Aldara

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
II/0067	Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to add data on the clinical experience gained with study X-03016-3284 (LEIDA 2) and a meta-analysis of X-03016-3271 and X-03016-3284. The RMP is updated accordingly (version 3.2). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	12/12/2016	SmPC	The product information was updated to include information on re-treating actinic keratosis lesions that have cleared after one or two courses of treatment and subsequently recur. If the treated area does not show complete clearance at a follow-up examination about 8 weeks after the last 4-weeks course of treatment, an additional 4-weeks course of Aldara treatment may be considered. A different therapy is recommended if the treated lesion(s) shows insufficient response to Aldara.

[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).

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					Actinic keratosis lesions that have cleared after one or two courses of treatment and subsequently recur can be re-treated with one or two further courses of Aldara cream following an at least 12 weeks treatment pause. Please refer to section 5.1 of the Summary of Product Characteristics for more information.
N/0068	Update of the package leaflet with revised contact details of the local representatives for Italy, Spain and France. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/06/2016	12/12/2016	PL	
IA/0066	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	04/12/2015	n/a		
N/0065	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/09/2015	18/02/2016	PL	
II/0063	B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	25/06/2015	n/a		
IB/0064	To update to QRD template 9 and to update the contact details of the local representative in Lithuania. In addition the MAH took this opportunity to make minor linguistic amendment.	04/02/2015	18/02/2016	SmPC, Annex II, Labelling and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
PSUSA/1729/201401	Periodic Safety Update EU Single assessment - IMIQUIMOD	11/09/2014	n/a		PRAC Recommendation - maintenance
II/0061	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/05/2014	n/a		
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/08/2013	18/02/2016	PL	
IA/0059/G	This was an application for a group of variations. B.II.c.2.a - Change in test procedure for an excipient - 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	04/07/2013	n/a		
IB/0058/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	15/04/2013	n/a		
IG/0277	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/03/2013	n/a		
N/0056	Update of the local representatives contact details for Romania, Slovenia, Ireland, Cyprus and Latvia.	01/12/2011	18/02/2016	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IA/0055	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	28/11/2011	n/a		
IA/0054	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/11/2010	n/a		
II/0052	Update of section 4.8 of the Summary of Product Characteristics (SmPC) to include additional information on safety in the paediatric population in line with the revised SmPC guideline, as requested by the CHMP. The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to update section 4.4 of the SmPC to correct an error concerning the availability of data on long-term clearance rate for treatment of Superficial Basal Cell Carcinoma (sBCC), to implement the standard term "Cutaneous Use" instead of the previous "For cutaneous use" in the Labelling and to notify a change of the local representative in Malta in the Package Leaflet (PL). Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/03/2010	27/04/2010	SmPC, Labelling and PL	Aldara has been evaluated in four randomised, vehicle-controlled, double-blind trials in children aged 2 to 15 years with molluscum contaginosum (MC). Based on information from the above-mentioned studies and investigator-initiated studies in infants or children, assessed within the procedure Aldara II-42, the adverse events which occurred more frequently in children receiving imiquimod were application site disorders and application site reactions. A review of the local skin reactions indicated no obvious difference in incidence or severity when compared to studies in adults, and this was reflected accordingly in section 4.8 of the SmPC. The data obtained from these studies in children did not indicate any differences in the safety profile compared to adults.
IA/0053	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	19/02/2010	n/a		

	site				
IB/0049	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	04/09/2009	04/09/2009	SmPC, Labelling and PL	
IA/0051	IA_09_Deletion of manufacturing site	03/09/2009	n/a		
II/0046	Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	28/08/2009	SmPC and PL	
IA/0050	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	28/08/2009	n/a		
IB/0048	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	12/08/2009	n/a		
R/0044	Renewal of the marketing authorisation.	26/06/2008	03/09/2008	SmPC, Annex II, Labelling and PL	Based on the review of the available information, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Aldara continues to be favourable. The renewal was granted with unlimited validity.
II/0045	Update of Summary of Product Characteristics, annex II and Package Leaflet To update section 4.8 of the SPC to include information on the post-marketing reports of cases of elevated liver enzymes as requested by the CHMP. Furthermore the MAH took the opportunity to update annex II to remove the condition to submit annual PSUR's. In addition the postal code for the manufacturing site was corrected in annex II and in the PL.	24/07/2008	03/09/2008	SmPC, Annex II and PL	Based on a review of the 26 case reports of hepatobiliary disorders out of which there were six serious case reports which suggested a causal relationship between imiquimod therapy and reports of elevated liver enzymes the Product Information was revised to reflect this information.

	Update of Summary of Product Characteristics and Package Leaflet				
II/0042	To update sections 4.2 "Posology and method of administration", 5.1 "Pharmacodynamic properties" and 5.2 "Pharmacokinetic properties" of the SPC following evaluation of paediatric studies in the treatment of molluscum contagiosum, as requested by the CHMP in October 2007. On the basis of the information provided by the Marketing Authorisation Holder and as set out in the appended variation assessment report, the CHMP considers this variation to be a Type II variation. Update of Summary of Product Characteristics	30/05/2008	07/07/2008	SmPC	
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/02/2008	n/a	Labelling and PL	
N/0040	The Marketing Authorisation Holder (MAH) updated the list of local representatives in Greece, Portugal, Hungary, Czech Republic, Poland and Slovakia. Furthermore the MAH took this opportunity to correct a minor mistake in the numbering in of the points describing pictures in the German Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/11/2007	n/a	PL	
T/0039	Transfer of Marketing Authorisation	02/08/2007	30/08/2007	SmPC, Labelling and	

				PL	
II/0038	Quality changes	26/04/2007	03/05/2007		
II/0036	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.4 and 5.1 of the SPC to reflect four-year follow-up data from two clinical studies assessing recurrence rates of superficial basal cell carcinoma (sBCC). Additionally a warning in section 4.4 "Special warnings and special precautions for use" concerning the potential consequences of not allowing time for sufficient healing of the skin prior to Aldara administration was expanded as requested by CHMP in July 2006 following the evaluation of PSUR 10. The MAH also took the opportunity of this variation to correct translation errors in the Dutch, Greek and Norwegian Product Information (PI). Update of Summary of Product Characteristics and Package Leaflet	22/03/2007	24/04/2007	SmPC and PL	On the basis of the observed results at the timepoint of the 48-month follow-up of two open-label studies evaluating the safety and long-term clinical efficacy of imiquimod 5% cream studies, the CHMP agreed to amend the statement in section 5.1 of the SPC regarding long-term clearance in sBCC . An estimated 79.3% [95% CI (73.7%-84.9%)] of all the subjects who initially received treatment became clinically clear and remained clear at 48 months, while data on recurrence rates beyond 48 months are not yet available. Further to the CHMP request following the assessment of the 10th PSUR, to expand the following warning in section 4.4 "Imiquimod cream therapy is not recommended until the skin has healed after any previous drug or surgical treatment", the CHMP agreed on the additional statement in section 4.4 of the SPC saying that application of Aldara to broken skin could result in increased systemic absorption of imiquimod leading to a greater risk of adverse events.
IB/0037	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	16/01/2007	n/a		
IB/0033	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	19/12/2006	n/a		
IA/0035	IA_13_a_Change in test proc. for active substance - minor change	14/12/2006	n/a		

IA/0034	IA_13_a_Change in test proc. for active substance - minor change	14/12/2006	n/a		
II/0026	Extension of Indication To update of section 4.1 "Therapeutic indications" of the Summary of Products Characteristics (SPC) to extend the current approved indications to the treatment of actinic keratosis (AKs). Consequently sections 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use", 4.8 "Undesirable effects", 5.1 "Pharmacodynamic properties" and 5.2 "Pharmacokinetic properties" of the SPC have been updated. Furthermore, following a review on adverse reactions, section 4.8 was updated to introduce alopecia, reduction in haematological parameters requiring clinical intervention and dermatological drug reactions. The Package Leaflet (PL) has been updated accordingly. The MAH took the opportunity to update the annexes according to the latest QRD templates. Additionally, the package leaflet has been amended following user testing results. The MAH also took the opportunity of this change to amend the list of local representatives for Iceland, the Netherlands, and Estonia and to correct a number of errors in the translations that have been identified in all languages except Czech. Extension of Indication	18/10/2006	29/11/2006	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion: Aldara-H-179-II-26-AR

II/0031	To update sections 4.4 "Special warnings and special precautions for use" and 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics to reflect a three year follow up data following evaluation of two clinical studies, assessing recurrence rates of specified basal cell carcinomas, as requested by CHMP in May 2006. Update of Summary of Product Characteristics	27/07/2006	01/09/2006	SmPC	The indication for the topical treatment of superficial basal cell carcinoma (sBCC) in adult patients was granted in 2004. The clinical trial programme for this indication included two ongoing long-term phase III studies to assess recurrence rates of sBCCs up to five years after treatment with imiquimod 5% cream, 5x/week (study 1412-IMIQ) or 7x/week (study 1413-IMIQ) for 6 weeks. The MAH committed to submit results from these studies at yearly intervals and at the end of the five-year follow-up period. With this variation the MAH updated the SPC based on the second of the interim reports for studies 1412 and 1413, reporting 3-year follow-up data.These data show that an estimated 80.5% [95% CI (75.4%, 85.6%)] of all the subjects who initially received treatment became clinically clear and remained clear at 36 months.
IA/0032	IA_13_a_Change in test proc. for active substance - minor change	16/08/2006	n/a		
IA/0030	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	16/06/2006	n/a		
II/0027	To update sections 4.4 and 4.5 of the SPC to include a warning for patients who are receiving immunosuppressive medication for (auto)immune conditions, following the evaluation of the PSUR 9. Furthermore, following concerns stated in the evaluation of the PSUR 9 the MAH requested to update section 4.4 to include a sentence to avoid the contact with the lips and nostrils and to remove a statement regarding limited use in patients older than 65. Additionally, the MAH took the opportunity	23/03/2006	27/04/2006	SmPC and PL	Precautions for use in patients with autoimmune conditions: following the evaluation of PSUR 9 (covering the period from 27 February 2004 to 26 February 2005), the MAH submitted this type II variation to update section 4.4 and 4.5 to warn prescribers to exercise caution when treating patients who are receiving immunosuppressive medication for (auto)immune conditions and advise balancing the benefit of imiquimod treatment with the potential risks for these patients. Furthermore, section 4.8 of the SPC was updated to state that rare reports have

	of this variation to include in section 4.4 a recommendation for interruption of dosing in the event of flu-like symptoms. Section 2 of the PL was revised to include a warning regarding use near the eyes, lips and nostrils. The MAH also took the opportunity of this variation to correct translation errors in the Spanish, French and Italian SPC, Dutch, Swedish and Hungarian SPC and PL and in the Lithuanian, Slovakian and Slovenian PL. Update of Summary of Product Characteristics and Package Leaflet				been received of exacerbation of autoimmune conditions. Precautions for use in organ transplant patients: the systemic concentration of Aldara is likely to be very low in the majority of patients. However, remains a theoretical chance that it attenuates the action of immuno-suppressants. Since graft-versus-host disease and the rejection of an organ are potentially life-threatening adverse effects, and since immuno-suppressed patients are more likely to require imiquimod therapy, it is important that prescribers are made aware of this and of the need to base imiquimod treatment on a careful benefit-risk assessment. Section 4.4 of the SPC was updated to reflect this information. Precautions for use near the eyes and nose: based on a review of all reactions that have occurred where Aldara was administered close to the eyes, nose, lips and hairline the warning in section 4.4 of the SPC and in section 2 of the PL to "avoid contact with the eyes" was extended to the lips and nostrils. Furthermore, an advice was introduced in section 2 of the PL on what action to take in the event that Aldara is accidentally applied to the eyes, lips and nostrils. Precautions for use in patients older than 65 years: since a large number of patients over the age of 65 years have been studied in clinical trials for sBCC and for actinic keratoses the statement regarding limited use in patients older than 65 was removed from section 4.4 of the SPC. P
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/12/2005	n/a	Labelling and PL	
II/0025	Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	28/10/2005	SmPC and PL	

IA/0024	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	30/11/2004	n/a		
N/0023	To update the list of local representatives in Austria, Cyprus, Finland, Germany, Iceland, the Netherlands, Norway and Portugal in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/10/2004	n/a	PL	
IA/0022	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	12/08/2004	n/a		
II/0020	Extension of Indication	03/06/2004	13/07/2004	SmPC and PL	The Marketing Authorisation Holder (MAH) applied for the extension of the therapeutic indication to include patients with superficial basal cell carcinoma. Furthermore, the MAH took the opportunity of the variation to update section 4.8 ("Undesirable effects") according to MedDRA, following a request from the CPMP in July 2003. The Package Leaflet (PL) has been revised accordingly. In addition, the MAH completed the list of local representatives in the PL to include the 10 new EU Member States and changed the format according to the latest EMEA/QRD template. Please refer to the Scientific Discussion: Aldara-H-179-II-20.
IA/0021	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	26/02/2004	n/a		
II/0018	Update of Summary of Product Characteristics and Package Leaflet	25/09/2003	27/01/2004	SmPC and PL	To update the SPC section 5.1 "Pharmacodynamic properties" to include information on median time to clearance and percentage of patients who achieved total clearance of their warts. Relevant changes are equally

					proposed for the PL.
R/0017	Renewal of the marketing authorisation.	24/07/2003	24/10/2003	SmPC, Annex II, Labelling and PL	
II/0015	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	26/06/2003	SmPC and PL	To update the SPC section 4.2 " Posology and method of administration" to include information on safety beyond 16 weeks and section 4.4 "Special warnings and special precautions for use" to include information on repeat treatment following the availability of new clinical data. Relevant changes are equally proposed for the PL.
II/0016	Update of Summary of Product Characteristics	20/02/2003	13/06/2003	SmPC	To update the SPC section 4.6 " Pregnancy and Lactation" to reflect new information on usage during pregnancy following the availability of new post marketing information.
II/0014	Update of Summary of Product Characteristics and Package Leaflet	20/02/2003	13/06/2003	SmPC and PL	To update the SPC, sections 4.2 "Posology and method of administration" to strengthen dosage and usage instructions, 4.4 "Special warnings and special precautions for use" and 4.8 "Undesirable Effects" to include warnings about the severity of application site reactions and warnings about female urinary symptoms following the CPMP assessment of Periodic Safety Update Report (PSUR) 6 covering the period 27 February 2001 - 26 February 2002. In addition, the MAH proposed to slightly amend section 4.4 regarding advice to uncircumcised men and sections 4.8 and 5.1 "Pharmacodynamic properties" concerning the likely application site reactions as a consequence of the mode of action. Finally the MAH amended section 6.4 " Special precautions for storage" to indicate that sachets should not be reused once opened. Relevant changes are equally proposed for the PL. In addition, the list of local representatives in the PL has been

					revised.
II/0012	Update of Summary of Product Characteristics and Package Leaflet	26/07/2001	21/11/2001	SmPC, Labelling and PL	
I/0013	15a_Change in IPCs applied during the manufacture of the product	14/05/2001	23/05/2001		
I/0011	04_Replacement of an excipient with a comparable excipient	27/10/2000	14/11/2000		
I/0010	04_Replacement of an excipient with a comparable excipient	27/10/2000	14/11/2000		
II/0008	Change(s) to shelf-life or storage conditions	21/09/2000	27/10/2000		
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/06/2000	01/08/2000	PL	
I/0006	25_Change in test procedures of the medicinal product	25/05/2000	n/a		
I/0005	25_Change in test procedures of the medicinal product	25/05/2000	n/a		
I/0004	25_Change in test procedures of the medicinal product	25/05/2000	n/a		
I/0007	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	06/04/2000	11/04/2000		
I/0003	25_Change in test procedures of the medicinal product	06/04/2000	11/04/2000		

N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/12/1999	09/03/2000	Labelling and PL	
I/0001	12_Minor change of manufacturing process of the active substance	16/12/1999	n/a		