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Inspections, Human Medicines Pharmacovigilance and Committees Division

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

16-19 October 2018

Opinions on paediatric investigation plans

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

- Evobrutinib, EMEA-002284-PIP01-17, from Merck KGaA, for the treatment of multiple sclerosis;
- Brincidofovir, EMEA-001904-PIP02-17, from Chimerix UK Limited, for the treatment of adenovirus in immunocompromised patients;
- Calcifediol, EMEA-002093-PIP02-17, from Vifor Fresenius Medical Care Renal Pharma France, for the treatment of secondary hyperparathyroidism (SHPT);
- Upadacitinib, EMEA-001741-PIP04-17, from AbbVie Ltd, for the treatment of atopic dermatitis;
- Janus Kinase-1 inhibitor, EMEA-002312-PIP01-17, from Pfizer Ltd, for the treatment of atopic dermatitis;
- Eubacterial Spores, Purified Suspension, Encapsulated, EMEA-001970-PIP02-17, from Seres Therapeutics UK Ltd., for the treatment of Clostridium difficile infection;
- Brigatinib, EMEA-002296-PIP01-17, from Takeda Pharm A/S, for the treatment of inflammatory myofibroblastic tumors, treatment of anaplastic large cell lymphoma and treatment of non-small cell lung cancer;
- Brincidofovir, EMEA-001904-PIP03-18, from Chimerix UK Limited, for the treatment of smallpox;
- Cenicriviroc, EMEA-001999-PIP02-17, from Allergan Pharmaceuticals International Limited, for the treatment of non-alcoholic steatohepatitis (NASH);
- Ixekizumab, EMEA-001050-PIP02-18, from Eli Lilly & Company Limited, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis and juvenile idiopathic arthritis);

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

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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.

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:

- Molibresib, EMEA-002406-PIP01-18, from GlaxoSmithKline Trading Services Limited, for the treatment of breast cancer;
- Crizotinib, EMEA-001493-PIP02-18, from Pfizer Limited, for the treatment of lung malignant neoplasms;
- Ipatasertib, EMEA-002396-PIP01-18, from Roche Registration GmbH, for the treatment of breast cancer and treatment of prostate cancer;
- Levodopa / carbidopa monohydrate / entacapone, EMEA-002421-PIP01-18, from LobSor Pharmaceuticals AB, for the treatment of Parkinson's disease and parkinsonism;
- Alectinib, EMEA-002431-PIP01-18, from Roche Registration GmbH, for the treatment of non-small cell lung cancer;
- Sarilumab, EMEA-001045-PIP04-18, from Sanofi-aventis recherche et développement, for the treatment of polymyalgia rheumatica;
- Dapagliflozin, EMEA-000694-PIP04-18, from AstraZeneca AB, for the treatment of chronic kidney disease;
- Flurpiridaz F18, EMEA-002413-PIP01-18, from GE Healthcare, Inc., for the diagnosis of coronary artery disease;
- Ibuprofen, EMEA-002400-PIP01-18, from Medherant Ltd., for the treatment of pain;
- Avadomide, EMEA-002405-PIP01-18, from Celgene Europe Limited, for the treatment of mature B-cell neoplasms;
- Atorvastatin / ezetimibe, EMEA-002410-PIP01-18, from QualipharmaCon Kft., for the treatment of hypercholesterolaemia;
- Pemigatinib, EMEA-002370-PIP01-18, from Incyte Biosciences Distribution B.V., for the treatment of cholangiocarcinoma and treatment of urothelial carcinoma;
- Selinexor, EMEA-002387-PIP01-18, from Karyopharm Europe GmbH, for the treatment of multiple myeloma;

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:

- Lenvatinib, EMEA-001119-PIP02-12-M04, from Eisai Europe Ltd, for the treatment of osteosarcoma, treatment of follicular thyroid cancer and treatment of papillary thyroid cancer;
- Idelalisib, EMEA-001350-PIP02-13-M04, from Gilead Sciences International Ltd, for the treatment of mature B-cell neoplasm;
- Certolizumab pegol, EMEA-001071-PIP03-14-M01, from UCB Pharma SA, for the treatment of psoriasis;
- Conestat alfa, EMEA-000367-PIP01-08-M08, from Pharming Group N.V., for the treatment of hereditary angioedema (HAE);
- Apremilast, EMEA-000715-PIP05-13-M03, from Celgene Europe Limited, for the treatment of Behcet's disease;
- Peanut flour, EMEA-001734-PIP01-14-M03, from Aimmune Therapeutics, for the treatment of peanut allergy;
- Ex vivo expanded human autologous epithelium containing stem cells, EMEA-001082-PIP02-11-M02, from Chiesi Farmaceutici S.p.A., for the treatment of limbal stem cell deficiency due to ocular burns;
- Nanobody directed towards the fusion protein of human respiratory syncytial virus, EMEA-001553-PIP01-13-M02, from Ablynx NV, for the treatment of lower respiratory tract disease caused by human respiratory syncytial virus (RSV);
- Idasanutlin, EMEA-001489-PIP01-13-M01, from Roche Registration GmbH, for the treatment of acute lymphoblastic leukaemia, treatment of acute myeloid leukaemia and treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue);
- Potassium citrate monohydrated / potassium hydrogen carbonate, EMEA-001357-PIP01-12-M02, from Advicenne Pharma, for the treatment of renal tubular acidosis;
- Dabigatran etexilate mesilate, EMEA-000081-PIP01-07-M11, from Boehringer Ingelheim International GmbH, for the prevention of thomboembolic events and treatment of thromboembolic events;
- Ixekizumab, EMEA-001050-PIP01-10-M04, from Eli Lilly & Company Limited, for the treatment of psoriasis;
- Ivacaftor, EMEA-000335-PIP01-08-M13, from Vertex Pharmaceuticals (Europe) Limited, for the treatment of cystic fibrosis;
- Enalapril (maleate), EMEA-001706-PIP01-14-M02, from Ethicare GmbH, for the treatment of heart failure;
- Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H3N2) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Yamagata lineage) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Victoria lineage) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H1N1), EMEA-001715-PIP01-14-M01, from Seqirus Netherlands B.V., for the prevention of influenza infection;

- Autologous CD34+ haematopoietic 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;
- Amikacin (sulfate), EMEA-000525-PIP01-08-M06, from Insmed Limited, for the treatment of *Pseudomonas aeruginosa* lung infection/colonisation in cystic fibrosis patients and treatment of nontubercolous mycobacterial (NTM) lung infection;
- Eculizumab, EMEA-000876-PIP03-14-M02, from Alexion Europe SAS, for the treatment of neuromyelitis optica spectrum disorders;
- Lixisenatide, EMEA-000916-PIP01-10-M06, from Sanofi-Aventis R&D, for the treatment of type 2 diabetes mellitus;
- Filgotinib, EMEA-001619-PIP04-17-M01, from Gilead Sciences International Ltd., for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, ankylosing spondylarthritis, psoriatic arthritis, and juvenile idiopathic arthritis);
- Letermovir, EMEA-001631-PIP01-14-M03, from Merck Sharp & Dohme (Europe), Inc., for the prevention of cytomegalovirus infection;
- (RS)-Bacoflen / Naltrexone HCl / D-Sorbitol, EMEA-002164-PIP01-17-M01, from Pharnext SA, for the treatment of Charcot-Marie-Tooth disease Type 1A;
- Tadalafil, EMEA-000452-PIP02-10-M05, from Eli Lilly and Company Ltd, for the treatment of pulmonary arterial hypertension;
- Liposomal combination of cytarabine and daunorubicin, EMEA-001858-PIP02-16-M02, from Jazz Pharmaceuticals Ireland Limited, for the treatment of acute myeloid leukaemia;
- Cholera vaccine, live attenuated, oral (strain CVD 103-HgR), EMEA-001490-PIP01-13-M01, from PaxVax Netherlands B.V., for the prevention of cholera;
- Secukinumab, EMEA-000380-PIP02-09-M04, from Novartis Europharm Limited, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, spondylarthritis, psoriatic arthritis and juvenile idiopathic arthritis);
- Ceftazidime / avibactam, EMEA-001313-PIP01-12-M08, from Pfizer Limited, for the treatment of infections due to aerobic Gram-negative organisms, treatment of intra-abdominal infections, treatment of pneumonia and treatment of urinary tract infections;
- Edoxaban (tosylate), EMEA-000788-PIP02-11-M08, from Daiichi Sankyo Europe GmbH, for the prevention of arterial thromboembolism, prevention of venous thromboembolism and treatment of venous thromboembolism;
- Fosnetupitant / palonosetron, EMEA-001198-PIP03-17-M01, from Helsinn Birex Pharmaceuticals Limited, for the prevention of chemotherapy-induced nausea and vomiting;
- Tolvaptan, EMEA-001231-PIP02-13-M06, from Otsuka Pharmaceutical Europe Ltd., for the treatment of dilutional hyponatraemia and treatment of polycystic kidney disease;
- Complex of povidone and iodine / dexamethasone, EMEA-001936-PIP01-16-M01, from Shire Pharmaceuticals Ireland Ltd, for the treatment of infectious conjunctivitis;
- Tezepelumab, EMEA-001613-PIP01-14-M02, from AstraZeneca AB, for the treatment of asthma;

- Risdiplam, EMEA-002070-PIP01-16-M02, from Roche Registration GmbH, for the treatment of spinal muscular atrophy;
- Lasmiditan, EMEA-002166-PIP01-17-M01, from Eli Lilly and Company Limited, for the treatment of migraine headaches;
- Phenylephrine hydrochloride / ketorolac trometamol, EMEA-001256-PIP02-12-M02, from Omeros Corporation, for lens therapeutic procedures
- Ixazomib, EMEA-001410-PIP02-17-M01, from Takeda Pharm A/S, for the treatment of multiple myeloma and treatment of lymphoid malignancies (excluding multiple myeloma)
- Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H1N1) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H3N2) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Yamagata lineage) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Victoria lineage) [QIVc], EMEA-002068-PIP01-16-M02, from Seqirus UK Limited, for prevention of influenza
- Pneumococcal polysaccharide serotype 1 – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 3 – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 4 – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 5 – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 6A – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 6B – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 7F – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 9V – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 14 – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 18C – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 19A – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 19F – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 22F – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 23F – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 33F – diphtheria CRM197 conjugate (15-valent pneumococcal polysaccharide conjugate vaccine [V114]), EMEA-002215-PIP01-17-M01, from Merck Sharp & Dohme (Europe), Inc., for prevention of disease caused by *Streptococcus pneumoniae*

Opinion on compliance checks

The PDCO adopted positive opinions on full compliance check for:

- Ranibizumab, EMEA-C-000527-PIP04-13-M01, from Novartis Europharm Limited, for the treatment of retinopathy of prematurity;
- Ceftaroline fosamil, EMEA-C-000769-PIP01-09-M08, from Pfizer Limited, for the treatment of complicated skin and soft tissue infections and treatment of community-acquired pneumonia;

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 6 applications were 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 13-16 November 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: 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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