Procedural steps taken and scientific information after the authorisation

Trudexa

MAJOR CHANGES[1]

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0037	Update of Summary of Product Characteristics To update section 5.1 of the SPC with 5 year results from an open label extension of a clinical trial in rheumatoid arthritis. Section 4.8 was consequentially updated.	24/05/2007	29/06/2007	SPC	Results from an open label extension study in rheumatoid arthritis indicated that the reduction in rate of progression of structural damage is maintained up to 5 years in a subset of patients. Data also showed that efficacy in terms of ACR (American College of Rheumatology) response (criteria used in rheumatoid arthritis which allows for standardisation of trial outcomes and permits comparisons of treatment efficacy across clinical trials) was maintained in a group of patients who continued throughout the study period. 114 out of 207 patients continued on adalimumab 40 mg every other week for 60 months. Among those, 86, 72 and 41 patients had ACR 20/50/70 response. The SPC was updated to reflect these results.
II/0036	Change(s) to the manufacturing process for the active substance	22/03/2007	14/05/2007		
II/0035	Update of Summary of Product Characteristics and Package Leaflet To update section 4.4 of the SPC	24/01/2007	05/03/2007	SPC, PL	Based on the current safety information for adalimumab, a warning was added to the product information (PI) related to the reactivation of chronic hepatitis B.

[1] Major changes e.g. Type II variations, Annex II applications, Renewals and Annual Reassessments
[2] SPC (Summary of Product Characteristics), Labelling, PL (Package Leaflet)

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	regarding hepatitis B reactivation further to the update of the company's core data sheet. The PL was updated accordingly. In addition the MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania), and corrected the list of local representatives for Finland, Portugal and United Kingdom.				Reactivation of hepatitis B has occurred in patients receiving TNF-antagonists including adalimumab, who are chronic carriers of this virus. In some rare cases, especially if taking other medicines that suppress the immune system, reactivation of hepatitis B virus (HBV) had a fatal outcome. The PI now states that patients are advised to contact their doctors if they are carriers of HBV, have active HBV or think they might be at risk of contracting HBV.
II/0034	Update of Summary of Product Characteristics. To update sections 4.5 and 5.1 of the SPC regarding antibodies to adalimumab as requested by the CHMP further to the assessment of pharmacokinetic data from a long term clinical trial.	24/01/2007	05/03/2007	SPC	Based on the assessment of pharmacokinetic data, the SPC was updated to revise the numbers of subjects positive for anti-adalimumab antibodies observed in the clinical setting in patients on adalimumab monotherapy and patients on adalimumab and methotrexate. The formation of anti-adalimumab antibodies was associated with increased elimination and reduced efficacy of adalimumab. Higher antibody values did not appear to affect safety.
II/0033	Extension of Indication To update sections 4.1 of the SPC to include treatment of adult patients with moderately to severe active Crohn's disease. Sections 4.2, 4.8, 5.1 and 5.2 were consequently updated. The PL was updated accordingly.	26/04/2007	04/06/2007	SPC, PL	Please refer to the Scientific Discussion: EMEA-H-481-II-33-AR.

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II/0032	Changes to the manufacturing process for the finished product	27/07/2006	03/08/2006		
II/0031	Changes to the test methods and/or specifications for the active substance	27/07/2006	03/08/2006		
II/0030	The Marketing Authorisation Holder applied for the addition of a new presentation in a single-use disposable pre-filled pen comprising the authorised pre-filled syringe sealed into a functional secondary packaging used to deliver the product. The presentation is available in 4 pack sizes: 1, 2, 4 and 6 pens.	21/09/2006	07/11/2006	SPC, Labelling, PL	The pen is composed of the approved prefilled syringe sealed into an autoinjector delivery system. The pen is for a single-use. The information provided in support of the pen confirm that this variation does not affect the quality of the product. The product information has been updated to include the presentations in a pre-filled pen.
II/0028	Changes to the manufacturing process for the finished product	01/06/2006	07/06/2006		
II/0027	Update of Summary of Product Characteristics, Annex II and Package Leaflet Update of sections 4.4 and 4.8 of the SPC further to the request from the CHMP following assessment of PSUR No 5, covering the period from 31 December 2004 to 30 June 2005. The changes relate to post-marketing reports on lupus-like illness, and data from recent clinical trials concerning immunogenicity of influenza and pneumococcal vaccines. Furthermore, the sections on infections and	21/09/2006	07/11/2006	SPC, PL	In line with the CHMP recommendations following assessment of the 5th PSUR, the marketing authorisation holder (MAH) applied to update the warnings and undesirable effects sections of the SPC. The update aimed to detail the occurrence of lupus-like syndromes, serious infections and opportunistic infections and to revise the wording on tuberculosis. The sections on malignancies and lymphomas were updated with the latest figures from clinical trials and post-marketing data with adalimumab and information available from other anti-TNF agents, in particular to revise the

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	malignancies were also updated according to the current knowledge for anti-TNF therapies. The PL was updated in accordance with the changes proposed to the SPC. Additionally, the Marketing Authorisation Holder took the opportunity to update the list of local representatives (Austria and Slovenia). The annex II was updated to reflect the amendment of the periodicity of PSUR submission.				wording regarding very rare cases of non melanoma skin cancer observed in patients taking adalimumab, and to include warning on the treatment of patients with chronic obstructive pulmonary disease as well as patients which are heavy smokers. Further to the assessment of available clinical trial data, the section on vaccinations was updated to reflect that patients on adalimumab may receive concomitant vaccination, except for live vaccines. The PL was update in accordance with the changes proposed to the SPC. The annex II was amended to reflect that the MAH should continue to submit PSURs every 6 months.
II/0026	Extension of indication Update of section 4.1 of the SPC to extend the indication of adalimumab to include treatment of patients with severe active ankylosing spondylitis. Sections 4.2, 4.8 and 5.1 have consequently been updated. The PL was updated in accordance with the changes proposed to the SPC.	27/04/2006	01/06/2006	SPC, PL	Please refer to the Scientific Discussion: EMEA-H-481-II-26-AR.
II/0025	Changes to the manufacturing process for the active substance	26/01/2006	31/01/2006		
II/0024	Update of Summary of Product	14/12/2005	20/01/2006	SPC, PL	In line with the CHMP recommendations

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	Characteristics and Package Leaflet Update of sections 4.4 and 4.8 following the CHMP assessment of PSUR No 4, covering the period from 1 July 2004 to 30 December 2004, to include the latest information from post-marketing reports and data from recent clinical trials on early rheumatoid arthritis and psoriatic arthritis. Minor corrections were introduced to section 4.2 of the SPC and section 3 of the PL. Furthermore, section 4.4 of the SPC and section 2 of the PL were updated with regard to latex in accordance with the Excipients Guideline. The PL was updated in accordance with the changes proposed to the SPC.				further to the assessment of the 4th PSUR, the MAH applied to update the warnings and undesirable effects sections of the summary of product characteristics. The warning section was updated regarding new onset of demyelinating disease and blood disorders. The undesirable effects section was updated mainly regarding hepatic enzyme elevations and hepatic events, lupus-like reactions, infections, pulmonary events and malignancies. The section 4.8 was reorganised in accordance to the medical dictionary for regulatory affairs (MedDRA) terminology. Furthermore, corrections were introduced in section 4.2 of the SPC on initiation and supervision of treatment of psoriatic arthritis and section 3 of the PL on the handling of the syringes. A warning was introduced regarding allergic reactions due to the rubber nature of the needle cover of the syringe (latex).
II/0023	Update of Summary of Product Characteristics Update of the SPC, section 4.4 to include warnings regarding co-administration with anakinra, tuberculosis and congestive heart failure and section 4.8 to include cutaneous vasculitis, following the assessment of the 3rd PSUR (reporting period 31.12.03-30.06.04).	16/03/2005	25/04/2005	SPC	In line with the CHMP recommendations further to the assessment of the 3rd PSUR, the MAH applied to update the warnings and undesirable effects sections of the Summary of Product Characteristics. The warning section on concurrent administration with anakinra was revised due to the occurrence of serious infections following concurrent use of anakinra with another TNF-antagonist. The wording on tuberculosis was also revised to include the

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					information that this disease, including fatalities, had been reported in patients taking Trudexa. This section was also updated to include the safety information that cases of worsening congestive heart failure have been reported in patients receiving adalimumab. The section 4.8 "Undesirable effects" was updated following reports of occurrence of cutaneous vasculitis in patients taking Trudexa. This adverse effect has been reported with a frequency of rare.
II/0022	Extension of Indication Update of section 4.1 of the SPC to include treatment of patients with Psoriatic Arthritis. Sections 4.2, 4.8, 4.9 and 5.1 have consequentially been updated. The PL was updated in accordance with the SPC.	23/06/2005	01/08/2005	SPC, PL	Please refer to the Scientific Discussion: EMEA-H-481-II-22-AR.
II/0021	Extension of Indication Update of section 4.1 of the SPC to include treatment of recently diagnosed patients with moderately to severe active Rheumatoid Arthritis (RA) who have not been previously treated with methotrexate. Sections 4.8 and 5.1 have consequentially been updated. The PL was updated in accordance with the SPC.	23/06/2005	01/08/2005	SPC, PL	Please refer to the Scientific Discussion: EMEA-H-481-II-21-AR.

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II/0020	Changes to the manufacturing process for the active substance Changes to the test methods and/or specifications for the active substance	21/04/2005	27/04/2005		
II/0019	Update of Summary of Product Characteristics Update of sections 4.4 and 4.8 of the SPC on malignancies and lymphoproliferative disorders following the assessment of the 3rd PSUR (reporting period 31.12.03-30.06.04).	15/12/2004	25/01/2005	SPC	In line with the CHMP recommendations further to the assessment of the 3rd PSUR, the MAH applied to update the text in sections 4.4 "Special warnings and special precautions for use" and 4.8 "Undesirable effects" on malignancies and lymphoproliferative disorders. The purpose was to revise the warnings section and include details of the post-marketing experience on malignancies and lymphoproliferative disorders, including incidence. In clinical trials, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. Additionally, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.
II/0018	Changes to the manufacturing process for the active substance	17/02/2005	25/02/2005		

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II/0017	Changes to the manufacturing process for the active substance	17/02/2005	25/02/2005		
II/0016	Changes to the manufacturing process for the finished product	15/12/2004	21/12/2004		
II/0014	Changes to the test methods and/or specifications for the active substance Changes to the test methods and/or specifications for the finished product	18/11/2004	23/11/2004		
II/0013	Changes to shelf-life or storage conditions	18/11/2004	23/11/2004		
II/0012	Changes to the manufacturing process for the active substance	29/07/2004	02/08/2004		
II/0011	Changes to the manufacturing process for the active substance	29/07/2004	02/08/2004		
II/0010	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4 and 4.8 of the SPC following the assessment of the first PSUR (reporting period 31 December 2002 - 30 June 2003) to include serious allergic reactions and warnings relating to surgical procedures.	03/06/2004	19/07/2004	SPC, PL	Based on the submitted data, the CHMP agreed that the MAH should include in section 4.4 (Special warnings and special precautions for use) a warning with regard to surgical procedures and patients who have undergone arthroplasty and to add to sections 4.4 and 4.8 (Undesirable effects) "serious allergic reactions including anaphylaxis". A consequential change to the Package Leaflet, in section 2 (Before you use Trudexa), is proposed in order to reflect the safety warning relating to the possible

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					risk of infection in patients undergoing surgery. Advice is already included in the current Package leaflet relating to allergic reactions and the existing wording also satisfactorily reflects the symptoms of anaphylaxis.
II/0008	Update of or changes to the pharmaceutical documentation	16/09/2004	22/09/2004		
II/0007	Changes to the manufacturing process for the active substance	26/02/2004	01/03/2004		
II/0006	Extension of Indication Update of SPC section 4.1 (Therapeutic indications) to include an additional statement in the therapeutic indications to reflect results of a clinical study on the reduction of the rate of progression of structural damage and improvement of physical function, and consequential changes of SPC section 5.1 (Pharmacodynamic properties).	22/04/2004	10/06/2004	SPC, Labelling, PL	Please refer to the Scientific Discussion: EMEA-H-481-II-06-AR.
II/0003	Changes to the test methods and/or specifications for the active substance	17/12/2003	19/12/2003		

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IA/0029	08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	Annex II	22/03/2006
IA/0015	28_Change in any part of primary packaging material not in contact with finished product		06/10/2004
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	29/03/2004
IA/0005	07_a_Replacement/add. of manufacturing site: Secondary packaging site		20/10/2003
IA/0004	07_a_Replacement/add. of manufacturing site: Secondary packaging site		20/10/2003
IA/0001	07_a_Replacement/add. of manufacturing site: Secondary packaging site		20/10/2003

[3] Minor changes e.g. Type I variations and Notifications
[4] Date of entry into force of the change