5 March 2015
EMA/PDCO/17136/2015
Procedure Management and Business Support Division

Paediatric Committee (PDCO)

Minutes of the 14-16 January 2015 meeting

Chair: Dirk Mentzer - Vice-chair: Koenraad Norga

Disclaimers

Some of the information contained in the PDCO minutes is considered commercially confidential or sensitive and therefore not disclosed in the present minutes. With regards to therapeutic indications listed against products it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. The procedures discussed by the PDCO are on-going and therefore certain aspects of them are considered confidential. Additional details on these procedures will be disclosed in the PDCO Committee meeting reports (after the PDCO Opinion is adopted), and on the Opinions and decisions on paediatric investigation plans webpage (after the EMA Decision is issued). Documents mentioned in these minutes cannot be released at present as they are currently in draft format or are classified as confidential. They will become public when adopted in their final form or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006). Of note, this set of minutes is a working document primarily designed for PDCO members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents under Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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I Introduction

I.1 Adoption of the minutes from previous meeting

The Minutes of the PDCO plenary session held on 10-12 December 2014 were adopted.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000192.jsp&mid=WC0b01ac0580028eab

I.2 Adoption of the Agenda

The agenda was adopted with amendments.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000192.jsp&mid=WC0b01ac0580028eab

I.3 Declaration of Conflict of Interest

Please refer to the Annex of this document.

I.4 External attendance

Please refer to the Annex of this document.

I.5 Leaving/New Members and Alternates

Please refer to the January 2015 PDCO monthly report published on the EMA Website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000192.jsp&mid=WC0b01ac0580028eab

II Opinions

II.1 Opinions on Products

II.2 Opinions on Compliance Check

II.3 Opinions on Modification of an Agreed Paediatric Investigation Plan

Please refer to the January 2015 PDCO monthly report published in the EMA Website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000192.jsp&mid=WC0b01ac0580028eab

III Discussion of applications

The PDCO discussed 72 procedures in total[1], of which:

- 24 paediatric investigation plan applications;
- 9 product-specific waiver applications;

[1] The procedures discussed by the PDCO are on-going and therefore are considered confidential. Additional details on these procedures will be disclosed in the PDCO Committee meeting reports (after the PDCO Opinion is adopted), and on the Opinions and decisions on paediatric investigation plans webpage (after the EMA Decision is issued).

- 4 compliance check procedures (interim and final);
- 35 requests for modifications of an agreed paediatric investigation plan.

IV Nomination

IV.1 Nomination of Rapporteurs and Peer reviewers

• List of letters of intent received for submission of applications with start of procedure March 2015[1] for Nomination of Rapporteur and Peer reviewer • Nomination of Rapporteur for requests of confirmation on the applicability of the EMA decision on class waiver	The PDCO approved the lists of Rapporteurs and Peer Reviewers.

IV.2 Nomination for other activities

• PDCO representation within coordination group of Enpr-EMA: expiry of 3-year term.	The Committee was informed that, due to the expiry of the 3-year term of PDCO representatives within coordination group of Enpr-EMA, there is a need to renew previous or nominate new representatives. PDCO members were invited to express their interest to participate in this activity. The renewed or new representatives will be nominated by the Committee at the February 2015 meeting.

V Update and finalisation of opinions and requests for modification

The opinions adopted during the Paediatric Committee meeting of January 2015 are published in the same month's meeting report published in the EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000192.jsp&mid=WC0b01ac0580028eab.

VI Discussion on the applicability of class waiver

Active substance	Proposed indication	Condition	Outcome	Potential paediatric interest of this medicine suggested by PDCO
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	Treatment of metastatic or unresectable, well differentiated, midgut neuroendocrine tumours, which overexpress	Treatment of gastroentero-pancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglio-blastoma,	Positive	Neuroblastomas, Medulloblastomas and Ewing sarcomas

	somatostatin receptors	phaeochromocytoma)		
Ramucirumab	• Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy; • Cyramza monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for which treatment in combination with paclitaxel is not appropriate. Proposed indications: • Treatment of non-small cell lung cancer (NSCLC); • Treatment of hepatocellular cancer; • Treatment of gastric cancer (other than second line); • Treatment of colorectal cancer; • Treatment of bladder cancer.	• Treatment of lung carcinoma (small and non-small cell carcinoma); • Treatment of liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma); • Treatment of gastric adenocarcinoma; • Treatment of adenocarcinoma of the colon and rectum; • Treatment of ureter and bladder carcinoma.	Positive	Paediatric solid tumours

VII Discussion on the inclusion of an indication within a condition in an agreed PIP/waiver

No requests were received for the month of January.

VIII Annual reports on deferrals

Annual report based on PIP decision for	Substances (abbrev.)	Product Name	Orphan	Difficulties progressing the PIP?	Outcome
EMEA-000479-PIP01-08-M02	insulin aspart insulin degludec	Ryzodeg	No	No	The PDCO noted the report.
EMEA-000409-PIP01-08	Sodium (4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4...	Tivicay	No	No	The PDCO noted the report.
EMEA-001032-PIP01-10	Macitentan	Macitentan	Planned	Yes	The PDCO was informed that the PIP was not progressing as planned.
EMEA-001181-PIP01-11	AGOMELATINE	Valdoxan, Thymanax	No	Yes	The PDCO was informed about a delay of the PIP. A modification procedure addressing the issue is ongoing.
EMEA-001276-PIP01-12	Sofosbuvir	Sovaldi	No	No	The PDCO noted the report.
EMEA-000311-PIP01-08	ustekinumab	Stelara	No	No	The PDCO noted the report.
EMEA-000311-PIP03-11	ustekinumab	Stelara	No	No	The PDCO noted the report.
EMEA-000139-PIP01-07	N.meningitidis 961c purified antigen / N.meningitidis 287-953 purified antigen	Bexsero	No	No	The PDCO was informed about a delay of the PIP. The applicant plans to submit a request for modification of the agreed PIP by the end of 2015.
EMEA-001308-PIP01-12	Paclitaxel	Abraxane	Yes	No	The PDCO noted the

Annual report based on PIP decision for	Substances (abbrev.)	Product Name	Orphan	Difficulties progressing the PIP?	Outcome
					report

IX Other topics

Guidelines	
Guideline on the evaluation of medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing Johannes Taminiau	The paediatric part of the guideline was presented and adopted by the PDCO.
Working groups	
Formulation Working Group work plan Brian Aylward	The PDCO was informed about the review of the time points in the PDCO procedures when input from the FWG will be required. The FWG Chair reported that a work plan of the working group is being drafted.
Update on the work of the Paediatric Inventory Working Group Birka Lehmann	The Chair of the Paediatric Inventory Working Group provided feedback on the progress made on two lists under development (i.e. in the areas of gastroenterology and endocrinology). The first lists are expected to be circulated to NCAs for comments at the next PDCO meeting.
Outcome of the PDCO Optimisation Working Group held in December 2014	The PDCO agreed with two proposals with a view to improving operation and efficiency of PDCO meetings: • Organisational Matters (ORGAM) meetings will be held monthly, in between plenary meetings. Agenda topics now included in the section 'Other topics' will be grouped, prioritised and discussed during ORGAM meetings. Topics that require face-to-face discussion/decision will still be included in the PDCO plenary agenda. PDCO members will receive technical/logistic information in the post-meeting mailing; • Rapporteur/peer reviewers are requested to attend plenary meetings in person when their procedures are included in the PDCO agenda. In case they are not able to attend the meeting at the EMA, they should delegate their presentation (e.g. to colleagues from same delegation or peer reviewer or EMA Paediatric Coordinator). Requests to participate via TC are accepted, in liaison with the PDCO Chair, only in

	exceptional circumstances.
D30 Products identified for the Non-Clinical Working Group Jacqueline Carleer	Report noted.
Product-related topics	
Art.31 Referral of Codeine: PDCO responses to the PRAC questions Angeliki Siapkara	The PDCO discussed and adopted the final responses to the PRAC questions on the Art.31 referral of codeine for the treatment of cough and cold. The adopted responses will be sent to the PRAC.
CHMP update on paediatric topics	The PDCO members were informed about one medicinal product with paediatric indication adopted by CHMP in December 2014.
Other topics	
Adaptive pathways – update on pilot phase	The Committee was informed of the status of the adaptive pathways pilot project.
Debriefing on outcome of Review and Reconnect exercise for Paediatrics	The Committee was informed of the implementation of an optimisation exercise aiming to streamline the existing Paediatric procedures and tools. Once the draft processes will be ready for discussion, PDCO members will be involved in their design and implementation. PDCO members joined the Chair in welcoming this initiative and expressed their interest in participating in its phases.
PDCO class waiver list review Koen Norga, Henk van den Berg	Comments on the class waiver list were discussed. The PDCO was informed on the EMA discussions concerning the decision-making on an Opinion.
Draft FDA Paediatric Clinical Pharmacology guidance	The Committee noted the publication for comments of the guidance.
Revision of the standard allergen PIP	The PDCO considered revising the standard allergen PIP in order to facilitate recruitment of patients with allergic rhinoconjunctivitis in long-term trials. One of the options would be to add the condition prevention of asthma to PIPs on allergic rhinitis/ rhinoconjunctivitis.
Paediatric considerations on Ebola	
In view of the current Ebola virus disease epidemic in West Africa, the PDCO considered that the needs of the paediatric population should be taken in account in the development of medicinal products for treatment and prevention of Ebola. While Ebola viral disease seems to affect children proportionally less than adults, still more than 13% of patients affected in the current epidemic in West Africa are below the age of 15 (WHO Ebola Response Team, N Engl J Med 2014; 371:1481-1495). Consequently, clinical studies with children appear	

necessary for both prevention and treatment of the disease.

The PDCO therefore wishes to advise companies developing these products to engage with the European Medicines Agency and apply for a Paediatric Investigation Plan as early as possible, if Marketing Authorisation in the European Union is planned, to prevent delays in the authorisation procedures. Modifications to the agreed PIP are of course possible at any stage after adoption of the PIP decision, and the PDCO pledges to provide opinions on both PIP and modification requests in the shortest possible time.

The clinical experience with products for the **treatment** or prevention of Ebola virus disease is still quite limited.

The PDCO reflects that development programs for the treatment of Ebola virus disease should consider the following:

- Studies to treat Ebola disease in children should be properly conducted, in principle as randomised controlled studies with appropriate comparator. Scientifically, placebo-controlled trials are recognised as being an optimal way of generating evidence on safety and efficacy, and from that perspective are the preferred option for clinical trials of therapeutic options in the treatment of Ebola virus. However it is also recognised that, despite the safety and efficacy of a particular intervention being unproven, local authorities and investigators might not accept to randomise patients to placebo in the context of treatment of Ebola virus disease based on ethical considerations. In light of these potential issues, well-justified alternative development strategies may also be acceptable.
- Considering the high mortality of the disease and lack of specific treatments, children and adolescents up to 18 years of age could be studied at the same time as adults in safety and efficacy studies. However, it is recommended that proposals are made on how to generate information to ensure appropriate and safe dosing in children. If children and adolescents are included in adult trials, they should constitute an appropriate proportion of participants, based on the incidence rates observed in the current epidemic.

The PDCO further reflects that development programs for **vaccines for the prevention** of Ebola virus disease should consider the following:

- Studies in children and adolescents appear necessary in the development of Ebola vaccines. In principle, immunogenicity and safety data are needed in all paediatric age groups. Immunobridging with extrapolation of efficacy may be proposed for some or all the age groups, with proper justification and a Data Safety Monitoring Board should be included in all trials.
- Considering the population distribution in Africa, in principle paediatric immunogenicity and safety studies should commence with as little delay as possible in relation to adult trials, in an appropriate and proportionate number of children and adolescents. However, clinical studies in children should start only after a sufficient number of adult participants have received the product and have been observed for a suitable period of time. Adolescents can be included in adult trials.

Finally, the PDCO invites pharmaceutical companies, to contact the European Medicines Agency at any time for a pre-submission meeting on paediatric development.

Involvement of PDCO in Art. 46 procedures and MAA procedures	The Committee discussed the possibility of nominating routinely a PDCO Peer Reviewer for all CHMP procedures of paediatric relevance (Art. 46 procedures; Marketing authorisations, new indications, routes or pharmaceutical forms where a PIP has been agreed). Concerns for the

	workload were expressed. It was agreed that PDCO Secretariat will provide, every month, a list of the new submissions to the CHMP that have potential paediatric relevance, for prioritisation of those which may benefit from support from the PDCO.
Outcome of Scientific Advice / Protocol Assistance with Start of Procedure December 2014 with paediatric questions	Selected SAWP procedures were discussed by the PDCO.
Improvement of SAWP-PDCO interactions Karl-Heinz Huemer	A presentation was given in order to inform PDCO members about the different steps of a SA procedure and related documents.
Information on neonatal activities	The PDCO was informed about topics discussed at the neonatal break out session. First announcement of the neonatal meeting organised by EnprEMA on 17 March 2015.
Breakout sessions	
Inventory: Gastroenterology	The draft list for Gastroenterology was discussed.
Inventory: Endocrinology	The draft list for Endocrinology was discussed.
Neonatology	Discussions took place around the Neonatal Guideline, collaboration approaches and contribution to neonatal meetings and neonatal PIPs.
Paediatric oncology	The group met in the margins of the plenary meeting.
PDCO Optimisation Exercise	Further meetings to be scheduled in 2Q2015.

Annex to the Minutes of the PDCO of January 2015

The List of participants includes any restrictions with respect to the involvement of members / alternates / experts following evaluation of declared interests for the meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Dirk Mentzer	Chair	Germany	Full involvement	
Karl-Heinz Huemer	Member	Austria	Full involvement	
Christoph Male	Alternate	Austria	No participation in discussions, final deliberations and voting	EMEA-001203-PIP02-14 EMEA-001229-PIP01-11-M01
Koenraad Norga	Member	Belgium	Full involvement	
Jacqueline Carleer	Alternate	Belgium	Full involvement	
Violeta Iotova	Member	Bulgaria	No participation in discussions, final deliberations and voting	EMEA-000916-PIP01-10-M04 EMEA-000783-PIP01-09-M02 EMEA-001324-PIP01-12-M01 EMEA-000470-PIP01-08-M09 EMEA-001030-PIP01-10-M03 EMEA-000479-PIP01-08-M03 EMEA-000694-PIP02-14 EMEA-001175-PIP01-11-M02
Marina Dimov Di Giusti	Alternate	Croatia	Full involvement	
Georgios Savva	Member	Cyprus	Full involvement	
Jaroslav Sterba	Member	Czech Republic	No participation in final deliberations and voting	EMEA-001627-PIP01-14 EMEA-001638-PIP01-14
Marianne Orholm	Member	Denmark	Full involvement	
Irja Lutsar	Member	Estonia	Full involvement	
Ann Marie Kaukonen	Member	Finland	Full involvement	
Maija Pihlajamaki	Alternate	Finland	Full involvement	
Sylvie Benchetrit	France	France	Full involvement	
Birka Lehmann	Member	Germany	Full involvement	
Immanuel Barth	Alternate	Germany	Full involvement	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ágnes Gyurasics	Member	Hungary	Full involvement	
Gylfi Oskarsson	Member	Iceland	Full involvement	
Brian Aylward	Member	Ireland	Full involvement	
Paolo Rossi	Member	Italy	Full involvement	
Francesca Rocchi	Alternate	Italy	Full involvement	
Dina Apele-Freimane	Member	Latvia	Full involvement	
Carola de Beaufort	Member	Luxembourg	Full involvement	
Hendrik van den Berg	Member	Netherlands	Full involvement	
Siri Wang	Member	Norway	Full involvement	
Ine Skottheim Rusten	Alternate	Norway	Full involvement	
Marek Migdal	Member	Poland	No participation in final deliberations and voting	EMEA-001699-PIP01-14 EMEA-000018-PIP01-07-M09 EMEA-001713-PIP02-14 EMEA-001700-PIP01-14
Jolanta Witkowska-Ozogowska	Alternate	Poland	Full involvement	
Helena Fonseca	Member	Portugal	Full involvement	
Hugo Tavares	Alternate	Portugal	Full involvement	
Dana Gabriela Marin	Member	Romania	Full involvement	
Michaela Meciakova	Member	Slovakia	Full involvement	
Stefan Grosek	Member	Slovenia	Full involvement	
Fernando de Andrés Trelles	Member	Spain	Full involvement	
Maria Jesús Fernández Cortizo	Alternate	Spain	Full involvement Connected via teleconference for EMEA-001577-PIP02-14 and EMEA-001313-PIP01-12-M03	
Ninna Gullberg	Member	Sweden	Full involvement	
Anna-Karin Hamberg	Alternate	Sweden	Full involvement	
Angeliki Siapkara	Member	United Kingdom	Full involvement	
Martina Riegl	Alternate	United Kingdom	Full involvement	
Paolo Paolucci	Alternate	Healthcare Professionals' Representative	Full involvement	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Johannes Taminiau	Member	Healthcare Professionals' Representative	Full involvement	
Doina Plesca	Alternate	Healthcare Professionals' Representative	No participation in discussions, final deliberations and voting	EMEA-001691-PIP01-14 EMEA-001087-PIP02-12-M01
Riccardo Riccardi	Member	Healthcare Professionals' Representative	Full involvement	
Paola Baiardi	Alternate	Patients' Organisation Representative	Full involvement	
Michal Odermarsky	Member	Patients' Organisation Representative	No participation in discussions, final deliberations and voting	EMEA-001577-PIP02-14 EMEA-001219-PIP01-11-M01 EMEA-000409-PIP01-08-M03 EMEA-001676-PIP01-14 EMEA-001695-PIP01-14
Tsveta Schyns-Liharska	Member	Patients' Organisation Representative	Full involvement	
Katherine McGinn	Expert - in person*	United Kingdom	Full involvement	
Susanne Kaul	Expert - via telephone*	Germany	Full involvement	
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the product(s) they have been invited to talk about.