EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 May 2013
EMA/PDCO/215721/2013
Human Medicines Development and Evaluation

Paediatric Committee (PDCO)

Minutes of the 10-12 April 2013 meeting

Chair: Daniel Brasseur

I Introduction

I.1 Adoption of the minutes from previous meeting

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

Adopted with modifications

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

See Annex I

I.4 External attendance

Please refer to the April 2013 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

I.5 Leaving/New Members and Alternates

Please refer to the April 2013 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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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 April 2013 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 66 procedures in total[1], of which:

- 33 paediatric investigation plan applications;
- 10 product-specific waiver applications;
- 3 compliance check procedures (interim and final);
- 20 requests for modifications of an agreed paediatric investigation plan.

IV Nomination of Rapporteurs and Peer reviewers

• List of letters of intent received for submission of applications with start of procedure June 2013[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.

V Update and finalisation of opinions and requests for modification

All opinions taken at this meeting (relating to adoption of opinions, recommendations, requests for modifications and applicability of class waivers) were made in the presence of the required quorum of members.

The opinions adopted during the Paediatric Committee meeting of April 2013 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.

[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).

VI Discussion on the applicability of class waiver

Class waiver number	Active substance	Proposed indication	Class-waived condition	Outcome
EMEA-02-2013	RO5424802	Treatment of non-small cell lung cancer	Treatment of lung carcinoma (small cell and non-small cell carcinoma)	Confirmed
EMEA-03-2013	Ixazomib citrate	1) Treatment of newly diagnosed multiple myeloma 2) Treatment of relapsed and/or refractory multiple myeloma	Treatment of multiple myeloma	Confirmed
EMEA-04-2013	Ibrutinib 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4 d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (EMEA-001397-PIP01-12)	Treatment of chronic lymphocytic leukaemia	Treatment of Chronic lymphocytic leukaemia	Confirmed
EMEA-05-2013	Ibrutinib 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4 d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (EMEA-001397-PIP01-12)	Treatment of follicular lymphoma	Treatment of Follicular lymphoma	Confirmed

Class waiver number	Active substance	Proposed indication	Class-waived condition	Outcome
EMEA-06-2013	Ibrutinib 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4 d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (EMEA-001397-PIP01-12)	Treatment of multiple myeloma	Treatment of Multiple myeloma	Confirmed
EMEA-07-2013	simtuzumab (GS-6624)	Treatment of metastatic colorectal adenocarcinoma	Treatment of adenocarcinoma of the colon and rectum	Confirmed
EMEA-08-2013	simtuzumab (GS-6624)	Treatment of primary, Post-Polycythemia Vera, and Post-Essential Thrombocythemia Myelofibrosis	Treatment of Myelofibrosis	Confirmed
EMEA-09-2013	simtuzumab (GS-6624)	Treatment of Metastatic Pancreatic Adenocarcinoma	Treatment of adenocarcinoma of the pancreas	Confirmed
EMEA-10-2013	Bay 86-9766, RDEA 119 (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide INN: Refametinib	Treatment of unresectable hepatocellular carcinoma alone or in combination with sorafenib in first line patients with RAS mutations	Treatment of liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma)	Confirmed

Class waiver number	Active substance	Proposed indication	Class-waived condition	Outcome
EMEA-11-2013	Bay 86-9766, RDEA 119 (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide INN: Refametinib	First line treatment of locally advanced, inoperable, or metastatic pancreatic cancer in combination with gemcitabine for those whom systemic palliative treatment with gemcitabine is indicated	Treatment of adenocarcinoma of the pancreas	Confirmed
EMEA-12-2013	Aleglitazar - RO0728804	Delay of the onset of type 2 diabetes in patients with cardiovascular disease and pre-diabetes	Peroxisome proliferator-activated receptor (PPAR)-gamma modulators, including dual and multiple PPAR modulators (e.g., thiazolidinediones, glitazars, triple modulators), in the treatment of type II diabetes mellitus (EMEA/386453/2008)	Not confirmed
EMEA-13-2013	HuMax-CD38 (Daratumumab)	Treatment of multiple myeloma	Treatment of multiple myeloma	Confirmed
EMEA-14-2013	5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine Company code: LDK378	treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)	Treatment of lung carcinoma (small cell and non-small cell carcinoma)	Confirmed

Class waiver number	Active substance	Proposed indication	Class-waived condition	Outcome
EMEA-15-2013	Moxetumomab pasudotox	Treatment of relapsed or refractory hairy cell leukaemia	Treatment of Hairy cell leukemia	Confirmed
EMEA-16-2013	Carfilzomib (Kyprolis)	Treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior therapies that included bortezomib and an immunomodulatory agent.	Treatment of multiple myeloma	Confirmed
EMEA-17-2013	Sulodexide (DOVIDA 2700 UI Anti Xa capsule soft)	Treatment of peripheral arterial disease due to atherosclerosis	Treatment of peripheral atherosclerosis	Confirmed

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

PIP number	Active substance	Proposed indication	Condition	Outcome
EMEA-000200-PIP01-08	Saxagliptin	Reduction of major CV events in patients with Type 2 diabetes who also have CV risk factors or established CV disease	Treatment of patients with type 2 Diabetes Mellitus	The PDCO considered the prevention of cardiovascular events in patients with type 2 diabetes a separate condition compared to treatment of type 2 diabetes. The applicant will have to address the proposed indication in a separate PIP or product-specific waiver request.
EMEA-000978-PIP01-10	Vemurafenib	Vemurafenib in combination with cobimetinib for the treatment of adult patients with unresectable or	Treatment of melanoma	The PDCO confirmed that the proposed indication was covered by the PIP condition. However, it was

		metastatic melanoma with BRAFV600 mutations		highlighted that the association with cobimetinib might influence the induction or inhibition of metabolic enzymes. Pharmacokinetics data should therefore be obtained in adolescents.

VIII Annual reports on deferrals

Annual report based on PIP decision for	Substances (abbrev.)	Product Name	Orphan drug	Difficulties progressing the PIP?	Outcome
EMEA-000065-PIP01-07-M03	Telbivudine	Sebivo	No	No	
EMEA-000116-PIP01-07-M05	Retigabine	Trobalt	No	No	
EMEA-000470-PIP01-08-M06	Sitagliptin	Januvia (and related products)	No	No	
EMEA-000696-PIP02-10-M02	Eslicarbazepine acetate	Exalief, Zebinix	No	Yes	The PDCO was informed that, depending on the analysis of ongoing studies, a modification of an agreed PIP might be applied for.

IX Other topics

Guidelines	
Draft guideline on the clinical investigation of medicinal products for the treatment of urinary incontinence	The committee discussed the feedback that was received from the Consistency Group on the paediatric part of the draft guideline. In line with the discussion the proposed wording was amended. A response will be sent to the Consistency Group.
Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia	The draft guideline has been adopted in March 2013 by CHMP and is opened for public consultation until 31 August 2013.

(EMA/CHMP/153191/2013)	
Working groups	
Paediatric inventory	The inventory discussed the ongoing lists for nephrology and neurology. In general it was decided to include the neonatal age group within the different therapeutic areas. These should be made available to neonatal experts, preterm infants should be considered specifically. A separate neonatal list, cross-referring to the other therapeutic areas and potentially including conditions only occurring in the newborn period is still considered necessary.
Paediatric oncology	The group discussed the forthcoming virtual meeting of the Paediatric oncology task force at the EMA, recent journal publications and development of paediatric medicines for neuroblastoma and lymphoma.
Formulation	No non-product related issues where reported to the Committee.
Non-Clinical	No non-product related issues where reported to the Committee.
Extrapolation	The group discussed the draft proposal to update the summary report to enable a focused discussion on extrapolation. A number of changes were proposed which will be implemented with a view to circulate to the group for endorsement before the next meeting.
Other topics	
Questionnaire for children and young people*	PDCO members were thanked for the great response to translating the questionnaire. Translations in Danish, Flemish, Slovak, Romanian, German, Spanish, French, and Dutch have been received. Helpful comments and suggestions were also received from other countries, namely Ireland and Italy. In order to move forward, and to identify a way of validating the questionnaire and develop an introductory video that would be considered suitable for this target audience, it was considered to participate in the EU Patient forum on their EMPATHY workshop for young people in July 2013.
1. Feedback from Workshop on Paediatric Investigation Plans in Type 2 Diabetes Mellitus on 25 February 2013	The draft minutes and conclusions of the workshop were presented to the PDCO. It was acknowledged that many paediatric patients will be required to complete all the agreed PIPs, although development is not simultaneous for all products. Among the conclusions the following points were highlighted: Faster beta cell destruction in children is associated with the need for paediatric efficacy data, but the extent of such data may be discussed (i.e. stronger role of extrapolation such as use of Bayesian methods or lower

	significance levels). Once paediatric data for the first product(s) from different classes becomes available, greater extrapolation and/or reduced requirements may be acceptable. Companies may wish to consider applying for modification of agreed PIPs according to proposals made during the meeting to make them more feasible and in line with the therapeutic needs (i.e. broadening of inclusion criteria, multi- or single company, multi-agent studies, simplification of PK studies, limited duration of placebo-controlled treatment phase, focus on investigations as add-on to metformin). The minutes and presentations from the meeting will be published shortly on the EMA website.
Summary of ongoing EMA investigation on pancreatic risks with GLP-1-based therapies	The article, *Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans (n=8) with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors*, published 22 March 2013, Diabetes raised concerns on potential pancreatic risks with GLP-1-based therapies. The Agency is currently reviewing the issue under Article 5(3) of Regulation (EC) 726/2004. The PDCO has agreed 11 PIPs with incretin-based therapies and will closely follow the current review by CHMP.
Revision of the Priority list of off-patent medicines	The revised priority list for off-patent medicines for children was adopted for public consultation.
Reflexion* on the revocation of the EMA decision on the list of class waiver	The PDCO discussed further comments of PDCO members on a number of the class waivers and on the development strategy for medicines, including paediatric medicines, as well as the next steps. It is planned to adopt an opinion in June.
Standard Allergen PIP	Changes to the Standard Allergen PIP, proposed by the working group, concerning the design and timing for initiation of immunotherapy paediatric trials were adopted by the PDCO. The revised document will be published on the website shortly.
Performance indicators and parameters for the 10-year report on the Paediatric Regulation	The PDCO discussed the progress in drafting a plan for the data collection and analysis to be used for the future reporting.
Presentation of the Annual report on rewards and incentives 2012* to the European Commission	A presentation of the main findings that are included in the 2012 Annual Report to the EC was given. The Report is planned to be sent by the Agency to the Commission by

(Art 50.1)	30 April 2012.
Template and guidance for Summary of Opinion*	The PDCO was informed that template and guidance are still under internal revision at the Agency.
Overview of CHMP Opinions	The PDCO members were informed about the final CHMP opinions adopted in March 2013 on medicinal products with paediatric interest. The PDCO members discussed the consequences and the appropriate action to be taken following the negative CHMP opinion on Kynamro (mipomersen).
Outcome of Scientific Advice / Protocol Assistance with Start of Procedure March 2013 with paediatric questions	The team from the Scientific Advice Section gave a presentation, with an update on the current procedures for Scientific Advice that include paediatric questions.
FIP-WHO TECHNICAL GUIDELINES: PROVISION BY HEALTH-CARE PROFESSIONALS OF CHILDREN-SPECIFIC PREPARATIONS THAT ARE NOT AVAILABLE AS AUTHORIZED PRODUCTS – POINTS TO CONSIDER	The revised WHO guideline on *Provision by health-care professionals of children-specific preparations that are not available as authorised products – points to consider* has been released for another external consultation, and was presented briefly to the PDCO. The guideline provides advice on compounded and modified (manipulated) formulations and it is important to assure that the advice given in the guideline would be acceptable from the EU perspective. PDCO Members were asked to review the guideline and provide their comments. A 2-week consultation phase within the Committee was agreed, with a deadline for written comments by 26th of April 2013.

Any other business

Note on access to documents

Documents marked with an asterisk* in these minutes cannot be released at present as they are currently in draft format. They will become public when adopted in their final form.

Annex I to the Minutes of the PDCO of April 2013

Documentation on Declaration of interest of members, alternates and experts

Based on the Declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of Committee members for the upcoming discussions.

In accordance with the Agency's revised Policy and Procedure on the handling of conflicts of interests, participants in this meeting were asked to declare any conflict of interests on the matters for discussion (in particular any changes, omissions or errors to the already declared interests).

Member, alternate, expert name	Outcome restriction following evaluation of electronic Declaration of Interests	Topics on the current Committee Agenda for which this restriction applies
Adriana Ceci	Restriction level DP	EMEA-000366-PIP02-09-M02
Adriana Ceci	Restriction level XR	EMEA-000087-PIP01-07-M03
Adriana Ceci	Restriction level DP	EMEA-001039-PIP02-12
Adriana Ceci	Restriction level DP	EMEA-001366-PIP01-12
Adriana Ceci	Restriction level XR	EMEA-14-2013
Alexandra Compagnucci	Restriction level XR	EMEA-001405-PIP01-12
Alexandra Compagnucci	Restriction level XR	EMEA-14-2013
Alexandra Compagnucci	Restriction level XR	EMEA-15-2013
Carine de Beaufort	Restriction level XR	EMEA-02-2013
Carine de Beaufort	Restriction level XR	EMEA-10-2013
Carine de Beaufort	Restriction level XR	EMEA-11-2013
Carine de Beaufort	Restriction level XR	EMEA-12-2013
Christoph Male	Restriction level XP	EMEA-000480-PIP01-08-M05
Dobrin Konstantinov	Restriction level DP	EMEA-000469-PIP01-08-M04
Dobrin Konstantinov	Restriction level XP	EMEA-001301-PIP02-12
Dobrin Konstantinov	Restriction level XP	EMEA-001301-PIP01-12
Gerard Pons	Restriction level DP	EMEA-000402-PIP02-11
Jaroslav Sterba	Restriction level XP	EMEA-000469-PIP01-08-M04
Jaroslav Sterba	Restriction level XP	EMEA-001397-PIP01-12
Jaroslav Sterba	Restriction level XP	EMEA-001259-PIP02-13

Member, alternate, expert name	Outcome restriction following evaluation of electronic Declaration of Interests	Topics on the current Committee Agenda for which this restriction applies
Jaroslav Sterba	Restriction level XP	EMEA-000227-PIP02-12
Jaroslav Sterba	Restriction level XP	EMEA-05-2013
Jean-Pierre Aboulker	Restriction level XR	EMEA-14-2013
Jean-Pierre Aboulker	Restriction level XR	EMEA-15-2013
Kolbeinn Gudmundson	Restriction level DP	EMEA-17-2013
Matthias Keller	Restriction level XR	EMEA-000366-PIP02-09-M02
Matthias Keller	Restriction level 4	EMEA-001305-PIP01-12
Paolo Rossi	Restriction level XR	EMEA-000576-PIP03-12
Paolo Rossi	Restriction level XR	EMEA-000469-PIP01-08-M04
Tadej Avcin	Restriction level XP	EMEA-000366-PIP02-09-M02

Note: the procedures identified in the table above are on-going and therefore considered commercially 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).

No new or additional conflicts were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Scientific Committee members and, where relevant, experts attending the plenary meeting, as announced by the Scientific Committee Secretariat at the start of meeting.

Restriction levels:

Evaluation of the conflict of interest	
Outcome	Impact
R-P	To be replaced for the discussions, final deliberations and voting as appropriate in relation to the relevant product or a competitor product.
XP	Where Individual product involvement is declared - PRODUCT INDICATION: - No involvement with respect to procedures involving the relevant product or a competitor product in the relevant indication i.e. no part in discussions, final deliberations and voting as appropriate as regards these medicinal products. - Cannot act as Rapporteur for these products - [Cannot act as Rapporteur for development of guidelines in concerned therapeutic area].
XC	Where cross product / general involvement is declared - COMPANY: - No involvement (as outlined above) with respect to products from the specified company. - Cannot act as Rapporteur for products from the relevant company(ies).

DP	Where Individual product involvement is declared - PRODUCT INDICATION: - Involvement in discussions only with respect to procedures involving the relevant product or a competitor product i.e. no part in final deliberations and voting as appropriate as regards these medicinal products. - Cannot act as Rapporteur for these products.
DC	Where cross product / general involvement is declared - COMPANY: - Involvement in discussions only with respect to products from the specified company. - Cannot act as Rapporteur on products from the relevant company(ies).
XR	Committee member cannot act as Rapporteur or Peer reviewer in relation to any medicinal product from the relevant company.
R-C	To be replaced for the discussions, final deliberations and voting as appropriate in relation to any medicinal product from the relevant company

Annex II to the Minutes of the PDCO of April 2013

List of Participants

Chair

Daniel BRASSEUR

Vice-chair

Dirk MENTZER

Members appointed by Member States or CHMP

Christoph MALE	Austria
Koenraad NORGA	Belgium
Dobrin KONSTANTINOV	Bulgaria
Jaroslav STERBA	Czech Republic
Marianne ORHOLM	Denmark
Pirjo LAITINEN-PARKONNEN	Finland
Gerard PONS	France
Dirk MENTZER	Germany
Stefanos MANTAGOS	Greece
Agnes GYURASICS	Hungary
Gylfi OSKARSSON	Iceland
Kevin CONNOLLY	Ireland
Paolo ROSSI	Italy
Dina APELE-FREMIANE	Latvia
Carine de BEAUFORT	Luxembourg
Hendrik van den BERG	The Netherlands
Siri WANG	Norway
Marek MIGDAL	Poland
Helena FONSECA	Portugal
Vlasta KAKOSOVA	Slovak Republic
Janez JAZBEC	Slovenia
Fernando DE ANDRÉS TRELLES	Spain

Marta GRANSTRÖM	Sweden
Julia DUNNE	United Kingdom

Alternates appointed by Member States or CHMP

Karl Heinz HUEMER	Austria
Jacqueline CARLEER	Belgium
Ann Marie KAUKONEN	Finland
Sylvie BENCHETRIT	France
Birka LEHMANN	Germany
Pending	Greece
Brian AYLWARD	Ireland
Francesca ROCCHI	Italy
Pending	Latvia
Johannes TAMINIAU	The Netherlands
Jolanda WITKOWSKA-OZOGOWSKA	Poland
Dana Gabriela MARIN	Romania
Viveca Lena ODLIND	Sweden
Angeliki SIAPKARA	United Kingdom

Members representing patients' organisations

Tsveta SCHYNS-LIHARSKA

Members representing health care professionals

Adriana CECI

Jean Pierre ABOULKER

Anthony James NUNN

Alternates representing health care professionals

Paolo PAOLUCCI

Experts

Peter BAUER	Medical statistician

European Medicines Agency

Agnes SAINT RAYMOND	Head of Sector, Human Medicines Special Areas
Paolo TOMASI	Head of Section, Paediatric Medicines
Sophie OLIVIER	Scientific Administrator, Paediatric Medicines

Anne-Sophie HENRY-EUDE	Scientific Administrator, Paediatric Medicines
Almudena SAIZ HERRANZ	Scientific Administrator, Paediatric Medicines
Benjamin PELLE	Scientific Administrator, Paediatric Medicines
Chrissi Pallidis	Scientific Administrator, Paediatric Medicines
Dobromir PENKOV	Scientific Administrator, Paediatric Medicines
Elin Haf DAVIES	Scientific Administrator, Paediatric Medicines
Giovanni LESA	Scientific Administrator, Paediatric Medicines
Gunter EGGER	Scientific Administrator, Paediatric Medicines
Irmgard EICHLER	Scientific Administrator, Paediatric Medicines
Janina KARRES	Scientific Administrator, Paediatric Medicines
Peter KÁROLYI	Scientific Administrator, Paediatric Medicines
Ralf HEROLD	Scientific Administrator, Paediatric Medicines
Ralph BAX	Scientific Administrator, Paediatric Medicines
Richard VESELY	Scientific Administrator, Paediatric Medicines
Thorsten OLSKI	Scientific Administrator, Paediatric Medicines
Alessandro JENKNER	National Expert on Secondment, Paediatric Medicines
Cristina BEJNARIU	Trainee
Aneta KRZYSCIAK	Assistant, Paediatric Medicines
Isabel PEREZ	Assistant, Paediatric Medicines
Sunni HOLTMAN	Assistant, Paediatric Medicines