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Inspections, Human Medicines Pharmacovigilance and Committees Division

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

13-16 November 2018

Opinions on paediatric investigation plans

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

- Bilastine, EMEA-000347-PIP02-16, from Faes Farma S.A., for the treatment of allergic conjunctivitis;
- Semaglutide, EMEA-001441-PIP03-17, from Novo Nordisk A/S, for the treatment of obesity;
- Bupivacaine / Meloxicam, EMEA-002246-PIP01-17, from Heron Therapeutics, B.V., for the treatment of acute postoperative pain;
- Rezafungin acetate, EMEA-002319-PIP01-17, from Cidara Therapeutics, Inc., for the treatment of invasive candidiasis;
- Evinacumab, EMEA-002298-PIP01-17, from Regeneron Ireland U.C., for the treatment of elevated cholesterol;
- Bupivacaine, EMEA-000877-PIP03-17, from Pacira Ltd, for the postsurgical analgesia;
- Ibrutinib, EMEA-001397-PIP04-17, from Janssen-Cilag International NV, for the treatment of chronic graft versus host disease (cGvHD)

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 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.

Adoption of an opinion following re-examination

The PDCO adopted opinions for the following products:

- Following the re-examination of the positive opinion on modification to an agreed PIP with a deferral

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adopted on 19 October 2018 for Autologous CD34+ hematopoietic stem cells transduced ex vivo with EFS lentiviral vector encoding for the human adenosine deaminase gene, EMEA-001974-PIP01-16-M02, from Orchard Therapeutics Limited, for the treatment of severe combined immunodeficiency due to adenosine deaminase deficiency, the PDCO adopted a revised positive opinion and

  - agreed to the changes regarding the measures of the paediatric investigation plan in the scope set out in Annex I of the opinion and
  - granted a deferral

- Following the re-examination of the positive opinion on modification to an agreed PIP with a deferral and a waiver adopted on 21 September 2018 for Peanut allergen extract, EMEA-001481-PIP01-13-M03, from DBV Technologies S.A, for the treatment of peanut allergy, the PDCO recommended to maintain its opinion and agreed to the changes regarding the measures and the timelines of the paediatric investigation plan in the scope set out in 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.

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:

- Synthetic double-stranded siRNA oligonucleotide targeted against transthyretin mRNA, with six phosphorothioate linkages in the backbone, and nine 2'-fluoro and thirty-five 2'-O-methyl nucleoside residues in the sequence, which is covalently linked via a phosphodiester group to a ligand containing three N- acetylgalactosamine residues, EMEA-002425-PIP01-18, from Alnylam Netherlands BV, for the treatment of transthyretin-mediated amyloidosis (ATTR amyloidosis);
- Germanium (68Ge) chloride / Gallium (68Ga) chloride, EMEA-002436-PIP01-18, from ITG Isotope Technologies Garching GmbH, for the radiolabelling agent;
- Anti-VEGF and anti-DLL4 dual variable domain immunoglobulin, EMEA-002420-PIP01-18, from AbbVie Ltd., for the treatment of colorectal malignant neoplasms;
- Palbociclib, EMEA-002146-PIP02-18, from Pfizer Europe MA EEIG, for the treatment of breast malignant neoplasms;
- Bruton's tyrosine kinase inhibitor, EMEA-002438-PIP01-18, from Principia Biopharma, Inc., for the treatment of Pemphigus;

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:

- Pimodivir, EMEA-001975-PIP01-16-M02, from Janssen-Cilag International NV, for the treatment of influenza;
- Ceftobiprole medocaril (sodium), EMEA-000205-PIP02-11-M03, from Basilea Pharmaceutica International Ltd., for the treatment of pneumonia;
- Dolutegravir, EMEA-000409-PIP01-08-M05, from ViiV Healthcare UK Ltd., for the human immunodeficiency virus (HIV-1) infection;
- Pazopanib, EMEA-000601-PIP01-09-M05, from Novartis Europharm Limited, for the treatment of Ewing sarcoma family of tumours, treatment of non-rhabdomyosarcoma soft tissue sarcoma and treatment of rhabdomyosarcoma;
- Dolutegravir / abacavir / lamivudine, EMEA-001219-PIP01-11-M04, from ViiV Healthcare UK Limited, for the treatment of human immunodeficiency Virus (HIV-1) infection;
- Rabeprazole (sodium), EMEA-000055-PIP01-07-M06, from Eisai Limited, for the treatment of duodenal ulcer, treatment of gastric ulcer, treatment of Helicobacter pylori in patients with peptic ulcer disease, treatment of Zollinger-Ellison syndrome and treatment of gastro-oesophageal reflux disease;
- Bedaquiline (fumarate), EMEA-000912-PIP01-10-M04, from Janssen-Cilag International NV, for the treatment of multi-drug resistant tuberculosis;
- Fenfluramine (hydrochloride), EMEA-001990-PIP01-16-M02, from Zogenix International Ltd, for the treatment of Dravet syndrome;
- Lumacaftor / ivacaftor, EMEA-001582-PIP01-13-M08, from Vertex Pharmaceuticals (Europe) Limited, for the treatment of cystic fibrosis;
- Darunavir / cobicistat, EMEA-001280-PIP01-12-M02, from Janssen-Cilag International NV, for the treatment of HIV-1 infection;
- Axicabtagene ciloleucel, EMEA-002010-PIP01-16-M01, from Kite Pharma EU B.V., for the treatment of mature B-cell neoplasms;
- Tisagenlecleucel, EMEA-001654-PIP01-14-M03, from Novartis Europharm Limited, for the treatment of B cell acute lymphoblastic leukaemia/lymphoblastic lymphoma;
- Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured, EMEA-001862-PIP01-15-M01, from Kite Pharma EU B.V., for the treatment of acute lymphoblastic leukaemia;
- Sildenafil, EMEA-000671-PIP01-09-M10, from Pfizer Limited, for the treatment of pulmonary arterial hypertension;

Opinion on compliance check

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

- Belimumab, EMEA-C-000520-PIP01-08-M05, from Glaxo Group Limited, for the treatment of systemic lupus erythematosus;
- Fidaxomicin, EMEA-C-000636-PIP01-09-M07, from Astellas Pharma Europe B.V., for the treatment of enterocolitis caused by *Clostridium difficile*;

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/measures 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.

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 next meeting of the PDCO will be held on 11-14 December 2018.

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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: https://www.ema.europa.eu/en/medicines/ema_group_types/ema_pip
3. More information about the PDCO and the Paediatric Regulation is available in the Regulatory section of the Agency's website: https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines-overview
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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