EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Thelin

Procedural steps taken and scientific information after the authorisation

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2]/ amended on	Product Information affected[3]	Summary
IA/0032	A.7 - Administrative change - Deletion of manufacturing sites	15/12/2010	n/a		
T/0031	Transfer of Marketing Authorisation Holder	21/06/2010	22/07/2010	SPC, Labelling, PL	
II/0029	Update of Summary of Product Characteristics, Annex II and Annex IV. Update of Summary of Product Characteristics	22/04/2010	05/07/2010	SPC, Annex II	The MAH submitted further safety data regarding the hepatotoxic potential of sitaxentan, triggered by a fatal outcome reported in a young female patient with PAH following a hepatotoxic reaction associated with the use of sitaxentan. Based on this information, a new contra-indication is added for patients with elevated direct bilirubin of > 2 x ULN prior to initiation of treatment. Consequently, elevated direct bilirubin as a potential maker of hepatotoxicity is introduced in the SPC and sections 4.2, 4.4 and 4.8 are amended. Annex II and Annex IV are amended accordingly.

[1] Notifications are issued for type I variations (unless part of a group or a worksharing application). Opinions are issued for all other procedures.
[2] No Commission Decision is issued for type IA and type IB variations or for type II variations and annual re-assessments that do not affect the annexes.
[3] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/02/2010	n/a	PL	
II/0018	Update of section 5.1 of the Summary of Product Characteristics with data in patients with pulmonary arterial hypertension in WHO functional class II further to a re-analysis of clinical studies STRIDE 1 and STRIDE 2 and to available data from STRIDE 4 study. Update of Summary of Product Characteristics	19/11/2009	21/12/2009	SPC	In this application, the MAH re-evaluated data from two previously submitted pivotal studies: STRIDE 1 (FPH01) and STRIDE 2 (FPH02), as well as data from study STRIDE 4, to support an extension of indication in pulmonary arterial hypertension WHO functional class (FC) II. Further to the assessment of the submitted data, the CHMP considered that efficacy data to support an extension of the indication in section 4.1 of the Summary of Product Characteristics (SPC) to WHO FC II patients was insufficient. Results of the 6-minute walk test were not statistically significant, while data on the effect on clinical worsening were based from a post-hoc analysis which also failed to show statistical significance. Benefit seen on FC and haemodynamics are supportive, but insufficient. However, the CHMP considered acceptable to include in section 5.1 of the SPC of the results of STRIDE 4 study, relevant haemodynamic data, effect on functional class and updated long-term survival data as the information can be useful to the prescriber. Please refer to Scientific Discussion Thelin-H-C-679-II-18.
IA/0025	09_Deletion of manufacturing site	28/09/2009	n/a	Annex II, PL	
IA/0026	09_Deletion of manufacturing site	28/09/2009	n/a		
IA/0027	09_Deletion of manufacturing site	28/09/2009	n/a		
IB/0023	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site, IA_07_b_01_Replacement/add. of	24/09/2009	n/a		

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	manufacturing site: Primary packaging site - Solid forms, IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site, 07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release				
IA/0028	09_Deletion of manufacturing site	24/09/2009	n/a		
IA/0024	07_a_Replacement/add. of manufacturing site: Secondary packaging site	11/09/2009	n/a		
IB/0021	13_b_Change in test proc. for active substance - other changes (replacement/addition)	03/09/2009	n/a		
IA/0022	13_a_Change in test proc. for active substance - minor change	18/08/2009	n/a		
II/0019	Update of DDPS (Pharmacovigilance)	25/06/2009	14/07/2009	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 using the standard text including the new version number of the agreed DDPS.
II/0020	Update of the microbiological quality acceptance criteria for some excipients and the finished product (Release and shelf life). Quality changes	25/06/2009	06/07/2009		
II/0015		19/02/2009	16/04/2009	SPC, Annex II, PL	Update of sections 4.4, 4.5, 4.8 and 4.9 of the Summary of Product Charactheristics (SPC) following the request from the CHMP in the assessment of the 3rd PSUR in order to align the SPC with the company Reference Safety Information and in line with the Guideline on SPC.

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					Particularly, the recommendations in treatment-emergent ALT/AST elevations in section 4.4 of the SPC were revised, the interaction wordings in section 4.5 of the SPC were updated and re-ordered and the adverse reactions in section 4.8 of the SPC were presented in a tabular format with where applicable, adverse reactions added or their frequency updated. The Package Leaflet has been updated accordingly. Furthermore, as a consequence to the change of the recommendations in case of treatment-emergent ALT/AST elevations in section 4.4 of the SPC, the conditions or restrictions with regard to the safe and effective use of the medicinal product were updated in Annex II and in Annex IV. The MAH also took the opportunity to make editorial and linguistic changes to the Product Information.
II/0016	Changes to QPPV, Update of DDPS (Pharmacovigilance)	18/12/2008	27/01/2009	Annex II	The Marketing Authorisation Holder applied to update the Detailed Description of the Pharmacovigilance System (DDPS) and change of the Qualified Person responsible for Pharmacovigilance. Consequently, Annex II has been updated using standard text including the numbers of the version agreed for the DDPS (version 1.1) and for the Risk Management Plan (version 5).
IA/0017	08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	29/10/2008	n/a	Annex II, PL	
IA/0014	09_Deletion of manufacturing site	30/06/2008	n/a		
IA/0013	08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	13/02/2008	n/a	Annex II, PL	
II/0010	Quality changes	20/09/2007	27/09/2007		
II/0009	Quality changes	19/07/2007	24/07/2007		
IB/0011	42_a_01_Change in shelf-life of	18/06/2007	n/a	SPC	

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	finished product - as packaged for sale				
IA/0012	38_a_Change in test procedure of finished product - minor change to approved test procedure	06/06/2007	n/a		
II/0004	Quality changes	24/05/2007	31/05/2007		
II/0006	Quality changes	24/05/2007	31/05/2007		
II/0003	Changes in conditions and restrictions with regard to the safe and effective use of the medicinal product introduced in the risk management plan (RMP), with corresponding updates to Annex II, the SPC (sections 4.4 and 4.8) and the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/02/2007	22/05/2007	SPC, Annex II, Labelling, PL	The increased risk of bleeding with Thelin, mainly in the form of epistaxis and gingival bleeding, has been reflected in the SPC through the addition of a warning (section 4.4) and an update of section 4.8, to add gingival bleeding as a common undesirable effect. Regarding the risks of Thelin associated with Pregnancy, the following warning has been added to section 4.4 of the SPC and section 4.6 has been updated accordingly: "Due to possible teratogenicity, the treatment must not be initiated in women of child-bearing potential unless they practice reliable contraception. If necessary, pregnancy testing should be undertaken (see Section 4.6). The conditions and restrictions with regard to the safe and effective use of the medicinal product introduced in the RMP have been updated in Annex II.
IA/0007	08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR not incl. BC/testing	10/04/2007	n/a	Annex II, PL	
II/0001	Quality changes	18/10/2006	23/10/2006		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/10/2006	n/a	Labelling, PL	