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Human Medicines Development and Evaluation

Minutes of Thalidomide follow-up meeting with patients' and victims' organisations

Monday 5 September 2011 –chaired by Xavier Luria

Role	Name	
Chair	Xavier Luria	
Present:	Rafael Basterrechea Estella	AVITE (Spanish Thalidomide association)
	Juana Maria Perez Torralbo	AVITE (Spanish Thalidomide association)
	Carmel Daly McDonnell	Irish Thalidomide Survivors Society
	Patrick McDonnell	Irish Thalidomide Survivors Society
	Greetje Goossens	Contactgroep Myeloom Patienten (CMP)
	Glenn Harrison	Thalidomide UK
	Nadia Malavasi	Italian Association of Thalidomide Victims
	Roberto Zucchini	Italian Association of Thalidomide Victims
	Rune Skarning Kristiansen	Norwegian Association for Thalidomiders
	Margaret Hogg	Thalidomide Society
	David Hogg	Thalidomide Society
	Björn Håkansson	FfdN (The Scandinavian Society for the Thalidomide cases)
	Zahra Hanaizi	EMA
	Francesco Pignatti	EMA
	Helen Goff	EMA
	Rosa Giuliani	EMA
	Stefanie Prilla	EMA
	Franck Diafouka	EMA
	Nathalie Bere	EMA
	Sabine Haubenreisser	EMA
	Pierre Demolis	AFSSAPS
	Rachida Belounis	AFSSAPS
	Christel Saussier	AFSSAPS
	Nathalie Deleau	AFSSAPS

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Role	Name	
	Tomas Salmonson (via TC)	MPA
	Karl-Mikael Kälkner (via TC)	MPA
	Sarah Morgan	MHRA
	Ineke Crijns (via TC)	MEB
Apologies:	Peter Arlett	EMA
	Juan Garcia	EMA
	Sabine Straus	CBG-MEB
	Jean-Michel Dogné	FAGG-AFMPS
	Joop Konings	Dutch Thalidomiders
Minutes:	Zahra Hanaizi	

1. Welcome & Tour de Table

The Chair welcomed the participants before proceeding to a Tour de Table.

2. Introduction on the role of the Agency and CHMP and objectives of the meeting

The objectives of the meeting were presented as follows:

- Update on safety aspects and Risk Management Plan (RMP) since the previous consultation
- Information on use of Thalidomide Celgene in the European Union (EU)
- Practical implementation of RMP for which the organisations provided input
- Provide reassurance on safety aspects of interest
- Agree on future follow-up

During this presentation, the Agency reminded the participants on the role of the Agency and CHMP in the marketing authorisation evaluation of Thalidomide Celgene, as well as the activities in which the Agency is not involved (e.g. pricing and reimbursement, no direct role in off-label use…).

3. Update on post-authorisation activities on Thalidomide Celgene

a) Overview of post-authorisation regulatory procedures

In this presentation, the participants were provided information on the status of marketing of the product as well as changes made since granting of the marketing authorisation.

Details on variations related to the safety and efficacy aspects were presented: most of the variations submitted by the Marketing Authorisation Holder to date were made further to request of the CHMP, subsequent to assessment of Periodic Safety Update Reports (PSUR) data or results of post-authorisation commitments.

b) Overview of PSURs, RMP revisions and reports of events of interest

The Rapporteur's assessors provided an extensive presentation including details on exposure data, analysis of post-marketing events of interest, updates of the Risk management Plan and data regarding the effectiveness of the RMP and Pregnancy Prevention Programme (PPP).

Of note, the following was highlighted:

- Based on data from the 5th PSUR, the cumulative exposure in the EU is estimated to approximately 76,000 patients. The off-label use represents approximately 19.5% of the total thalidomide prescriptions in the EU. Overall, it is estimated that 3.8% of patients are female of childbearing potential.
- No pregnancy of a female patient was reported in the EU since the launch of Thalidomide Celgene under the PPP. Three reports of pregnancy of a female partner of a male patient have been reported and further data has been requested.
- Data on thromboembolic events was presented. Review of these events led to the update of the product information, amendments of the educational materials and distribution of a Direct Healthcare Professional Communication.
- With regard to the important identified risk of peripheral neuropathy, according to PSUR data the reporting rate of the adverse reaction remains stable since the approval. It was clarified that the time of occurrence of these events was variable, from early after treatment initiation up to shortly after withdrawal of therapy.
- The RMP has been regularly updated and assessed since the approval to include important identified and potential risks from the post-marketing experience.
- Due to local data privacy laws, collection of demographic data or data on off-label use is not available to the marketing authorisation holder in all EU member states.

c) Discussion

The Rapporteur and Co-Rapporteur introduced the discussion by providing reassurance that the off-label use that is reported with Thalidomide Celgene is under close monitoring. As an example, in France, special derogations have been granted for use in other specific indications based on available literature data. The controlled distribution and PPP conditions applied to Thalidomide Celgene in its authorised indication are also applied to those off-label indications. Differences of off-label use can be observed in throughout the EU. However, it was emphasized that off-label use did not mean that it was used without any control.

It was also highlighted that the marketing authorisation of Thalidomide Celgene allowed the introduction of a common EU RMP and of a controlled distribution system. However, due to national laws, differences remain at the local level, particularly with regard to off-label use, use of unlicensed thalidomide and collection of data.

With regard to generics of Thalidomide Celgene, it was reminded that should generic product be authorised after expiry of its market exclusivity, similar conditions would be applied to the marketing authorisations of generics.

Further to a question raised on the reporting of pregnancies, it was clarified that forms are implemented so that the information is reported. The effectiveness of the PPP can be measured through the fact that no pregnancy of female patient has been reported since the launch of Thalidomide Celgene in the EU.

Comment was made that in Japan, a group is ensuring that patients receive the correct information and question was raised whether such actions are in place in the EU. Despite differences of local legislation and particularly privacy data law, it was highlighted that providing the information should be documented. Furthermore, the patient organisation representative provided the perspective from the

patient community: Since the PPP implementation, patients are well informed and very conscious of the issue and motivated to adhere to the programme, meaning that the patient information has reached its target audience.

A question was raised in relation to the ongoing review by the CHMP on reports of second primary malignancies with Revlimid (lenalidomide). The participants were informed that a review of these events is currently ongoing also for thalidomide and that the outcome would be shared with the participants upon finalisation.

Overall, the organisations welcomed the data presented and were reassured of the close monitoring of the marketing of the medicinal product.

4. Implementation of the Risk Management Plan and PPP

a) Introduction

The Agency introduced this topic by reminding the elements constituting the RMP/PPP and the additional risk minimisation activities in place, which include educational materials.

b) Practical example of implementation in the Member States

Representatives of 3 national competent authorities provided input on the implementation of the controlled distribution system and RMP/PPP in their respective Member States, as follows.

France (AFSSAPS)

An outline of the French controlled distribution system, from the prescription to the dispensation to the patient, was presented.

The French prescription survey implemented for thalidomide was presented: this mandatory survey enables collection of data in order to monitor the real-life conditions of use and off-label use. Recent results of the survey indicated that the authorised indication and specific derogations for off-label use in France are respected. The PPP is correctly respected that the time of dispensation and treatment initiation. The national survey conducted by a regional centre of pharmacovigilance showed no emerging safety issue. Overall, the objectives of the RMP are considered to be fulfilled.

Sweden (MPA)

A questionnaire was prepared by the MPA in order to collect data that cannot be routinely collected due to national laws. Preliminary results of this questionnaire (124 responses analysed) were presented. Overall, very few patients are of childbearing potential. The use of the patient card is generally low; however, the patient received the information by other means. The off-label use exists but at a low frequency.

United Kingdom (MHRA)

An outline of the UK controlled distribution system, including use of a prescription authorisation form (PAF), was presented.

In the UK, an annual audit has been put in place by Celgene, further to approval of the audit process and data collection by the MHRA. The objective of the annual audit is to give an indication on the nature and extent of off-label prescribing as well as to ensure compliance with the PAF.

The use of unlicensed thalidomide in the UK was also presented. Use of unlicensed thalidomide may occur when the licensed product does not meet the clinical need (e.g. lack of tolerability due to

difficulty to swallow capsules, lower dose required). In 2009, the use of unlicensed thalidomide was estimated to 12% in the UK and has since decreased. It was highlighted that the supply of unlicensed thalidomide was closely monitored and that the manufacturers, importers and suppliers of unlicensed thalidomide were inspected by the MHRA. The MHRA also insists that information on pregnancy prevention is supplied with every order of thalidomide.

c) Discussion

The participants discussed the results of survey/questionnaires/audit. During the discussion, feedback was also provided by a representative from the Dutch competent authorities (MEB). Even though Thalidomide Celgene is not launched in the Netherlands, experience on implementation of PPP for other products was shared.

5. New legislation: strengthening pharmacovigilance in the EU

This presentation provided a background to the new legislation on pharmacovigilance, the main changes of interest to the patients' and victims' organisations and the implementation plan.

Particularly, the upcoming call for expression of interest to be organised by the European Commission for nomination of patients' organisations representatives was highlighted to the participants.

6. Closing remarks & follow-up

The Rapporteur thanked the organisations for their participation in building this efficient risk management tool. The Co-Rapporteur concluded that RMP is a continuous process and that monitoring of its effectiveness will continue.

The Chair informed the participants that the Agency will continue sharing the PSUR assessment reports of Thalidomide Celgene as well as any information of interest on the medicinal product.

The Agency will consider the organisation of a future follow-up meeting after the 5-year renewal of the marketing authorisation (due April 2013).