EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines Pharmacovigilance and Committees Division

PDCO monthly report of opinions on paediatric investigation plans and other activities

20-23 June 2017

Opinions on paediatric investigation plans

The Paediatric Committee (PDCO) adopted opinions agreeing paediatric investigation plans (PIPs) for the following medicines:

- Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Victoria lineage) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Yamagata lineage) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H3N2) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H1N1), EMEA-002068-PIP01-16, from Seqirus UK Limited, for the prevention of influenza;
- Tocilizumab, EMEA-000309-PIP04-17, from Roche Registration Limited, for the treatment of systemic sclerosis;
- Liposomal combination of cytarabine and daunorubicin, EMEA-001858-PIP02-16, from Jazz Pharmaceuticals Ireland Limited, for the treatment of acute myeloid leukaemia;
- Venetoclax, EMEA-002018-PIP02-16, AbbVie Ltd, for the treatment of malignant neoplasms of the haematopoietic and lymphoid tissue and treatment of solid malignant tumours;
- Fc- and CDR-modified humanised monoclonal antibody against C5, EMEA-002077-PIP01-16, from Alexion Europe SAS, for the treatment of paroxysmal nocturnal haemoglobinuria.

The PDCO adopted an opinion on the **refusal** of a PIP for the following application:

- Methacholine chloride, EMEA-002120-PIP01-17, from MWK Healthcare Ltd, for the diagnosis of asthma.

For this product the PDCO granted a product-specific waiver on its own motion for all subsets of the paediatric population in the specified condition, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

A PIP sets out a programme for the development of a medicine in the paediatric population. The PIP aims to generate the necessary quality, safety and efficacy data through studies to support the authorisation of the medicine for use in children of all ages. These data have to be submitted to the European Medicines Agency, or national competent authorities, as part of an application for a marketing authorisation for a

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new medicine, or for one covered by a patent. In some cases, a PIP may include a waiver of the studies in one or more paediatric subsets, or a deferral.

Opinions on product-specific waivers

The PDCO adopted positive opinions for product-specific waivers, recommending that the obligation to submit data obtained through clinical studies with children be waived in all subsets of the paediatric population, for the following medicines:

- H-Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Lys-Leu-Ser-Ser-Ile-Glu-Ser-Asp-Val-OH (YGRKKRRQRRRKLSSIESDV), EMEA-002108-PIP01-16, from NoNO Inc., for the treatment of acute ischaemic stroke;
- DaxibotulinumtoxinA, EMEA-002149-PIP01-17, from Revance Therapeutics Inc, for the treatment of glabellar lines;
- Recombinant humanized anti-alpha-synuclein IgG1 monoclonal antibody, EMEA-002137-PIP01-17, from Roche Registration Limited, for the treatment of Parkinson's disease;
- 5,7-Dihydroxy-2-[3-hydroxy-4-methoxy-2-(2-methyl-2-propenyl)phenyl]-6,8-bis(2-methyl-2-propenyl)-4H-chromen-4-one, EMEA-002148-PIP01-17, from Ilkos Therapeutic Inc, for the treatment of venous and mixed (venous/arterial) leg ulcers;
- Empagliflozin, EMEA-000828-PIP05-17, from Boehringer Ingelheim International GmbH, for the prevention of cardiovascular events in patients with chronic heart failure;
- Macitentan, EMEA-001032-PIP02-17, from Actelion Registration Ltd., for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH);
- Diclofenac sodium, EMEA-002132-PIP01-17, from Dimethaid (UK) Limited, for the treatment of inflammation and treatment of pain;
- Pexastimogene devacirepvec, EMEA-002124-PIP01-17, from Transgene S.A., for the treatment of hepatocellular carcinoma;
- Osimertinib (as mesylate), EMEA-002125-PIP01-17, from AstraZeneca AB, for the treatment of lung carcinoma (small cell and non-small cell carcinoma).

Waivers can be issued if there is evidence that the medicine concerned is likely to be ineffective or unsafe in the paediatric population, or that the disease or condition targeted occurs only in adult populations, or that the medicine, or the performance of trials, does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Opinions on modifications to an agreed PIP

The PDCO also adopts, every month, opinions on modifications to an agreed PIP, which can be requested by the applicant when the plan is no longer appropriate or when there are difficulties that render the plan unworkable. The PDCO adopted positive opinions, agreeing change(s), for the following products:

- Ivacaftor / lumacaftor, EMEA-001582-PIP01-13-M06, from Vertex Pharmaceuticals (Europe) Limited, for the treatment of cystic fibrosis;
- Dolutegravir / abacavir / lamivudine, EMEA-001219-PIP01-11-M03, from ViiV Healthcare UK Limited, for the treatment of human immunodeficiency virus (HIV-1) infection;

- Recombinant fusion protein linking coagulation factor IX with albumin, EMEA-001107-PIP01-10-M03, from CSL Behring GmbH, for the treatment of hereditary factor IX deficiency;
- Apixaban, EMEA-000183-PIP01-08-M05, from Bristol-Myers Squibb / Pfizer EEIG, for the prevention of arterial thromboembolism and prevention of venous thromboembolism;
- Allantoin, EMEA-001590-PIP01-13-M04, from Scioderm, Inc., for the treatment of epidermolysis bullosa;
- Brentuximab vedotin, EMEA-000980-PIP01-10-M05, from Takeda Pharma A/S, for the treatment of Hodgkin lymphoma and treatment of anaplastic large cell lymphoma;
- Elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide, EMEA-001460-PIP01-13-M02, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus (HIV-1) infection;
- Coagulation Factor VIIa (Recombinant), EMEA-001203-PIP02-14-M02, from LFB SA, for the treatment of acquired haemophilia and treatment of congenital coagulation disorders;
- Damoctocog alfa pegol, EMEA-001229-PIP01-11-M03, from Bayer AG, for the treatment of hereditary factor VIII deficiency;
- Obeticholic Acid (6 alpha-ethylchenodeoxycholic acid), EMEA-001304-PIP02-13-M03, from Intercept Pharma Ltd., for the treatment of biliary atresia and treatment of primary biliary cirrhosis;
- Sotagliflozin, EMEA-001517-PIP01-13-M01, from sanofi-aventis R&D, for the treatment of type 2 diabetes mellitus;
- Sotagliflozin, EMEA-001517-PIP02-14-M01, from sanofi-aventis R&D, for the treatment of type 1 diabetes mellitus;
- Canagliflozin, EMEA-001030-PIP01-10-M07, from Janssen-Cilag International NV, for the treatment of type 2 Diabetes Mellitus;
- Zanamivir, EMEA-001318-PIP01-12-M02, from GlaxoSmithKline Trading Services Limited, for the prevention of influenza and treatment of influenza;
- Liraglutide, EMEA-000128-PIP01-07-M08, from Novo Nordisk A/S, for the treatment of type 2 diabetes mellitus;
- Semaglutide, EMEA-001441-PIP02-15-M01, from Novo Nordisk, for the treatment of type 2 diabetes mellitus;
- Bivalent anti-human myostatin adnectin recombinant human IgG1-Fc fusion protein, EMEA-001793-PIP01-15-M02, from Bristol-Myers Squibb International Corporation, for the treatment of Duchenne Muscular Dystrophy;
- Romiplostim, EMEA-000653-PIP01-09-M05, from Amgen Europe B.V., for the treatment of disease-related thrombocytopenia in myelodysplastic syndrome and treatment of immune thrombocytopenia (idiopathic thrombocytopenic purpura);
- Recombinant Varicella Zoster Virus (VZV) glycoprotein E, EMEA-001426-PIP01-13-M01, from GlaxoSmithKline Biologicals SA, for the prevention of varicella zoster virus (VZV) reactivation;
- Treosulfan, EMEA-000883-PIP01-10-M04, from medac Gesellschaft für klinische Spezialpräparate mbH, for the conditioning treatment prior to haematopoietic progenitor cell transplantation;

- Decitabine, EMEA-000555-PIP01-09-M06, from Janssen-Cilag International NV, for the treatment of acute myeloid leukaemia;
- Asfotase alfa, EMEA-000987-PIP01-10-M03, from Alexion Europe SAS, for the treatment of hypophosphatasia;
- Luspatercept, EMEA-001521-PIP01-13-M01, from Celgene Europe Ltd, for the treatment of myelodysplastic syndromes and treatment of beta-thalassaemia;
- Sodium zirconium cyclosilicate, EMEA-001539-PIP01-13-M02, from AstraZeneca AB, for the treatment of hyperkalaemia;
- Recombinant Fusion Protein Linking Coagulation Factor VIIa with Albumin (rVIIa-FP), EMEA-001886-PIP01-15-M01, from CSL Behring GmbH, for the treatment of Haemophilia A and treatment of Haemophilia B;
- Recombinant Fusion Protein Linking Coagulation Factor VIIa with Albumin (rVIIa-FP), EMEA-001886-PIP02-15-M01, from CSL Behring GmbH, for treatment of congenital Factor VII deficiency.

The PDCO adopted an opinion on the **refusal** of modification to an agreed PIP for the following application:

- Chlorhexidine gluconate / isopropyl alcohol, EMEA-000989-PIP01-10-M02, from 3M Health Care Limited, for the prevention of infection prior to invasive procedures.

For this product the PDCO granted a product-specific waiver on its own motion for all subsets of the paediatric population in the specified condition, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Opinion on compliance check

The PDCO adopted positive opinions on (full) compliance check for:

- Split influenza virus, inactivated containing antigen equivalent to A/H3N2-like strain / Split influenza virus, inactivated containing antigen equivalent to B-like strain (B/Yamagata lineage) / Split influenza virus, inactivated containing antigen equivalent to B-like strain (B/Victoria lineage) / Split influenza virus, inactivated containing antigen equivalent to A/H1N1-like strain, EMEA-C-001254-PIP01-11-M02, from Sanofi Pasteur SA, for the prevention of influenza infection.

A compliance check is performed to verify that all the measures agreed in a PIP and reflected in the Agency's decision have been conducted in accordance with the decision, including the agreed timelines. Full compliance with all studies/measured contained in the PIP is one of several prerequisites for obtaining the rewards and incentives provided for in Articles 36 to 38 of the Paediatric Regulation.

Before the submission of a request for a compliance check, applicants are encouraged to consult the Agency's Procedural advice for validation of a new marketing authorisation application or extension/variation application and compliance check with an agreed PIP.

Adoption of an opinion following re-examination

The PDCO adopted opinions for the following products:

- Following the re-examination of the positive opinion on a modification of an agreed PIP adopted on 19 May 2017 for ivacaftor, EMEA-001640-PIP01-14-M02, from Vertex Pharmaceuticals (Europe) Ltd., for

the treatment of cystic fibrosis, the PDCO recommended to revise its opinion and to agree to the changes regarding the measures in the scope set out in the Annex I of the opinion.

- Following the re-examination of the positive opinion on a modification of an agreed PIP adopted on 21 April 2017 for rivaroxaban, EMEA-000430-PIP01-08-M10, from Bayer Pharma AG, for the prevention of thromboembolic events and treatment of thromboembolic events, the PDCO recommended to revise its opinion and to agree to the changes regarding the measures in the scope set out in the Annex I of the opinion.

A re-examination of the opinion can be requested by the applicant within 30 days following receipt of the opinion of the PDCO. The grounds for the re-examination should be based only on the original information and scientific data provided in the application that were previously available to the PDCO and on which the initial opinion was based. This may include new analysis of the same data or minor protocol amendments to a previously proposed study. Significant changes to the previous plan cannot be part of the re-examination process.

Written procedures

The PDCO adopted positive opinions for the following products:

- Apremilast, EMEA-000715-PIP05-13-M01, from Celgene Europe Limited, for the treatment of Behcets Disease, on 14 June 2017;
- Raltegravir, EMEA-C-000279-PIP01-08-M05, from Merck Sharp & Dohme (Europe), Inc., for the treatment of Human Immunodeficiency Virus (HIV-1) infection, on 19 June 2017.

Withdrawals

The PDCO noted that 1 application was withdrawn during the late stages of the evaluation (30 days or less before completion of the procedure).

Other matters

The PDCO Chair welcomed the new member from Lithuania, Sigita Burokiene.

The PDCO Chair welcomed the new alternate from Lithuania, Goda Vaitkeviciene.

The PDCO thanked Marta Granström for her work at the end of her mandate as alternate for Denmark.

The next meeting of the PDCO will be held on 18-21 July 2017.

– END –

Notes:

1. As of 26 January 2009, pharmaceutical companies that submit an application for a marketing authorisation for a medicinal product, or those that submit an application for an extension of indication, a new route of administration, or a new pharmaceutical form of a medicinal product already authorised in the European Union, have to provide either the results of studies in children conducted in accordance with an approved PIP, or an Agency's decision on a waiver or on a deferral.

2. PDCO opinions on PIPs and waivers are transformed into Agency's decisions within the timeframe laid down by the Paediatric Regulation (Regulation (EC) No 1901/2006, as amended). The decisions can be found on the Agency's website at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d129

3. More information about the PDCO and the Paediatric Regulation is available in the Regulatory section of the Agency's website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cd

4. This meeting report, together with other information on the work of the Agency's, can be found on the Agency's website: http://www.ema.europa.eu

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