Procedural steps taken after granting the Marketing Authorisation

For procedures finalised after 1 February2004 please refer to module 8B**.**

Scope	Application number	Type of modification[1]	Notification/ Opinion issued on[2]	Commission Decision Issued/amended on
On 8 February 2002 the Marketing Authorisation Holder (MAH) applied for a change in or addition of manufacturing site(s) for part or all of the manufacturing process.	I-0001	I	13.02.02	06.03.02
On 14 March 2002 the MAH applied for a change in the batch size of finished product.	I-0002	I	08.04.02	11.04.02
On 14 March 2002 the MAH applied for minor changes in manufacture of the medicinal product.	I-0003	I	08.04.02	11.04.02
On 14 March 2002 the MAH applied for minor changes in manufacture of the medicinal product.	I-0004	I	08.04.02	11.04.02
On 01 July 2002 the MAH applied for a change in or addition of manufacturing site(s) for part or all of the manufacturing process.	I-0005	I	06.08.02	30.08.02
On 16 July 2002 the MAH applied for changes of section 4.4 (Special warnings and special precautions for use) and 4.5 (Interaction with other medicinal products and other forms of interaction) of the Summary of Products Characteristics (SPC) as well as the corresponding relevant sections of the Package Leaflet (PL) of Viread 245 mg film-coated tablets, further to the CPMP assessment of the results of the pharmacokinetic study (GS-01-932), which evaluated the effect of tenofovir disoproxil fumarate (TDF) on the pharmacokinetics of didanosine following concomitant use of Viread tablets and Videx EC 400 mg gastro-resistant capsules. Moreover, the MAH proposed some minor linguistic corrections of the language versions of the SPC and the Package Leaflet (PL).	II-0006	II	19.09.02	05.12.02
On 3 September 2002, the MAH applied to update the SPC and the relevant sections of the PL with regard to safety of TDF based on long term data of clinical studies supplied and on data assessed in the first Periodic Safety Update Report (31/10/02 - 30/04/02): - Inclusion, in Section 4.4 (Special warnings and special precautions for use), of warning statements with regard to renal and bone toxicity and amendment of the information on concomitant use of nephrotoxic medicinal products and of the recommendation for monitoring of serum creatinine and serum phosphorus. - Inclusion, in section 4.5 (Interaction with other medicinal products and other forms of interaction), of minor wording changes. - In Section 4.6 (Pregnancy and lactation), information with regard to the establishment of a pregnancy register is provided. - Amendment, in section 4.8 (Undesirable effects), of the information on experience from pivotal clinical trials and inclusion of experience from Post Marketing Surveillance.	II-0007	II	20.02.03	19.05.03
On 3 September 2002, the MAH applied to extend the indication of TDF to include the initial therapy of HIV-1 infection in treatment naïve adults. Moreover, the MAH proposed to amend section 5.1 (Pharmacodynamic properties) in order to update the ATC code and the final 48-weeks data of clinical studies. The MAH took also the opportunity to update section 4.4 (Special warning and precautions for use) and 5.3 (Preclinical safety data) in line with the assessment of the safety data submitted.	II-0008	II	20.02.03	19.05.03
On 3 September 2002, the MAH applied to include dosage guidelines for patients with renal impairment in section 4.2 (Posology and method of administration) based on the results of the new clinical study, aimed at evaluating the pharmacokinetics of TDF in subjects with normal and impaired renal function. Amendments in section 4.3 (contraindication), 4.4 (Special warnings and special precautions for use) and 5.2 (Pharmacokinetic properties) are also proposed and an update of the Package Leaflet (PL), section 2 (Before you take Viread) in accordance with SPC changes.	II-0009	II	20.02.03	19.05.03

[1] In accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended: **I** refers to a minor variation (Type I variation); **II** refers to a major variation (Type II variation); **I/II** refers to a minor variation following the procedure set out in Article 6, 7 and 8 of the Regulation; **X** refers to an Annex II application.
T refers to a transfer of a Marketing Authorisation in accordance with Commission Regulation (EC) No 2141/96 of 7 November 1996.
N refers to a notification in accordance with Article 10(3) of Council Directive 92/27/EEC of 31 March 1992.
S refers to an annual reassessment.

[2] For Notifications and Type I variations, the date of entry into force of the change is the EMEA Notification date. The Commission Decision will be amended accordingly.

On 3 September 2002, the MAH applied for changes of section 5.3 (Preclinical Safety Data, third paragraph only on genotoxicity studies) of the SPC of Viread 245 mg film-coated tablets, further to the CPMP assessment of the results of the *in vivo/in vitro* unscheduled DNA synthesis test and the availability of the preliminary histopathology data from the rat carcinogenicity study.	II-10	II	21.11.02	27.03.03
On 4 November 2002 the MAH applied for a change in or addition of manufacturing site(s) for part or all of the manufacturing process.	I-0011	I	10.12.02	12.12.02
On 22 November 2002 the MAH applied for minor changes in the labelling and addition in the PL of the local representatives of the MAH not connected to the SPC.	N-0012	N	Corrigendum 06.02.03	-
On 23 December 2003 the MAH applied for changes of section 4.2. (Posology and method of administration) of the SPC of Viread 245 mg film-coated tablets and corresponding section 3 (How to take your medicine) of the PL, further to the CPMP assessment of a follow-up measure concerning the feasibility of patients disintegrating the tablets in liquids for ingestion by drinking. The MAH took this opportunity to make a slight typographical amendment to the dosage recommendation for patients with renal impairment.	II-0013	II	19.03.03	09.07.03
On 23 December 2003 the MAH applied for a type II variation to include in section 4.4 (Special warning and precautions for use) of the SPC, a class labelling statement with respect to lactic acidosis further to the request of the CPMP as a result of the assessment of the first PSUR (covering the time period 31/10/01-30/04/02). Relevant changes have also been implemented in the PL.	II-0014	II	19.03.03	09.07.03
On 23 December 2003 the MAH applied for a type II variation to include in section 5.1 (Pharmacodynamic properties) of the SPC a precautionary measure regarding the deleterious effect of the M41L and L210W mutations.	II-0015	II	19.03.03	09.07.03
On 14 January 2003 the MAH applied for a change in or addition of manufacturing site(s) for part or all of the manufacturing process.	I-0016	I	22.02.03	04.03.03
On 14 January 2003 the MAH applied for a change in or addition of manufacturing site(s) for part or all of the manufacturing process.	I-0017	I	22.02.03	04.03.03
On 24 February 2003 the MAH applied for an update of sections 4.4 (Special warnings and special precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction) and 5.2 (Pharmacokinetic Properties) of the Summary of Product Characteristics (SPC) concerning data provided from studies that investigate the concomitant use of Viread and a reduced dose of didanosine, as well as studies of potential interactions with methadone and a combined estrogen/progestin oral contraceptive. Relevant changes are equally proposed for the PL	II-0018	II	24.07.03	20.10.03
On 11 February 2003 the MAH applied for an update of the SPC to include the class labelling on Lipodystrophy in sections 4.4 (" Special warnings and special precautions for use") and 4.8 ("Undesirable Effects"). Relevant changes are equally proposed for the PL.	II-0019	II	19.03.03	10.07.03
On 24 April 2003 the MAH applied for a change in the name of a manufacturer of the medicinal product.	I-0021	I	31.05.03	09.07.03
On 24 April 2003 the MAH applied for a change in the name of a manufacturer of the medicinal product.	I-0022	I	31.05.03	11.06.03
On 10 June 2003 the MAH applied for a minor change of manufacturing process of the active substance.	I-0023	I	09.07.03	17.07.03
On 10 June 2003 the MAH applied for a minor change of manufacturing process of the active substance.	I-0025	I	09.07.03	17.07.03
On 10 June 2003 the MAH applied for a minor change of manufacturing process of the active substance.	I-0026	I	09.07.03	17.07.03
On 10 June 2003 the MAH applied for a minor change of manufacturing process of the active substance.	I-0027	I	09.07.03	17.07.03
On 10 June 2003 the MAH applied for a minor change of manufacturing process of the active substance.	I-0028	I	09.07.03	17.07.03
Annual reassessment	S-0020	S	25.04.03	01.08.03
On 2 July 2003 the MAH applied to amend section 4.8 (Undesirable effects) of the SPC of Viread 245 mg film-coated tablets to incorporate the additional adverse drug reaction of "*acute renal failure*" and "*proteinuria*" in the post-marketing experience information. This variation also aims to modify this same section to use MedDRA System Organ Class headings rather than the COSTART Body system headings currently used as requested by the CPMP further to the assessment of variation EMEA/H/C/419/II/07.	II-0029	II	25.09.03	14.01.04
On 3 July 2003 the MAH applied for an update of the section 4.2 (Posology and method of administration), section 4.4 (Special warnings and special precautions of use) and 5.2 (Pharmacokinetic properties) of the SPC of Viread 245 mg film-coated tablets to implement the class labelling on liver impairment adopted by the CPMP for all anti-retroviral medicinal products on 25 April 2003.	II-0030	II	20.11.03	30.01.04

In addition, the MAH proposes changes to sections 5.2 and 4.2, based on pharmacokinetic data from the final Study report in non-infected subjects with either normal hepatic function or varying degrees of hepatic impairment, as well as the inclusion, in section 4.4, of a warning regarding the potential risk of hepatitis flares following discontinuation of Viread in patients co-infected with hepatitis B. Changes to the Package Leaflet (PL) in accordance with the proposed changes to the SPC have also been proposed.				
On 21 July 2003 the MAH applied for a change in or addition of manufacturer(s) of active substance	I-0031	I	22.08.03	-
On 15 September 2003 the MAH applied for an update to section 5.3 (Preclinical safety data) of the SPC of Viread 245 mg film-coated tablets in view of the results obtained from long-term carcinogenicity studies in the rat and mouse. The submission of this final report was requested by the CPMP, as Specific Obligation stated in the MAH's letter of undertaking dated 17 October 2001.	II-0032	II	20.11.03	30.01.04