1 February 2019
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Inspections, Human Medicines Pharmacovigilance and Committees Division

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

29 January - 01 February 2019

## Opinions on paediatric investigation plans

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

- Ridinilazole, EMEA-002250-PIP02-17, from Summit (Oxford) Limited, for the treatment of Clostridium Difficile infection;
- Dihomo-γ-linolenic acid, EMEA-002364-PIP02-18, from DS Biopharma Ltd., for the treatment of atopic dermatitis;
- (R)-azasetron (besylate), EMEA-002165-PIP02-18, from Sensorion SA, for the prevention of platinum-induced ototoxic hearing loss and treatment of sudden sensorineural hearing loss;
- Recombinant Influenza hemagglutinin-strain A (H1N1 subtype) / Recombinant Influenza hemagglutinin-strain A (H3N2 subtype) / Recombinant Influenza hemagglutinin-strain B (Victoria lineage) / Recombinant Influenza hemagglutinin-strain B (Yamagata lineage), EMEA-002418-PIP01-18, from Sanofi Pasteur, for the prevention of Influenza infection;
- Molgramostim, EMEA-002282-PIP01-17, from Savara ApS, for the treatment of pulmonary alveolar proteinosis;
- Spartalizumab, EMEA-002351-PIP01-18, from Novartis Europharm Limited, for the treatment of melanoma;
- Lenabasum, EMEA-002069-PIP02-17, from Corbus Pharmaceuticals Holdings Inc, for the treatment of systemic sclerosis;
- 1-{[(2S,3S)-2-carboxylato-3-methyl-4,4,7-trioxo-4-{6}-thia-1-azabi-cyclo[3.2.0]heptan-3-yl]methyl}-3-methyl-1H-1,2,3-triazol-3-ium, EMEA-002240-PIP02-17, from Allecra Therapeutics GmbH, for the treatment of urinary tract infections;
- Guselkumab, EMEA-001523-PIP03-18, from Janssen-Cilag International NV, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis);

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5510
**Send a question via our website** www.ema.europa.eu/contact

- Chemically modified recombinant human sulfamidase, EMEA-002380-PIP01-18, from Swedish Orphan Biovitrum AB, for the treatment of mucopolysaccharidosis type IIIA;
- Pretomanid, EMEA-002115-PIP01-17, from Global Alliance for TB Drug Development, for the treatment of multi-drug-resistant tuberculosis
- Mavacamten, EMEA-002231-PIP01-17, from MyoKardia, Inc., for the treatment of hypertrophic cardiomyopathy;
- N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide / tezacaftor / ivacaftor, EMEA-002324-PIP01-17, from Vertex Pharmaceuticals (Europe) Ltd, for the treatment of cystic fibrosis;
- ivacaftor / tezacaftor / potassium (benzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl)cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide, EMEA-002191-PIP02-17, from Vertex Pharmaceuticals (Europe) Ltd, for the treatment of cystic fibrosis;
- Avapritinib, EMEA-002358-PIP02-18, from Blueprint Medicines (Netherlands) B.V., for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms);
- Isoflurane, EMEA-002320-PIP01-17, from Sedana Medical AB, for the sedation of mechanically ventilated 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 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 a PIP with deferral adopted on 14 December 2018 for empagliflozin, EMEA-000828-PIP06-18, from Boehringer Ingelheim International GmbH, for the treatment of type 1 diabetes mellitus, the PDCO recommended to maintain its opinion and agreed to changes to the paediatric investigation plan and to the deferral 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:

- N-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl) pyridin-2-yl) acetamide, EMEA-002470-PIP01-18, from Almirall S.A., for the treatment of actinic keratosis;
- Upadacitinib, EMEA-001741-PIP06-18, from AbbVie Ltd, for the treatment of vasculitides;
- Relugolix / estradiol / norethisterone acetate, EMEA-002428-PIP01-18, from Myovant Sciences Ireland Limited, for the treatment of leiomyoma of uterus;
- Eltrombopag, EMEA-000170-PIP02-10-M03, from Novartis Europharm limited, for the treatment of secondary thrombocytopenia;
- Rosuvastatin (calcium) / amlodipine (besylate), EMEA-002456-PIP01-18, from Abbott Laboratories Limited, for the prevention of cardiovascular events, treatment of hypertension, treatment of dyslipidaemia and treatment of ischemic coronary artery disorders;
- Genetically modified Mycobacterium bovis bacille Calmette-Guérin genetic background Danish strain, subtype Prague), EMEA-002461-PIP01-18, from medac Gesellschaft für klinische Spezialpräparate mbH, for the treatment of ureter and bladder carcinoma;
- Empagliflozin, EMEA-000828-PIP06-18, from Boehringer Ingelheim International GmbH, for the treatment of chronic kidney disease

The PDCO adopted an opinion on the **refusal** of a request for waiver for:

- pyrimidinyl-aminopyridine dual leucine zipper kinase inhibitor, EMEA-002469-PIP01-18, from Roche Registration GmbH, for the treatment of amyotrophic lateral sclerosis

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:

- Ustekinumab, EMEA-000311-PIP04-13-M01, from Janssen-Cilag International NV, for the treatment of Crohn's disease;
- Galcanezumab, EMEA-001860-PIP03-16-M02, from Eli Lilly and Company Limited, for the prevention of migraine headaches;
- Acalabrutinib, EMEA-001796-PIP03-16-M01, from Acerta Pharma, BV, for the treatment of mature B cell neoplasms;
- Methoxyflurane, EMEA-000334-PIP01-08-M08, from Medical Developments UK Ltd, for the treatment of acute pain;
- Dabrafenib (mesilate), EMEA-001147-PIP01-11-M06, from Novartis Europharm Limited, for the treatment of melanoma and treatment of solid malignant tumours (excluding melanoma);
- Carotuximab, EMEA-002138-PIP01-17-M01, from TRACON Pharma Limited, for the treatment of soft

tissue sarcoma;

- Humanised anti-IL-6 receptor (IL-6R) monoclonal antibody, EMEA-001625-PIP01-14-M02, from Chugai Pharma Europe LTD., for the treatment of neuromyelitis optica;
- Crizanlizumab, EMEA-002141-PIP01-17-M01, from Novartis Europharm Limited, for the treatment of sickle cell disease;
- Isavuconazonium (sulfate), EMEA-001301-PIP02-12-M03, from Basilea Pharmaceutica International Ltd., for the treatment of invasive aspergillosis and treatment of mucormycosis;
- Olaratumab, EMEA-001760-PIP01-15-M03, from Eli Lilly and Company Limited, for the treatment of osteosarcoma and treatment of soft tissue sarcoma;
- Autologous cartilage derived cultured chondrocytes, EMEA-001823-PIP01-15-M01, from TETEC AG, for the treatment of cartilage disorders;
- Lefamulin, EMEA-002075-PIP01-16-M01, from Nabriva Therapeutics AG, for the treatment of community-acquired pneumonia;
- 3-({5-chloro-1-[3-(methylsulfonyl)propyl]-1H-indol-2-yl}methyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one), EMEA-001838-PIP01-15-M02, from Janssen-Cilag International NV, for the treatment of lower respiratory tract disease caused by human respiratory syncytial virus (RSV);
- Erenumab, EMEA-001664-PIP02-15-M03, from Novartis Europharm Limited, for the prevention of migraine headaches;
- Lacosamide, EMEA-000402-PIP03-17-M03, from UCB Pharma S.A., for the treatment of generalised epilepsy and epileptic syndromes;
- *Neisseria meningitidis* serogroup B recombinant lipoprotein (rLP2086; subfamily A; *Escherichia coli*) / *Neisseria meningitidis* serogroup B recombinant lipoprotein (rLP2086; subfamily B; *Escherichia coli*), EMEA-001037-PIP02-11-M05, from Pfizer Europe MA EEIG, for the invasive meningococcal disease caused by *N. meningitidis* serogroup B.;
- Tralokinumab, EMEA-001900-PIP02-17-M02, from LEO Pharma A/S, for the treatment of atopic dermatitis;
- Trametinib (dimethyl sulfoxide), EMEA-001177-PIP01-11-M05, from Novartis Europharm Limited, for the treatment of melanoma and treatment of all conditions included in the category of malignant neoplasms (except melanoma, haematopoietic and lymphoid tissue);
- Rituximab, EMEA-000308-PIP01-08-M04, from Roche Registration GmbH, for the treatment of autoimmune arthritis and treatment of diffuse large B-cell lymphoma;
- Avalglucosidase alfa, EMEA-001945-PIP01-16-M01, from Genzyme Europe B.V., for the treatment of Pompe disease;
- Upadacitinib, EMEA-001741-PIP03-16-M01, from AbbVie Ltd, for the treatment of Crohn's disease;
- Upadacitinib, EMEA-001741-PIP02-16-M01, from AbbVie Ltd, for the treatment of ulcerative colitis;
- Peginterferon beta-1a, EMEA-001129-PIP01-11-M03, from Biogen Idec Ltd, for the treatment of multiple sclerosis;
- Tofacitinib, EMEA-000576-PIP03-12-M02, from Pfizer Limited, for the treatment of ulcerative colitis;

- Alogliptin, EMEA-000496-PIP01-08-M06, from Takeda Development Centre Europe Ltd, for the treatment of type 2 diabetes melitus;
- Apremilast, EMEA-000715-PIP02-11-M03, from Celgene Europe Limited, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis);
- Ambrisentan, EMEA-000434-PIP01-08-M05, from Glaxo Group Limited, for the treatment of pulmonary arterial hypertension;
- 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-M02, from Seqirus Netherlands B.V., for prevention of influenza infection

The PDCO adopted opinions on the **refusal** of modifications to an agreed PIP for the following applications:

- Chemically modified extract of grass pollen from Holcus lanatus, Phleum pratense and Poa pratensis, EMEA-001016-PIP01-10-M01, from Granzer Regulatory Consulting & Services, for the treatment of allergic rhinitis / rhino-conjunctivitis;
- Chemically modified extract of grass pollen from Holcus lanatus, Phleum pratense and Poa pratensis, EMEA-001017-PIP01-10-M01, from Granzer Regulatory Consulting & Services, for the treatment of allergic rhinitis / rhino-conjunctivitis;
- Chemically modified house dust mites allergen extract (dermatophagoides pteronyssinus and dermatophagoides farina), EMEA-001014-PIP01-10-M01, from Granzer Regulatory Consulting & Services, for the treatment of allergic rhinitis / rhino-conjunctivitis;
- Chemically modified extract of trees pollen from birch and alder, EMEA-001013-PIP01-10-M01, from Granzer Regulatory Consulting & Services, for the treatment of allergic rhinitis / rhino-conjunctivitis;
- Chemically modified house dust mites allergen extract of Dermatophagoides pteronyssinus and Dermatophagoides farinae, EMEA-001011-PIP01-10-M01, from Granzer Regulatory Consulting & Services, for the treatment of allergic rhinitis / rhino-conjunctivitis;
- Chemically modified extract of trees pollen from birch and alder, EMEA-001012-PIP01-10-M01, from Granzer Regulatory Consulting & Services, for the treatment of allergic rhinitis / rhino-conjunctivitis

# Opinion on compliance check

The PDCO adopted positive opinions on full compliance check for:

- Rituximab, EMEA-C-000308-PIP02-11-M01, from Roche Registration GmbH, for the treatment of microscopic polyangiitis and treatment of granulomatosis with polyangiitis (Wegener's);
- pembrolizumab, EMEA-C-001474-PIP01-13-M01, from Merck Sharp & Dohme (Europe), Inc., for the treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue);
- Rabeprazole (sodium), EMEA-C-000055-PIP01-07-M06, from Eisai Ltd., for the treatment of gastro-oesophageal reflux disease, treatment of Zollinger-Ellison syndrome, treatment of duodenal ulcer, treatment of gastric ulcer and treatment of Helicobacter pylori in patients with peptic ulcer

disease

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 3 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 26 February-01 March 2019.

## – 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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