EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Macugen

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
IB/0065	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/07/2016		SmPC	
IA/0064/G	This was an application for a group of variations A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	04/02/2016	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).

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PSUSA/2324/ 201506	Periodic Safety Update EU Single assessment - PEGAPTANIB	14/01/2016	n/a		PRAC Recommendation - maintenance
R/0062	Renewal of the marketing authorisation.	24/09/2015	19/11/2015	SmPC, Annex II, Labelling and PL	Based on the review of the available cumulative data, the CHMP is of the opinion that the quality, safety and efficacy of Macugen continues to be adequately and sufficiently demonstrated in the approved indication and therefore considers that the benefit-risk balance continues to be favourable. The CHMP was of the opinion that the renewal of the marketing authorisation should be granted with unlimited validity.
PSUV/0061	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
T/0060	Transfer of Marketing Authorisation	28/07/2014	01/09/2014	SmPC, Labelling and PL	
IAIN/0059	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	15/07/2014	n/a		
II/0058	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	22/05/2014	n/a		
PSUV/0057	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
IB/0056/G	This was an application for a group of variations.	16/10/2013	n/a		

	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.2.z - Changes in the manufacturing process of the AS - Other variation 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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised				
II/0054	Update of SmPC sections 4.4. and 4.8 to amend the existing warning on the risk of elevated intraocular pressure and provide information on the increase in intraocular pressure after repeated injections. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	27/06/2013	03/06/2014	SmPC, Annex II, Labelling and PL	Based on a previous review of the results from a prospective epidemiologic cohort study investigating the incidence of ocular adverse events among patients with age-related macular degeneration receiving intravitreal injections of Macugen, which was concluded in December 2012, the CHMP expressed concerns in relation to a small sustained increase in ocular pressure that was observed in patients receiving repeated Macugen injections. This concern was further investigated during the review of PSUR 11, where case series from the medical literature were reported, which were supportive of this association. Additional analyses of the cohort study data revealed a statistically significant correlation between the number of events of increased eye pressure and the number of injections received and therefore

					the CHMP agreed to update the existing warning on elevated eye pressure in SmPC section 4.4 and to provide additional information on the size of the effect and the underlying data in section 4.8. Section 4 of the package leaflet was updated accordingly. Other changes to the product information were related to QRD wording and an update of the list of local representatives concerning Greece, Spain, Cyprus and Croatia.
IAIN/0055/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	28/05/2013	03/06/2014	Annex II and PL	
IB/0053/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or	11/02/2013	n/a		

	addition of a site where batch control/testing takes place				
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
II/0047	Update of sections 4.2, 4.4, 4.8 and 6.6 of SmPC in order to: - include additional instruction (section 4.2) on expelling the volume overfill for obtaining the proper injection volume, with a cross-reference with section 6.6 of the SmPC; - include a warning (section 4.4) that the injection of the entire volume of the prefilled syringe could result in serious adverse events; - add a reference under post marketing experience (section 4.8) of cases of increased in pressure inside the eye reported when the excess volume in the pre-filled syringe was not expelled before injection; - include additional language and photographs to clarify the procedure for administering Macugen (section 6.6). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	23/08/2012	SmPC, Annex II, Labelling and PL	In order to improve and clarify the instructions for use of Macugen to decrease the chances of injecting more than the recommended dose from the prefilled syringe, sections 4.2, 4.4, 4.8, and 6.6 of the SmPC were updated. Accordingly, the Package Leaflet (PL) Sections 3 and 6, the text on the Carton and the text on the Pouch have also been updated in line with the above.

IG/0169/G	This was an application for a group of variations. 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 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	08/06/2012	n/a		
IA/0050/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.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.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	05/06/2012	n/a		

IA/0048/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	30/05/2012	n/a		
IA/0045	A.7 - Administrative change - Deletion of manufacturing sites	11/04/2011	n/a		
IG/0044/G	This was an application for a group of variations. 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 C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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	02/03/2011	n/a	Annex II	
R/0043	Renewal of the marketing authorisation.	21/10/2010	20/12/2010	SmPC, Annex II, Labelling	Based on the review of the available information the CHMP is of the opinion that the quality, safety and efficacy of this

				and PL	medicinal product continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of Macugen continues to be favourable. The CHMP is however of the opinion that one additional five-year renewal on the basis of Pharmacovigilance grounds is required. Changes were made to the product information to bring it in line with the current Agency/QRD template and SmPC guideline.
IA/0042	To remove the three manufacturing sites. A.7 - Administrative change - Deletion of manufacturing sites	20/05/2010	n/a		
II/0039/G	This was an application for a group of variations. To update the binding specificity test method used to determine the biological activity of pegaptanib sodium in both the finished product and the active substance . The associated binding specificity acceptance criteria in the drug product specification is tightened. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent	22/04/2010	03/05/2010		

IB/0041	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	08/03/2010	n/a	SmPC	
IB/0040	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	08/03/2010	n/a		
IA/0038	IA_05_Change in the name and/or address of a manufacturer of the finished product	23/10/2009	n/a		
IA/0037	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	23/10/2009	n/a		
IA/0036	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	23/10/2009	n/a		
IB/0035	IB_33_Minor change in the manufacture of the finished product	11/08/2009	n/a		
II/0034	Update of Detailed Description of the Pharmacovigilance System (DDPS) Update of DDPS (Pharmacovigilance)	25/06/2009	24/07/2009	Annex II	The Detailed Description of the Pharmacovigilance System (DDPS) has been updated (version 2.0) in order to reflect various organisational changes as well as the change of the global safety database. Consequently, Annex II has been updated with the new version number of the agreed DDPS.
N/0033	Update of the representative contact details for Germany, Ireland, Slovenia and United Kingdom in section 6 of the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/03/2009	n/a	PL	

IA/0032	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	06/08/2008	n/a		
IA/0031	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	31/07/2008	n/a		
IA/0030	IA_09_Deletion of manufacturing site	31/07/2008	n/a		
II/0026	New site of manufacture of the active substance, together with minor changes in the manufacturing process and testing methodology. Quality changes	19/03/2008	28/03/2008		
IA/0029	IA_37_a_Change in the specification of the finished product - tightening of specification limits IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	27/02/2008	n/a		
IA/0028	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	12/02/2008	n/a		
IA/0027	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	05/02/2008	n/a		
II/0018	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Update of Summary of Product Characteristics	13/12/2007	28/01/2008	SmPC	In accordance with Article 8(3)(ia) of directive 2001/83/EC as amended, the MAH submitted a Detailed Description of the Pharmacovigilance System (DDPS) for Macugen, with their Marketing Authorisation Application. This is now being updated.
II/0016	Update of section 4.2 of the Summary of Product	18/10/2007	21/12/2007	SmPC and PL	Following a request by the CHMP (FUM 014) and after

	Characteristics (SPC) to include guidance on stopping or withholding treatment following the overall assessment of the response to Clinical Follow up Measures (FUM 014 and 014.1). In addition, some changes are being made to Section 4 of the PL (side effects), to bring it in line it with section 4.8 of the SPC. The contact details of local representatives for Ireland, Latvia and Slovakia in the PL are also being updated. Update of Summary of Product Characteristics and Package Leaflet				consultation with an independent panel of ophthalmologists experienced in the treatment of neovascular AMD, the MAH made a proposal for a definition of the conditions that could lead to Macugen treatment discontinuation and proposed the corresponding changes to the SPC. The concept to "consider stopping treatment" if patients are not responding to Macugen therapy was acceptable in principle to the CHMP, and the recommendations on considering the appropriateness of stopping or continuing treatment is now conveyed in the SPC after introduction of a statement in section 4.2 (Posology) explaining that "After 2 consecutive injections of Macugen, if a patient does not demonstrate a treatment benefit (loss of less than 15 letters of visual acuity) at the 12-week visit, consideration should be given to stopping or withholding Macugen therapy."
II/0017	Changes to the finished product primary and secondary container/closure, and the product manufacturing process, including a new process for sterilisation of the outer wrap. New presentation(s)	20/09/2007	30/11/2007	SmPC, Labelling and PL	The Marketing Authorisation Holder applied for changes to the primary container (replacement of needle syringe with Luer lock syringe, preassembly of syringe parts), new sterilising process for external surface of the pouch. As a consequence of these changes, a second foil overpouch is no longer needed and some analytical methods have been revised. Sections 6.5 and 6.6 are amended in that regard and the Labelling and PL accordingly.
IA/0025	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	23/11/2007	n/a		
IA/0024	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	12/11/2007	n/a		
IA/0019	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	29/10/2007	n/a		

IA/0015	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	03/04/2007	n/a		
IA/0014	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	03/04/2007	n/a		
IA/0013	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	03/04/2007	n/a		
IA/0012	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	03/04/2007	n/a		
IA/0011	IA_13_a_Change in test proc. for active substance - minor change IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	03/04/2007	n/a		
IA/0010	IA_13_a_Change in test proc. for active substance - minor change IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	03/04/2007	n/a		
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/03/2007	n/a	Labelling and PL	
IA/0009	IA_06_a_Change in ATC code: Medicinal products for human use	01/03/2007	n/a	SmPC	
IA/0006	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	27/10/2006	n/a		

IA/0005	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	05/10/2006	n/a	Annex II and PL	