Procedural steps taken and scientific information after the authorisation

Raptiva

MAJOR CHANGES[1]

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
A20/0028	Pursuant to Article 20 of Regulation (EC) No 726/2004 of 31 March 2004, the European Commission requested on 16 January 2009, the opinion of the CHMP on measures necessary to ensure the safe and effective use of the above mentioned medicinal product further to an increased concern over progressive multifocal leukoencephalopathy (PML) events.	19/02/2009	Marketing Authorisation suspended on 17/04/2009	Marketing Authorisation suspended on 17/04/2009	Please refer to the Scientific Conclusions: EMEA/H/C/000542/A20/0028
II/0027	Change(s) to the manufacturing process for the active substance Addition of an active substance quality control testing site.	19/02/2009	27/02/2009		
II/0026	Update of sections 4.4 and 4.8 of the SPC and sections 2 and 4 of the PL in order to include a description of a recently reported case of progressive multifocal leukoencephalopathy (PML) in the post-marketing surveillance setting.	23/10/2008	25/11/2008	SPC, PL	
II/0024	Change in a purification solution in the active substance manufacture.	23/10/2008	29/10/2008		
II/0022	Replacement of the currently supplied needle for reconstitution with a single-use sterile vial adapater (called "EasyMix") for reconstitution for all approved pack-sizes.	24/07/2008	28/08/2008	SPC, Labelling, PL	

[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)

II/0019	To update Section 4.4 “Special Warnings and Precautions for Use” of the SPC with a rewording of the discontinuation guidance, Section 4.8 “Undesirable Effects” with an update of information on overall incidence of adverse events and Section 5.1 “Pharmacodynamic Properties” with an update of the clinical particulars following the outcome of a benefit-risk reassessment and long term data. Sections 2 and 3 of the PL have been updated accordingly.	24/04/2008	20/06/2008	SPC, PL	Please refer to the scientific discussion Raptiva EMEA/H/C/542/II/19 Assessment Report.
II/0018	Update of section 4.8 of the SPC and section 4 of the PL to include 'facial palsy (Bell's palsy)' with 'uncommon' frequency. The contact details for Portugal have also been updated in the list of local representatives in section 6 of the PL.	20/09/2007	29/11/2007	SPC, PL	Further to information provided by spontaneous reports in relation to Raptiva and cases of facial palsy, the MAH submitted a cumulative review of facial palsy following a request from EMEA of the 02 April 2007. Based on the assessment of provided data, the CHMP concluded on 21 June 2007 that there seems to be an increased incidence of facial palsy of psoriasis patients treated with efalizumab compared to the general population and that 'facial palsy (Bell's palsy)' should be included in the Product Information with 'uncommon' frequency. Section 4.8 of the SPC and section 4 of the PL have been updated accordingly.
II/0017	Change(s) to the manufacturing process for the active substance	20/09/2007	25/09/2007		
II/0016	Update of the Summary of Product Characteristics (SPC) sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) and the corresponding section 4 of the Package Leaflet (PL) as requested by the CHMP following assessment of the review of inflammatory neuropathy syndromes reported with efalizumab.	24/01/2007	23/02/2007	SPC, PL	A cumulative review of inflammatory neuropathy syndromes reported with efalizumab was performed in the MAH global safety database. The MAH identified four cases of inflammatory neuropathy syndromes, including two cases of myelitis. Additionally, there were also two cases of Guillain Barre Syndrome presented besides a recent case of Miller Fisher Syndrome. Guillain Barre Syndrome and Miller Fisher Syndrome, a syndrome related to Guillain Barre Syndrome, are inflammatory

					neuropathies and the cases of myelitis were cases of chronic inflammatory demyelinating polyneuropathy. The pathogenesis of this chronic neuropathy seems to differ from that of Guillain Barre Syndrome. The CHMP concluded that based on the epidemiological data and on the mechanism of action of efalizumab, a causal relationship between efalizumab and inflammatory neuropathies cannot be excluded. The following warning was added to section 4.4 and reflected in section 4.8 and Patient Leaflet. "Inflammatory polyradiculoneuropathy" "Cases of inflammatory polyradiculoneuropathy have been observed in patients receiving Raptiva. Patients have recovered after discontinuation of Raptiva, therefore Raptiva should be stopped following the diagnosis of inflammatory polyradiculoneuropathy."
II/0015	Update of sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the Summary of Product Characteristics (SPC) as requested by CHMP further to the assessment of PSUR4. The MAH also applied for minor changes in Package Leaflet (PL) section 4 and an update of the contact details of some local representatives. In addition the Bulgarian and Romanian local representatives were included. The Product Information was also updated in accordance to QRD templates version 7.2.	24/01/2007	23/02/2007	SPC, PL	Infections: The cases of infections reported during the PSUR 4 covered period were analysed by the MAH, the MAH concluded that the SPC should be amended for the sections on Warnings as well as on Undesirable effects. The CHMP agreed. Consequently in section 4.4 "Special warnings and precautions for use" the following sentence has been amended as follows: "Raptiva is a selective immunosuppressor that alters T-lymphocyte function and may affect host defences against infections. It has the potential to increase the risk or the severity of infections, e.g. tuberculous pneumonia, and reactivate latent, chronic infections. Patients developing an infection during treatment with Raptiva should be monitored

					and according to severity Raptiva should be discontinued. In a patient with history of clinically significant recurring infections, Raptiva should be used with caution." 'Severe infections' was also added to the table in section 4.8 of the SPC. This reaction was placed under SOC 'infections and infestations' with frequency 'not known'. Lymphoproliferative disorders : Although it is still unclear whether or not the use of efalizumab is associated with an increased risk of lymphoproliferative disorders in psoriasis patient, the CHMP proposed to reword the warning as follows: "It is not yet known whether or not Raptiva can increase the risk of lymphoproliferative disorders or other malignancies in psoriasis patients. Raptiva should be discontinued if a malignancy develops while the patient is on treatment." Arthritis The MAH has reworded section 4.4 regarding arthritis as requested: Cases of arthritis have been observed during treatment or after discontinuation of Raptiva. It is recommended to discontinue Raptiva if arthritis occurs during treatment.
II/0013	Change(s) to the manufacturing process for the active substance	01/06/2006	08/06/2006		
II/0012	Change(s) to the manufacturing process for the active substance	01/06/2006	08/06/2006		

II/0008	Change(s) to the manufacturing process for the active substance	27/04/2006	04/05/2006		
II/0007	Change(s) to the test method(s) and/or specifications for the active substance	27/04/2006	04/05/2006		
II/0010	The variation relates to an update of the Summary of Product Characteristics (SPC) following the assessment of the Periodic Safety Update Report 2 (PSUR) covering the period from 27 October 2004 to 26 April 2005. Section 4.4 of the SPC is updated to include or strengthen warnings regarding infections, immune-mediated haemolytic anaemia, vaccinations and section 4.8 is updated to include immune-mediated haemolytic anaemia, interstitial pneumonitis, arthritis, and erythema multiform and to revise the wording on hypersensitivity. Sections 2 and 4 of the Package Leaflet (PL) were updated accordingly. Section 4.5 of the SPC was updated with regard to the antibody response during immunisation. Minor rewording in sections 4.2, 4.6 and 4.8 were also made. Additionally the product information (SPC, Annex II, Labelling and PL) was updated in accordance with the latest QRD template.	23/02/2006	29/03/2006	SPC, Labelling, PL	Following assessment of the second Periodic Safety Update Report, the CHMP requested an update of section 4.4 to include or strengthen warnings regarding opportunistic infections and tuberculosis and an update of section 4.8 of the SPC with regard to immune-mediated haemolytic anaemia, interstitial pneumonitis, arthritis, and erythema multiforme. In the context of a post-marketing follow-up measure the MAH submitted the final report of a clinical study on the immune responses during and after efalizumab treatment. This study showed that the model of T-cell dependent antibody response was lowered during efalizumab treatment. Therefore, Section 4.5 (Interaction with other medicinal products and other forms of interaction) of the SPC was updated with regard to the antibody response during immunisation to reflect appropriately clinically relevant effects of efalizumab on the responses to Tetanus toxoid booster vaccination and Pneumococcal vaccination and reduction in cellular immune response (e.g. Candida recall antigen).
II/0006	This variation relates to an update of section 4.8 of the SPC to include meningitis aseptic and corresponding changes to section 4 of the Package leaflet as requested by the CHMP following assessment of the first Periodic Safety Update Report.	27/07/2005	08/09/2005	SPC, PL	Following assessment of the first Periodic Safety Update Report an update of section 4.8 of the SPC was requested by the CHMP to include meningitis aseptic. The corresponding section of the Package leaflet was updated to add headaches.

II/0005	Change(s) to the manufacturing process for the active substance	27/07/2005	04/08/2005		
II/0003	Change(s) to the manufacturing process for the finished product	20/01/2005	27/01/2005		
II/0002	Change(s) to the manufacturing process for the finished product	20/01/2005	25/01/2005		

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IA/0030	05_Change in the name and/or address of a manufacturer of the finished product		01/04/2009
IA/0025	05_Change in the name and/or address of a manufacturer of the finished product	Annex II, PL	11/09/2008
IB/0021	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	SPC, Labelling, PL	03/07/2008
IB/0020	42_a_01_Change in shelf-life of finished product - as packaged for sale	SPC	14/05/2008
IB/0014	42_a_01_Change in shelf-life of finished product - as packaged for sale	SPC	25/08/2006
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	Labelling	16/02/2006
IA/0009	16_b_Submission of new TSE certificate relating to active substance - other substances		23/11/2005
IB/0004	37_b_Change in the specification of the finished product - add. of new test parameter		05/01/2005
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	18/11/2004

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