBV polymerase using the international consensus nomenclature.Two typographical errors have been highlighted in section 5.2 (Pharmacokinetic properties) and corrections proposed. Update of Summary of Product Characteristics				adefovir dipivoxil, serum HBV DNA and ALT levels returned towards baseline. Treatment with adefovir dipivoxil resulted in improvement in the liver fibrosis (from 0-96 weeks therapy) when analysed using the Ishak score (median change: D= -1), but not when analysed using the Knodell fibrosis score. In an open-label study in chronic lamivudine-resistant hepatitis B patients co-infected with HIV. Adefovir dipivoxil 10mg was added to ongoing lamivudine therapy. Of the 35 patients initially enrolled, 29 completed 144 weeks treatment. They showed progressive reductions in serum HBV DNA levels and ALT levels throughout the course of treatment. Resistence: genotypic analyses were performed in the 87 patients with detectable HBV DNA out of 238 treated for 96 weeks from several clinical studies. A novel conserved site mutation was identified in the D domain of the HBV polymerase gene (rtN236T), which conferred clinical resistance to adefovir dipivoxil. This mutation has been observed in < 2 % (4/238) of patients treated for up to 96 weeks and is associated with reduced susceptibility to adefovir in vitro and with a progressive rebound in viral load in vivo. In addition, mutation rtA 181V was observed in 2 patients but could not be undoubtedly associated with resistance to adefovir dipivoxil.
N/0003	This notification relates to changes in addresses of the local representative holders in Italy and Austria as well as typographical and consistency corrections. Other changes include the re-ordering of the Belgium local representative title in order to correct the PL template and a minor change in the Greek address following	09/01/2004	29/01/2004	PL	

	comments received after the EMEA's review of Viread. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
I/0001	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	24/04/2003	02/05/2003		