24 August 2018
EMA/PDCO/582591/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Paediatric Committee (PDCO)

Minutes of the written procedure of 21-24 August 2018

Chair: Dirk Mentzer – Vice-Chair: Koenraad Norga

Disclaimers

Some of the information contained in this set of minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes 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. Additional details on some of these procedures will be published 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).

Of note, this set of minutes is a working document primarily designed for PDCO members and the work the Committee undertakes.

Further information with relevant explanatory notes can be found at the end of this document.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of 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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1. Introductions

1.1. Adoption of agenda

The agenda was adopted.

1.2. Adoption of the minutes

The minutes of the July 2018 PDCO were adopted and will be published on the EMA website.

2. Opinions

Disclosure of some information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

2.1. Opinions on Products

2.1.1. Atorvastatin calcium trihydrate/ Indapamide/ / Perindopril arginine - EMEA-002395-PIP01-18

Les Laboratoires Servier; Treatment of Cardiovascular diseases, Prevention of Cardiovascular diseases

Day 60 opinion

Cardiovascular Diseases

Summary of committee discussion:

Based on the assessment of this application the PDCO agrees with the applicant's request for a waiver. The PDCO recommends granting a waiver for Atorvastatin calcium trihydrate / Indapamide / Perindopril arginine for all subsets of the paediatric population (0 to 18 years of age) in the condition of Treatment of Cardiovascular diseases and Prevention of Cardiovascular diseases.
The PDCO emphasises that the granting of a waiver for the condition mentioned above should not prevent the applicant from considering a development in the paediatric population in indications where there is a paediatric need.

2.1.2. 3-(3-(3,5-Dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid - EMEA-002363-PIP01-18

Eidos Therapeutics, Inc.; Treatment of transthyretin-mediated amyloidosis (ATTR amyloidosis)

Day 60 opinion

Cardiovascular Diseases / Neurology

Summary of committee discussion:

Based on the assessment of this application the PDCO agrees with the applicant's request for a waiver. The PDCO recommends granting a waiver for 3-(3-(3,5-Dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid for all subsets of the paediatric population (0 to 18 years of age) in the condition of Treatment of transthyretin amyloidosis (ATTR amyloidosis).

2.1.3. Cell-free solution of lysed Escherichia coli culture, strain Laves - EMEA-002393-PIP01-18

Laves-Arzneimittel GmbH; Treatment of irritable bowel syndrome, treatment of colitis (excluding infective)

Day 60 opinion

Gastroenterology-Hepatology

Summary of committee discussion:

Based on the assessment of this application the PDCO agrees with the applicant's request for a waiver. The PDCO recommends granting a waiver for Cell-free solution of lysed Escherichia coli culture, strain Laves for all subsets of the paediatric population (0 to 18 years of age) in the condition of Treatment of irritable bowel syndrome, treatment of colitis (excluding infective).

2.1.4. Ianalumab - EMEA-002338-PIP02-18

Novartis Europharm Limited; Primary Sjögren's Syndrome (pSS)

Day 60 opinion

Immunology-Rheumatology-Transplantation

Summary of committee discussion:

A positive Opinion was adopted at Day 60.
Based on the assessment of this application, the PDCO agrees with the applicant's request for a waiver. The PDCO recommends granting a waiver for ianalumab for all subsets of the paediatric population (0 to 18 years of age) in the condition of treatment of Sjögren's Syndrome.

2.1.5. Sarilumab - EMEA-001045-PIP02-18

Sanofi-aventis recherche et développement; Vasculitides

Day 60 opinion

Immunology-Rheumatology-Transplantation

Summary of committee discussion:

The PDCO confirmed the outcome of the Day 30 discussion and agreed with the applicant's request for a waiver. The PDCO granted a full product-specific waiver for sarilumab, a monoclonal antibody directed against the interleukin (IL)-6 receptor for children from birth to less than 18 years of age for the condition "treatment of vasculitides" due to expected lack of significant therapeutic benefit over existing treatments.
The PDCO emphasises that the granting of a waiver for the condition mentioned above should not prevent the applicant from considering a development in the paediatric population in indications where there is a paediatric need.

2.1.6. A synthetic ribonucleic acid oligonucleotide directed against superoxide dismutase 1 (SOD1) messenger ribonucleic acid - Orphan - EMEA-002403-PIP01-18

Biogen Idec Ltd; Treatment of Amyotrophic lateral sclerosis

Day 60 opinion

Neurology

Summary of committee discussion:

Based on the assessment of this application the PDCO agrees with the applicant's request for a waiver.
The PDCO recommends granting a waiver for synthetic ribonucleic acid oligonucleotide directed against superoxide dismutase 1 (SOD1) messenger ribonucleic acid for all subsets of the paediatric population (0 to 18 years of age) in the condition of Treatment of amyotrophic lateral sclerosis.

2.1.7. Autologous dendritic cells pulsed with allogeneic tumour cell lysate - Orphan - EMEA-002381-PIP01-18

Amphera BV; Treatment of malignant mesothelioma

Day 60 opinion

Oncology

Summary of committee discussion:

Based on the assessment of this application, the PDCO agrees with the applicant's request for a waiver. The PDCO recommends granting a waiver for Autologous dendritic cells pulsed with allogeneic tumour cell lysate for all subsets of the paediatric population (0 to 18 years of age) in the condition of Treatment of malignant mesothelioma.
The PDCO emphasises that the granting of a waiver for the condition mentioned above should not prevent the applicant from considering a development in the paediatric population in indications where there is a paediatric need.

2.1.8. Brentuximab vedotin - Orphan - EMEA-000980-PIP04-18

Takeda Pharma A/S; Treatment of mature T and NK neoplasms (excluding anaplastic large-cell lymphoma and cutaneous T-cell lymphoma)

Day 60 opinion

Oncology

Summary of committee discussion:

The PDCO's view expressed at Day 30 was endorsed.
Based on the assessment of this application, the PDCO agrees with the applicant's request for a waiver. The PDCO recommends granting a waiver for brentuximab vedotin for all subsets of the paediatric population (from birth to less than 18 years of age) in the condition of 'treatment of mature T and NK neoplasms (excluding anaplastic large-cell lymphoma and cutaneous T-cell lymphoma)', it was also agreed to remove the T-cell lymphoma from the condition as that condition is already covered by another product-specific waiver (EMEA-000980-PIP02-15, P/0168/2015).
The applicant is recommended however to consider to open the adult studies to paediatric patients when appropriate, to allow the inclusion of those rare paediatric patients that have tumour types in common with adult patients.
The PDCO emphasises that the granting of a waiver for the condition mentioned above should not prevent the applicant from considering a development in the paediatric population in indications where there is a paediatric need.

2.1.9. Pamiparib - EMEA-002389-PIP01-18

BeiGene, Ltd.; Treatment of gastric and gastroesophageal junction adenocarcinoma

Day 60 opinion

Oncology

Summary of committee discussion:

The view expressed at Day 30 has been confirmed by the PDCO. The additional information provided following the Day 30 discussion are acknowledged.
Overall, the PDCO agrees with the applicant's request for a waiver. The PDCO recommends granting a waiver for pamiparib for all subsets of the paediatric population (0 to 18 years of age) in the condition of 'treatment of gastric and gastroesophageal junction adenocarcinoma'.

2.1.10. Diphtheria Toxin Interleukin-3 Fusion Protein - Orphan - EMEA-002244-PIP02-18

Stemline Therapeutics, Inc.; Treatment of blastic plasmacytoid dendritic cell neoplasm

Day 60 opinion

Oncology

Summary of committee discussion:

Based on the assessment of this application, the PDCO agrees with the applicant's request for a waiver. The PDCO recommends granting a waiver for Diphtheria Toxin Interleukin-3 Fusion Protein for all subsets of the paediatric population (0 to 18 years of age) in the condition of Treatment of blastic plasmacytoid dendritic cell neoplasm.

2.1.11. Telisotuzumab vedotin - EMEA-002361-PIP01-18

AbbVie Ltd.; Lung carcinoma (small cell and non-small cell carcinoma)

Day 60 opinion

Oncology

Summary of committee discussion:

The PDCO adopted a positive opinion in line with comments previously raised at Day 30. Based on the assessment of this application, the PDCO agrees with the applicant's request for a waiver. The PDCO recommends granting a waiver for telisotuzumab vedotin for all subsets of the paediatric population (0 to 18 years of age) in the condition of treatment of lung carcinoma (small cell and non-small cell carcinoma).

2.1.12. Eflapegrastim - EMEA-002385-PIP01-18

Spectrum Pharmaceuticals, Inc.; Treatment of Chemotherapy- Induced Neutropenia / Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Day 60 opinion

Oncology / Haematology-Hemostaseology

Summary of committee discussion:

The PDCO adopted a negative Opinion on this full waiver request for eflapegrastim, a novel long-acting recombinant human G-CSF analogue for the treatment of chemotherapy- induced neutropenia on 24 August 2018, in line with the detailed discussion during the July 2018 PDCO plenary.
The PDCO considers that long acting G-CSF preparations are still needed in children of all age ranges for the treatment of chemotherapy- induced neutropenia (no long acting G-CSF preparations are currently authorized for treating children with chemotherapy-induced neutropenia).

2.2. Opinions on Compliance Check

The members of the PDCO have been invited to comment on issues of possible non-compliance

2.2.1. Ticagrelor - EMEA-C2-000480-PIP01-08-M11

AstraZeneca AB; Prevention of thromboembolic events

Day 30 letter

Cardiovascular Diseases

Summary of committee discussion:

The PDCO considered this partial compliance check in line with the comments provided by the assessment team and considered that the completed studies are compliant with the latest Agency's Decision (P/0205/2018) of 19 July 2018.

2.2.2. Bedaquiline (fumarate) - EMEA-C2-000912-PIP01-10-M03

Janssen-Cilag International NV; Treatment of multi-drug resistant tuberculosis

Day 30 letter

Infectious Diseases

Summary of committee discussion:

The completed study was checked for compliance.
The PDCO considered that the completed study is compliant with the latest Agency's Decision (P/0371/2016) of 04 January 2017.
The PDCO finalised on 24 August 2018 this partially completed compliance procedure and confirmed the compliance of all those studies contained in the agreed paediatric investigation plan that were to be completed until this date.

2.2.3. Lamivudine (3TC) / Dolutegravir (DTG) - EMEA-C1-001940-PIP01-16-M01

ViiV Healthcare UK Limited; Treatment of human immunodeficiency virus (HIV-1) infection

Day 30 letter

Infectious Diseases

Summary of committee discussion:

The completed study(ies) was/were checked for compliance.
The PDCO discussed the completed study and considered that it was compliant with the latest Agency's Decision (P/0151/2018) of 18 May 2018.
The PDCO finalised on 24 August 2018 this partially completed compliance procedure.

2.2.4. Ataluren - EMEA-C3-000115-PIP01-07-M09

PTC Therapeutics International, Limited; Duchenne/Becker Muscular Dystrophy

Day 30 letter

Neurology

Summary of committee discussion:

The completed study was checked for compliance.
The completed study is compliant with the latest Agency's Decision (P/0393/2017 of 19 December 2017).
The PDCO finalised on 24 August 2018 this partially completed compliance procedure and confirmed the compliance of all those studies contained in the agreed paediatric investigation plan that were to be completed until this date.

2.2.5. Larotrectinib - EMEA-C1-001971-PIP02-16-M01

Bayer AG; Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haemtopoietic and lymphoid tissue neoplasms).

Day 30 letter

Oncology

Summary of committee discussion:

The studies checked for compliance were considered compliant with the latest Agency's Decision (P/0182/2018) of 15 June 2018.
The PDCO finalised on 24 August 2018 this partially completed compliance procedure and confirmed the compliance of all those studies/key elements contained in the agreed paediatric investigation plan that were to be completed until this date.

2.2.6. Glycerol Phenylbutyrate - EMEA-C-000297-PIP02-12-M02

Horizon Pharma Ireland Limited; Treatment of Urea Cycle Disorders

Day 30 discussion

Action: For comments (adoption in September).

Endocrinology-Gynaecology-Fertility-Metabolism

2.2.7. Luspatercept - EMEA-C1-001521-PIP01-13-M02

Celgene Europe Ltd; Treatment of beta-thalassaemia

Day 30 adoption

Haematology-Hemostaseology

The completed studies were checked for compliance.
The PDCO discussed the completed studies and considered that these are compliant with the latest Agency's Decision (P/0122/2018) of 11 April 2018.
The PDCO finalised on 24 August 2018 this partially completed compliance procedure and confirmed the compliance of all those studies contained in the agreed paediatric investigation plan that were to be completed until this date.

2.3. Opinions on Modification of an Agreed Paediatric Investigation Plan

No items

2.4. Opinions on Re-examinations

No items

2.5. Opinions on Review of Granted Waivers

No items

2.6. Finalisation and adoption of opinions

No items

2.7. Partial Compliance Checks completed by EMA

No items

3. Comments on Products

Disclosure of some information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

3.1. Comments on Products D60-D30

3.1.1. EMEA-002378-PIP01-18

Treatment of acute heart failure

RfM-Day 60

Cardiovascular Diseases

3.1.2. Dihomo-γ-linolenic acid (DGLA) - EMEA-002364-PIP01-18

Treatment of moderate to severe atopic dermatitis

RfM-Day 60

Dermatology

3.1.3. Dihomo-γ-linolenic acid (DGLA) - EMEA-002364-PIP02-18

Treatment of atopic dermatitis / Treatment of pruritus associated with mild to moderate atopic dermatitis, Treatment of mild to moderate atopic dermatitis

RfM-Day 60

Dermatology

3.1.4. Pyridoxal 5'-phosphate monohydrate - Orphan - EMEA-002404-PIP01-18

Medicure Pharma Europe Limited; Treatment of pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency

RfM-Day 60

Endocrinology-Gynaecology-Fertility-Metabolism

3.1.5. Tirzepatide - EMEA-002360-PIP01-18

Treatment of Type 2 diabetes mellitus

RfM-Day 60

Endocrinology-Gynaecology-Fertility-Metabolism

3.1.6. Iclaprim mesylate - EMEA-002391-PIP01-18

Infection with Gram-positive bacteria / Treatment of acute bacterial skin and skin structure infections caused by susceptible strains of Gram-positive bacteria

RfM-Day 60

Infectious Diseases

3.1.7. Oteseconazole - EMEA-002392-PIP01-18

Treatment of vulvovaginal candidiasis

RfM-Day 60

Infectious Diseases

3.1.8. Ofatumumab - EMEA-002397-PIP01-18

Treatment of relapsing remitting multiple sclerosis

RfM-Day 60

Neurology

3.1.9. Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signaling domains - Orphan - EMEA-002369-PIP01-18

Celgene Europe Limited; Treatment of mature B-cell neoplasms / Treatment of pediatric BCMA+ relapsed or refractory B non-Hodgkin lymphoma

RfM-Day 60

Oncology

3.1.10. Vinorelbine Tartrate (liposomal) - EMEA-002365-PIP01-18

Treatment of osteosarcomas, treatment of rhabdomyosarcoma, treatment of Ewing's

sarcoma, treatment of non-rhabdomyosarcoma soft-tissue sarcomas / treatment of relapsed or refractory Ewing's sarcoma, treatment of relapsed or refractory rhabdomyosarcoma, treatment of relapsed or refractory osteosarcomas, treatment of relapsed or refractory non-rhabdomyosarcoma soft-tissue sarcomas

RfM-Day 60

Oncology

3.1.11. Benzimidazole-containing ENaC inhibitor - EMEA-002394-PIP01-18

Treatment of cystic fibrosis / Improve lung function and reduce pulmonary exacerbations for patients with CF in conjunction with standard therapies

RfM-Day 60

Pneumology - Allergology

3.1.12. EMEA-002398-PIP01-18

Treatment of cystic fibrosis in individuals with cystic fibrosis who are homozygous for the F508del mutation and are receiving treatment with a CFTR modulator

RfM-Day 60

Pneumology - Allergology

3.1.13. Nintedanib - Orphan - EMEA-001006-PIP05-18

Boehringer Ingelheim International GmbH; Treatment of fibrosing Interstitial Lung Diseases (ILD)

RfM-Day 60

Pneumology - Allergology / Oncology

3.1.14. EMEA-002373-PIP01-18

Schizophrenia

RfM-Day 60

Psychiatry

3.2. Comments on Compliance Check

The members of the PDCO have been invited to comment on issues of possible non-compliance

3.2.1. Human normal immunoglobulin - EMEA-C-001797-PIP01-15-M01

Octapharma Pharmazeutika Produktionsges.m.b.H; Treatment of primary immunodeficiency

Day 30 discussion

Immunology-Rheumatology-Transplantation / Haematology-Hemostaseology

3.2.2. Ranibizumab - EMEA-C1-000527-PIP04-13-M01

Novartis Europharm Limited; Treatment of retinopathy of prematurity

Day 30 discussion

Ophthalmology

3.3. Discussions on Modification of an Agreed Paediatric Investigation Plan

No items

4. Nominations

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

4.1. List of letters of intent received for submission of applications with start of procedure 16 October 2018 or Nomination of Rapporteur and Peer reviewer

Summary of committee discussion:

The PDCO approved the lists of Rapporteurs and Peer Reviewers.

4.2. Nomination of Rapporteur for requests of confirmation on the applicability of the EMA decision on class waiver.

Summary of committee discussion:

The PDCO approved the lists of Rapporteurs and Peer Reviewers.

4.3. Nominations for other activities

No items

5. Scientific Advice Working Party (SAWP) and Paediatric Committee (PDCO) Interaction

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

6. Discussion on the applicability of class waivers

Disclosure of some information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

6.1. Discussions on the applicability of class waiver for products

No items

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

7.1. Discussion on the possibility to include an indication within a condition in an agreed PIP/waiver

No items

8. Annual reports on deferrals

No items

9. Organisational, regulatory and methodological matters

9.1. Mandate and organisation of the PDCO

No items

9.2. Coordination with EMA Scientific Committees or CMDh-v

No items

9.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

No items

9.4. Cooperation with International Regulators

No items

9.5. Contacts of the PDCO with external parties and interaction with the Interested Parties to the Committee

No items

9.6. PDCO work plan

No items

9.7. Planning and reporting

No items

10. Any other business

No items

11. Breakout sessions

No items

12. Explanatory notes

The Notes give a brief explanation of relevant agenda items and should be read in conjunction with the agenda.

Paediatric investigation plan (PIP) (section 2.1 Opinion on PIPs and section 3.1 Discussions on PIPs)
A paediatric investigation plan (PIP) is a development plan aimed at ensuring that the necessary data are obtained through studies in children, when it is safe to do so, to support the authorisation of a medicine for children. Pharmaceutical companies submit proposals for PIPs to the European Medicines Agency's Paediatric Committee (PDCO). This Committee is responsible for agreeing or refusing the plan.

Compliance checks (section 2.2 Opinions on Compliance check, section 3.2 Discussions on Compliance check)
A compliance check may be necessary before any application for marketing authorisation (even for an adult indication) can be considered valid, if there was no deferral for at least one of the studies agreed in the PIP, or after the due date of initiation or completion of a study/measure. The same applies to some regulatory applications for authorised products, as described above.

Modification of an Agreed Paediatric Investigation Plan (section 2.3 Opinions on Modification of an agreed PIP, section 3.3 Discussions on Modification of an agreed PIP)
The development plan for a medicine can be modified at a later stage as knowledge increases. Modifications can also be made if the applicant encounters such difficulties with the implementation of a PIP, which render it unworkable or no longer appropriate.
In some cases, studies can be deferred until after the studies in adults have been conducted. This ensures that research in children is done only when it is safe and ethical to do so. Even when studies are deferred, the PIP will include details of the paediatric studies and their timelines.

Class waiver (section 6 Discussion on the applicability of class waiver)
As some diseases do not affect children (for example Parkinson's disease), the development of medicines for these diseases should not be performed in children. In these cases, a PIP is not required and it will be waived**.** For more information on the classes of diseases subject to waivers, see class waivers.

Annual reports on deferrals (section 8)
If the medicinal product is approved in the EU, annual reports on the deferred measures in the PIP must be submitted to the Agency.

More detailed information on the above terms can be found on the EMA website:
www.ema.europa.eu/