Baraclude

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
IA/0079/G	This was an application for a group of variations. 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	04/07/2024	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).

	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				
IAIN/0078/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.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	04/07/2024		Annex II and PL	
IA/0077/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - 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	04/12/2023	n/a		

IA/0076	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	03/11/2023	n/a		
PSUSA/1224/202203	Periodic Safety Update EU Single assessment - entecavir	01/12/2022	n/a		PRAC Recommendation - maintenance
IB/0074	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	14/06/2022	n/a		
IAIN/0073	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	31/01/2022	30/01/2023	Annex II and PL	
IB/0072	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/11/2021	n/a		
IB/0071/G	This was an application for a group of variations. 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	14/10/2021	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
N/0070	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/09/2021	30/01/2023	PL	
IB/0068	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	21/06/2021	n/a		
IA/0069	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	17/06/2021	n/a		
IB/0067/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 B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	20/10/2020	n/a		
IG/1223/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	17/04/2020	22/01/2021	Annex II and PL	

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
II/0064	Update of sections 4.8 and 5.1 of the SmPC in order to reflect the completion of the two paediatric studies AI463028 (Evaluation of the pharmacokinetics, safety, tolerability and efficacy of Entecavir (ETV) in paediatric subjects with chronic hepatitis B virus (HBV) infection who are HBeAg-Positive) and AI463189 (A Comparative study of the antiviral efficacy and safety of ETV versus placebo in paediatric subjects with Chronic Hepatitis B Virus (HBV) infection who are HBeAg-Positive). Section 5.1 is also updated to reflect the outcome of study AI463080 (Randomized, observational study of ETV to assess long-term outcomes associated with nucleoside/nucleotide monotherapy for patients with Chronic HBV Infection: The REALM Study). Moreover, section 5.2 of the SmPC is also updated to remove information on the pharmacokinetics of entecavir in lamivudine-experienced paediatric patients, at the request of the CHMP; and section 5.3 to make reference to the clinical data in section 5.1 in respect to carcinogenicity. The RMP version 15 has also been approved, which implements Revision 2 of the EU-RMP template. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.1 and to make minor editorial changes to the PI.	17/04/2020	22/01/2021	SmPC, Annex II, Labelling and PL	Study 080 was a randomized, observational open-label Phase 4 study to assess long-term risks of entecavir (ETV) treatment (n=6,216) or other standard of care hepatitis B virus (HBV) nucleoside (acid) treatment (non-ETV) (n=6,162) for up to 10 years in subjects with chronic HBV (CHB) infection. The principal clinical outcome events assessed in the study were overall malignant neoplasms (composite event of hepatocellular carcinoma (HCC) and non-HCC malignant neoplasms), liver related HBV disease progression, non-HCC malignant neoplasms, HCC, and deaths, including liver related deaths. Results from study 080 suggest that ETV was not associated with an increased risk of malignant neoplasms compared to use of non-ETV, as assessed by either the composite endpoint of overall malignant neoplasms (ETV n=331, non-ETV n=337; HR=0.93 [0.8-1.1]), or the individual endpoint of non-HCC malignant neoplasm (ETV n=95, non-ETV n=81; HR=1.1 [0.82-1.5]). The reported events for liver-related HBV disease progression and HCC were comparable in both ETV and non-ETV groups. The most commonly reported malignancy in both ETV and non-ETV groups was HCC followed by gastrointestinal malignancies.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0063	Update of section 4.8 of the SmPC in order to add neutropenia as a very common adverse reaction in paediatric patients, based on the cases reported from both paediatric studies AI463189 and AI463028. The package leaflet is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/01/2020	22/01/2021	SmPC and PL	Neutropenia is added as a very common adverse reaction in paediatric patients, based on the cases reported from both paediatric studies AI463189 and AI463028. Study AI463189, there were 14 neutropenia cases out of 119 patients treated with ETV 0.015 mg/kg up to 0.5 mg daily through 48 weeks, whereas there were 2 neutropenia cases out of 60 patients treated with placebo during the same period. In AI463028, there were 2 neutropenia cases out of 24 lamivudine treatment-naïve patients treated with ETV 0.015 mg/kg up to 0.5 mg daily through 48 weeks.
IG/1193	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/01/2020	n/a		
N/0062	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/05/2019	22/01/2021	PL	
IG/1059	A.1 - Administrative change - Change in the name and/or address of the MAH	15/02/2019	25/03/2019	SmPC, Labelling and PL	
IAIN/0060	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	28/01/2019	25/03/2019	PL	
II/0059	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	13/09/2018	25/03/2019	SmPC, Annex II, Labelling	

	data			and PL	
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/06/2018	25/03/2019	Labelling and PL	
IB/0057/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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	13/04/2018	n/a		
IA/0056/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 an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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	12/02/2018	n/a		
II/0053	Submission of the final study report for study AI463080, a long-term outcomes study (10 years),	11/01/2018	n/a		The final analysis report with data from study AI463080 provides evidence that the risk of overall malignant

	to assess the rates of malignant neoplasm (all, non-hepatocellular carcinoma, and hepatocellular carcinoma), liver-related events of HBV disease progression, and mortality. Risk Management Plan Version 14 has been updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				neoplasms (all, non-hepatocellular carcinoma or hepatocellular carcinoma), liver-related hepatitis B virus disease progression and death does not differ between long-term entecavir use - and non- entecavir -treated subjects. Therefore no amendment to the product information was warranted based on these data.
IB/0054/G	This was an application for a group of variations. 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 the manufacturing process B.II.d.1.a - Change in the specification parameters	20/12/2017	n/a		

	and/or limits of the finished product - Tightening of specification limits				
IA/0055	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	18/12/2017	n/a		
PSUSA/1224/201703	Periodic Safety Update EU Single assessment - entecavir	26/10/2017	n/a		PRAC Recommendation - maintenance
IA/0051/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	14/02/2017	n/a		
IB/0050/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 an ASMF holder or supplier of the AS, starting material, reagent or	14/04/2016	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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.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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
II/0049	Update of sections 4.8 and 5.1 of the SmPC to add long term efficacy, safety and resistance data on the paediatric population from the AI463189 "expanded cohort" (180 subjects) study; the RMP (v.13) is updated accordingly. In addition, the MAH took the opportunity to combine the SmPCs of Baraclude 0.5 mg tablets and Baraclude 1 mg tablets and to update Annex A to include unit dose blisters. The Package Leaflet (PL) is updated to reflect a change in the contact details of a local representative. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	03/03/2017	SmPC and PL	In this variation, the MAH provided week 96 efficacy, safety and resistance data from the AI463189 "expanded cohort" (180 subjects). This updated interim analysis does not alter any of the main conclusions reached in the recent assessment of variation II/41, in which a paediatric extension of indication for Baraclude was granted based on the presently discussed AI463189 study. The paediatric resistance assessment is based on data from nucleoside-treatment-naive paediatric patients with HBeAg-positive chronic HBV infection in two ongoing clinical trials (028 and 189). The two trials provide resistance data in 183 patients treated and monitored in Year 1 and 180 patients treated and monitored in Year 2. Genotypic evaluations were performed for all patients with available samples who had virologic breakthrough through Week 96 or HBV DNA ≥ 50 IU/ml at Week 48 or Week 96. During Year 2, genotypic resistance to ETV was detected in 2 patients (1.1% cumulative probability of resistance through Year 2).

N/0048	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/11/2015	03/03/2017	PL	
IG/0602	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)	11/09/2015	n/a		
IA/0046	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/12/2014	n/a		
IA/0045	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	24/10/2014	n/a		
II/0041	Extension of indication to include treatment of chronic HBV infection in paediatric patients from 2 to <18 years of age with compensated liver disease and evidence of active viral replication and persistently elevated serum ALT levels. Consequently, the MAH proposed the update of sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet was proposed to be updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/07/2014	22/08/2014	SmPC and PL	Please refer to the CHMP assessment report EMEA/H/C/000623/II/0041.

IAIN/0044	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	12/06/2014	22/08/2014	SmPC and PL	
II/0043	Submission of the final study report, 5 years follow-up of Study AI463048: Comparison Of The Efficacy And Safety Of Entecavir Versus Adefovir In Subjects Chronically Infected With Hepatitis B Virus And Evidence Of Hepatic Decompensation. This submission fulfils a post-authorisation measure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/04/2014	n/a		The study AI463048 final analyses provide a high-level descriptive and limited understanding of the clinical outcomes that can be observed with long-term treatment of patients with decompensated liver function due to chronic HBV. Three key clinical outcome events of interest in this decompensated population (death; the diagnosis of hepatocellular carcinoma [HCC]; and "disease progression" defined by the occurrence of specified adverse events [AEs] of decompensation) were assessed over the entire study observation period. No signals of specific concerns have been identified. Therefore, no update of the product information for Baraclude is needed in the view of these data.
II/0042	Update of sections 4.2 and 4.4 of the SmPC to initiate combination therapy with entecavir plus a second antiviral agent, instead of entecavir monotherapy, in patients with lamivudine-resistant hepatitis B virus infection. Section 4.1 of the SmPC was updated to include a cross reference to section 4.2 with respect to patients with lamivudine-refractory hepatitis B. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9. The requested variation proposed amendments to	23/01/2014	22/08/2014	SmPC, Annex II and PL	The use of entecavir in patients with prior lamivudine resistance, is well-known to cause a decrease in sensitivity to entecavir, as well as a lowering of the barrier to further resistance. The product information already contained a warning on this issue that was strengthened. When starting therapy in patients with a documented history of lamivudine-resistant HBV, combination use of entecavir plus a second antiviral agent (which does not share cross resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy.

	the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0039/G	This was an application for a group of variations. 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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	21/12/2012	n/a		
IG/0254	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
II/0038	Update of section 5.1 of the SmPC to include clinical study data on liver transplant recipients. The PL is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the PL. Furthermore, the PI is being brought in line with the latest QRD template version 8.1. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	24/10/2012	SmPC, Annex II, Labelling and PL	The MAH submitted the final results of study AI463109, a non-comparative study conducted in 65 patients that had a post-orthotopic liver transplant due to hepatitis B related liver failure or hepatocellular carcinoma. The dose of ETV evaluated was 1.0 mg once daily, which was considered appropriate to the patient population studied. There were no virological recurrences by the protocol-specified definition (plasma HBV-DNA ≥ 50 IU/mL). The clinical implications of HBV recurrence are still unclear; therefore a description of this observation is included in the SmPC. There were no new or unexpected safety concerns have been identified in the population studied. The CHMP

					considered that the clinical benefit-risk for the use of entecavir in patients with post-orthotopic liver transplant is favourable; therefore a description of study outcomes in the Product Information was accepted.
R/0035	Renewal of the marketing authorisation.	17/03/2011	12/05/2011	SmPC, Annex II and PL	
IB/0037	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	28/04/2011	n/a		
IA/0036	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	16/03/2011	n/a		
II/0033	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/01/2011	28/02/2011	SmPC, Annex II and PL	Please refer to the Assessment Report: Baraclude-H-623-II-33-AR
IA/0034	A.7 - Administrative change - Deletion of manufacturing sites	12/11/2010	n/a	Annex II and PL	
II/0030	Update of sections 4.8 and 4.4 of the SmPC to include a description of the adverse reaction 'lactic acidosis' as requested by CHMP further to assessment of PSUR 7. In addition, the MAH has taken the opportunity to add 'increased transaminases' as a postmarketing event in section	22/07/2010	26/08/2010	SmPC, Annex II and PL	Cases of lactic acidosis have been reported, often in association with hepatic decompensation, other serious medical conditions or drug exposures. Due to a number of emerging case reports of lactic acidosis and acidemia in patients on entecavir therapy, this adverse event has been included in the product information. Lactic acidosis is

	4.8. The Product Information is updated in accordance with QRD guidelines and the list of representatives is updated in the PL. The version number of the RMP is also updated in Annex II. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				considered a putative class effect of nucleoside analogues as they may interfere with the functioning of DNA polymerase gamma. Furthermore a cumulative review of cases with reported events specifically related to hepatic transaminase elevations was undertaken to evaluate the adequacy of information contained in the product information with respect to such events. Based on this review "transaminases increased" has been included as an adverse reaction.
IA/0032	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	11/08/2010	n/a	Annex II	
IA/0031/G	This was an application for a group of variations. 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) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	30/07/2010	n/a		
IA/0029/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	12/03/2010	n/a	Annex II	

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/09/2009	n/a	PL	
IA/0028	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	21/09/2009	n/a		
II/0026	Update of section 4.8 of the SPC and section 4 of the PL to include alopecia and anaphylactoid reactions as requested by the CHMP further to the assessment of PSUR 5. In addition, section 4.9 is updated to reflect that overdose reports have been received in PSURs. Annex II reflects the current Risk Management Plan version (version 3.0). Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	03/08/2009	SmPC, Annex II and PL	A cumulative review assessed in PSUR 5 (covering period: 29.3.08 - 28.9.08) identified a total of 30 spontaneous cases of alopecia. Two cases were serious. In ten cases the time to onset of alopecia was between 1 and 3 months after initiation of entecavir treatment. Alopecia is now listed as an adverse reaction to entecavir. Alopecia has been associated with hepatitis B therapies. As regards anaphylactoid reactions, 2 cases were reported in PSUR 5: one of drug hypersensitivity and one of hypersensitivity being the first cases life-threatening. Based on these cases, anaphylactoid reaction has been added to the list of adverse reactions to entecavir treatment. Section 4.8 of the SPC and section 4 of the PL are amended in accordance. Overdose reports have been received and included in the PSURs for Baraclude, therefore section 4.9 of the SPC has been updated to reflect these reports.
II/0025	Change in the formulation of the finished product. Change in formulation	29/05/2009	07/07/2009	SmPC and PL	
II/0020	Update of section 5.1 with long-term data on the	23/04/2009	08/06/2009	SmPC	Two-hundred and three HBeAg positive and HBeAg

	effects of entecavir on liver necroinflammation and fibrosis as evaluated in a subset of nucleos(t)ide-naive HBeAg-positive and HBeAg-negative chronic HBV subjects from Study AI463901. Update of Summary of Product Characteristics				negative patients from the pivotal studies AI463022 and AI463027, respectively were eligible to roll-over to study AI463901 and continued treatment with entecavir (ETV) but at an increased dose of 1 mg once daily and initially also with lamivudine. Of the fifty seven patients with evaluable baseline and long-term biopsies, 55 had histologic improvement and 50 had a ?1-point decrease in Ishak fibrosis score. Of the 43 with a baseline Ishak fibrosis score of ?2, 58 % had a ?2-point decrease. Regression of fibrosis was seen in all 10 patients with advanced fibrosis or cirrhosis. At the time of the biopsy, all 57 patients had HBV DNA < 300 copies/ml and 49/57 (86%) had serum ALT ?1 X ULN. All 57 patients remained positive for HBsAg. The results of this study demonstrated that long-term ETV therapy for approximately 6 years in nucleoside-naïve patients with chronic hepatitis B resulted in improvement of liver necroinflammation and fibrosis. The clinical benefit of long term viral suppression of HBV has now been confirmed with long-term histology data.
IB/0022	IB_33_Minor change in the manufacture of the finished product	24/03/2009	n/a		
IA/0024	IA_28_Change in any part of primary packaging material not in contact with finished product	05/03/2009	n/a		
IA/0023	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	05/03/2009	n/a		
II/0021	Update of Detailed Description of the Pharmacovigilance System	22/01/2009	26/02/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 3.0) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to

	Update of DDPS (Pharmacovigilance)				notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text with the new version number of the agreed DDPS.
II/0019	Update of section 4,1, 4.2, 4.4 and 5.1 of the SPC to reflect the results of long term resistance data from "Year 5 Resistance Summary Report" which includes a cumulative review of all viral variants observed to have the two specified substitutions at rtI169 and rtV173. In addition, Annex IIB is updated under "Other Conditions", to include standard text with relevant version numbers of the Detailed Description of the Pharmacovigilance System as well as the Risk Management Plan. Update of Summary of Product Characteristics	18/12/2008	10/02/2009	SmPC and Annex II	The 5-year resistance data suggests that the rate of entecavir resistance in nucleoside-naïve patients is very low and maintained through five years of therapy. The cumulative probability of genotypic entecavir resistance (ETVr) and virologic breakthrough due to resistance in nucleoside-naïve patients was 1.2% and 0.8%, respectively. However, in lamivudine-refractory patients, the rate of resistance increased with time and the cumulative probability of genotypic ETVr is high: 6%, 15%, 36%, 47% and 51% in year 1 through 5, respectively. The cumulative probability of virologic breakthroughs with ETVr was 1%, 11%, 27%, 41% and 44% over the same time frame. Based on the data provided and taking into account the current treatment options available for lamivudine-refractory patients, it became clear that the eventual place of ETV in LVD-refractory patients is restricted to those with low baseline HBV DNA and those with an early response at week 24. These characteristics were shown to predict a lower risk of subsequent development of resistance on long-term ETV treatment.
II/0017	To update section 4.8 of the Summary Product Characteristics to add "rash" to the post marketing subsection following assessment of Baraclude's PSUR 3 covering the period 29 March 2007 - 28 September 2007. Section 4 of the PL is updated accordingly. In addition, an updated version (version 2.5) of the	26/06/2008	22/08/2008	SmPC and PL	Further to the assessment of post-marketing and clinical safety data and review of 26 non-serious reported cases of "rash" that occurred during the period covered by the entecavir 3rd PSUR, no definitive information about causality adjudication between entecavir and rash was provided. However, the times of occurrence of "rash" indicated a relationship. The product information for

	Detailed Description of the Pharmacovigilance System was included in this submission. Furthermore, the MAH updated section 6 "further information" of the PL with the contact details for its local representative in Romania and made some editorial changes (spelling corrections) in the BG, ES, ET, FI, FR, HU, IT, LV, NO, PL, RO and SK product information. Update of Summary of Product Characteristics and Package Leaflet				entecavir was updated to include "rash" in the undesirable effects section identified during post-approval use of Baraclude. The updated version of the DDPS provided was written according to the structure described in Volume 9A.
IB/0018	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec. IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	27/05/2008	n/a		
IA/0016	IA_13_a_Change in test proc. for active substance - minor change	19/02/2008	n/a		
IB/0014	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/01/2008	30/01/2008	SmPC, Labelling and PL	
IB/0013	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/01/2008	30/01/2008	SmPC, Labelling and PL	
IA/0015	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	14/01/2008	n/a		

II/0007	Update of Summary of Product Characteristics and Package Leaflet. To update sections 4.4 and 5.1 of the SPC concerning the use of Baraclude in HIV/HBV co-infected patients and the potential for the development of HIV resistance, following CHMP request and a Direct Healthcare Professional Communication (DHPC) on the subject. The MAH took the opportunity of this variation to revise section 4.8 of the SPC to re-order the list of System Organ Classes (SOCs). Section 2 of the PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/10/2007	21/11/2007	SmPC and PL	New analysis of the in vitro/cell culture data and clinical data available confirm the signal that the use of entecavir as monotherapy in co-infected patients is associated with a risk of emergence of HIV resistance. On the basis of these data a strong warning that therapy with ETV "should not be used" in HIV/HBV co-infected patients nor as a treatment to HIV infection is now included in the SPC.
IA/0012	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	29/10/2007	n/a	Annex II and PL	
IA/0011	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 IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	29/10/2007	n/a	Annex II and PL	
II/0010	Quality changes	18/10/2007	24/10/2007		

II/0005	To update section 5.1 of the SPC on resistance data from a longer follow-up period of 144 weeks, supported by the "year 3 resistance summary report". Furthermore, the MAH took the opportunity of this variation to update the local representative contact in Denmark. Update of Summary of Product Characteristics and Package Leaflet	19/07/2007	22/08/2007	SmPC and PL	The 3-year resistance report summarises the current understanding of entecavir resistance (ETVr) emergence in patients infected with hepatitis B virus (HBV) infection. The evaluation was based on genotypic and phenotypic data from patients treated with entecavir (ETV) for up to three years (Week 144) in 6 clinical trials conducted in nucleoside-treatment-naïve and lamivudine (LVD)-refractory patients treated with 0.5 mg or 1.0 mg ETV, respectively. ETV therapy has been shown to be associated with establishment of a high genetic barrier to resistance in nucleoside-naïve patients. In contrast, in LVD-refractory patients the genetic barrier of ETVr is decreased requiring only a single aminoacid substitution in LVDr HBV. In this LVD-refractory population genotypic resistance increased with time and emerged in 6%, 8%, and 19% of patients in years 1, 2, and 3. This corresponds to a cumulative probability of genotypic ETVr of 6%, 15% and 35% respectively. The CHMP considers that the findings presented in this 3-year resistance report do not change the risk-benefit profile of entecavir.
IA/0009	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	02/08/2007	n/a		
IA/0008	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	02/08/2007	n/a		
II/0006	Quality changes	24/05/2007	30/05/2007		
II/0002	To update sections 4.2 and 4.4 of the SPC with	22/03/2007	26/04/2007	SmPC, Annex	Entecavir is mainly eliminated by the kidney. Therefore,

	information on a alternative dosing schedule proposed for patients with renal impairment (including patients undergoing haemodialysis) in addition to the current dosing scheme with the Oral Solution. Sections 2 and 3 of the PL were updated accordingly. Furthermore, the MAH took the opportunity to update the contact details for the local representatives in Belgium, Denmark, Greece, Latvia, Luxembourg, Norway, Portugal and Spain in the PL, to update the Product Information according to the latest EMEA/QRD template and to make minor administrative and editorial corrections to the annexes. Update of Summary of Product Characteristics and Package Leaflet			II, Labelling and PL	patients with renal impairment may require dose adjustment depending on the degree of their renal impairment. The original dosing recommendations for patients with renal impairment consisted of adjusting the daily dose of oral solution. These recommendations were based on pharmacokinetic data from a clinical study. This variation proposes an alternative dosing schedule for patients with renal impairment in addition to the current one with the oral solution, based on additional analyses performed with data from the same study. This alternative dosage recommendation consists of increasing the dosage interval between two doses of Baraclude film-coated tablets depending on the degree of renal impairment. However, this alternative is recommended only when the oral solution is not available. Furthermore, since the safety and effectiveness of the proposed dose modifications have not been clinically evaluated, the virological response should be closely monitored. This information was included in the SPC and the possibility of an alternative dosing schedule was also mentioned in the PL.
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/04/2007	n/a	PL	
IA/0004	IA_13_a_Change in test proc. for active substance - minor change	07/02/2007	n/a		
IA/0001	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	13/07/2006	n/a		