EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2019
EMEA/582190/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

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

15-18 October 2019

Opinions on paediatric investigation plans

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

- Marizomib, EMEA-002452-PIP01-18, from Celgene Europe B.V., for the treatment of malignant glial tumors;
- 3-[5-[(1R,2S)-2-(2,2-difluoropropanoylamino)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propoxy]indazol-1-yl]-N-[(3R)-tetrahydrofuran-3-yl]benzamide, EMEA-001976-PIP02-18, from AstraZeneca AB, for the treatment of asthma;
- Ketamine (hydrochloride) / sufentanil (citrate), EMEA-001739-PIP02-16, from Copenhagen University Hospital, Rigshospitalet, for the treatment of acute pain;
- Hydrocortisone (hemisuccinate), EMEA-002305-PIP01-17, from LABORATOIRE AGUETTANT, for the prevention of bronchopulmonary dysplasia;
- Remimazolam (as besylate), EMEA-001880-PIP02-19, from PAION Deutschland GmbH, for the general anaesthesia and sedation during medical procedures;
- Selpercatinib, EMEA-002544-PIP01-18, from Eli Lilly and Company Limited, for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms);
- Iodine (^{131}I) murine IgG1 monoclonal antibody against B7-H3, EMEA-002101-PIP02-18, from Y-mAbs Therapeutics A/S, for the treatment of paediatric neuroblastoma patients with central nervous system (CNS) relapse as evidenced by CNS/leptomeningeal (LM) metastases;
- Larotrectinib, EMEA-001971-PIP03-18, from Bayer AG, for the treatment of malignant neoplasms of the central nervous system;
- Iclaprim (mesylate), EMEA-002391-PIP02-19, from Motif Bio plc, for the treatment of acute bacterial skin and skin structure infections;
- Zanubrutinib, EMEA-002354-PIP02-18, from BeiGene Ireland, Ltd, for the treatment of

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

lymphoplasmacytic lymphoma and treatment of mature B-cell neoplasms (excluding lymphoplasmacytic lymphoma);

- Artesunate, EMEA-002402-PIP02-18, from ACE Pharmaceuticals BV, for the treatment of severe malaria from Plasmodium falciparum;
- Ganaxolone, EMEA-002341-PIP01-18, from Marinus Pharmaceuticals Inc., for the cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder;
- Crizotinib, EMEA-001493-PIP03-18, from Pfizer Europe MA EEIG, for the treatment of anaplastic large cell lymphoma and treatment of inflammatory myofibroblastic tumour;
- Synthetic double-stranded siRNA oligonucleotide directed against lactate dehydrogenase A mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues, EMEA-002493-PIP01-18, from Dicerna EU Limited, for the treatment of primary hyperoxaluria;
- Narsoplimab, EMEA-002479-PIP01-18, from Omeros London Limited, for the treatment in in haematopoietic stem cell transplantation;
- Ritonavir / atazanavir (sulfate), EMEA-002588-PIP01-19, from Pharmaceutical Oriented Services Ltd, for the treatment of human immunodeficiency virus (HIV-1) infection;
- Phenobarbital, EMEA-002532-PIP01-18, from Proveca Limited, for the treatment of epilepsy;

The PDCO adopted an Opinion on the refusal of a PIP, including deferral for:

- Ivosidenib, EMEA-002247-PIP02-17, from Agios Pharmaceuticals, Inc., for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) and treatment of malignant neoplasms of the central nervous system;

For this medicine 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 clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset(s).

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:

- Loxoprofen (sodium hydrate), EMEA-002626-PIP01-19, from Lead Chemical Co., Ltd, for the treatment of pain;
- Aciclovir, EMEA-001066-PIP02-11-M03, from VECTANS PHARMA, for the treatment of herpes simplex labialis;
- Sulindac / eflornithine (hydrochloride monohydrate), EMEA-001518-PIP03-19, from Cancer Prevention Pharma (Ireland) Limited, for the treatment of familial adenomatous polyposis;
- A fully humanized immunoglobulin G4 proline, alanine, alanine (IgG4 PAA) based bispecific antibody directed against cluster of differentiation 3 (CD3) receptor complex and G protein coupled receptor

family C group 5 member D (GPRC5D), EMEA-002615-PIP01-19, from Janssen-Cilag International N.V., for the treatment of multiple myeloma;

- Savolitinib, EMEA-002627-PIP01-19, from AstraZeneca AB, for the treatment of lung cancer
- ^{177}Lu-Satoreotide tetraxetan, EMEA-002629-PIP01-19, from Ipsen Pharma, for the treatment of breast cancer, treatment of lung cancer and treatment of neuroendocrine tumours (excluding neuroblastoma);
- Sitravatinib malate, EMEA-002633-PIP01-19, from Mirati Therapeutics, Inc., for the treatment of non-small cell lung cancer;
- Duvelisib, EMEA-002587-PIP01-19, from Verastem, Inc., for the treatment of mature B cell malignancies;
- Ezetimibe / atorvastatin, EMEA-002649-PIP01-19, from ELPEN Pharmaceutical Co. Inc, for the treatment of hypercholesterolemia;
- Thiocolchicoside / diclofenac (sodium), EMEA-002580-PIP01-19, from WIN MEDICA S.A., for the treatment of pain;
- Satoreotide trizoxetan, EMEA-002632-PIP01-19, from Ipsen Pharma, for the diagnosis of breast cancer, diagnosis of lung cancer and diagnosis of neuroendocrine tumours (excluding neuroblastoma);
- Gefapixant citrate salt, EMEA-002267-PIP02-19, from Merck Sharp & Dohme (Europe), Inc., for the treatment of unexplained or chronic refractory cough;
- (3S,7S)-22-(3-(((2-((5-(2-Carboxyethyl)-2-hydroxybenzyl)(carboxymethyl)amino)ethyl)(carboxymethyl)amino)methyl)-4-hydroxyphenyl)-5,13,20-trioxo-4,6,12,19-tetraazadocosane-1,3,7-tricarboxylic acid, EMEA-002622-PIP01-19, from Advanced Nuclear Medicine Ingredients (ANMI), for the visualisation of prostate specific membrane antigen in prostate cancer;
- Canakinumab, EMEA-000060-PIP07-19, from Novartis Europharm Limited, for the treatment of gout.

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:

- Rimiducid, EMEA-001870-PIP01-15-M02, from Beliicum Pharma Ltd, for the treatment of graft versus host disease;
- Mexiletine (hydrochloride), EMEA-002012-PIP01-16-M02, from Lupin Europe GmbH, for the treatment of myotonic disorders;
- Dupilumab, EMEA-001501-PIP01-13-M06, from Regeneron Pharmaceuticals, Inc, for the treatment of atopic dermatitis;
- Inotuzumab ozogamicin, EMEA-001429-PIP01-13-M03, from Pfizer Europe MA EEIG, for the treatment of B cell acute lymphoblastic leukaemia;

- 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 (H3N2) / Influenza virus surface antigens (Haemagglutinin and neuraminidase) of strain A (H1N1), EMEA-001894-PIP01-15-M01, from Seqirus GmbH, for the prevention of influenza infection;
- Ruxolitinib (phosphate), EMEA-000901-PIP04-17-M01, from Novartis Europharm Limited, for the treatment of chronic graft versus host disease;
- Fitusiran (synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues), EMEA-001855-PIP01-15-M01, from Genzyme Europe B.V., for the treatment of haemophilia A and treatment of heamophilia B;
- Daclatasvir, EMEA-001191-PIP01-11-M03, from Bristol-Myers Squibb Pharma EEIG, for the treatment of chronic viral hepatitis C
- Zanamivir, EMEA-001318-PIP01-12-M03, from GlaxoSmithKline Trading Services Limited, for the treatment of influenza and prevention of influenza;
- Chloroprocaine (hydrochloride), EMEA-000639-PIP03-16-M01, from Sintetica GmbH, for the peripheral nerve block (local anaesthesia by perineural injection);
- Peginterferon beta-1a, EMEA-001129-PIP01-11-M04, from Biogen Idec Ltd, for the treatment of multiple sclerosis;
- Lubiprostone, EMEA-000245-PIP01-08-M06, from Sucampo AG, for the treatment of constipation
- Ibrutinib, EMEA-001397-PIP04-17-M01, from Janssen-Cilag International N.V., for the treatment of chronic graft versus host disease;
- Apremilast, EMEA-000715-PIP02-11-M04, from Celgene Europe B.V., for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis);
- Liraglutide, EMEA-000128-PIP02-09-M03, from Novo Nordisk A/S, for the treatment of obesity;
- Abemaciclib, EMEA-002342-PIP01-18-M01, from Eli Lilly and Company Limited, for the treatment of Ewing's Sarcoma;
- Teduglutide, EMEA-000482-PIP01-08-M05, from Shire Pharmaceuticals Ireland Limited, for the treatment of short bowel syndrome;
- Bilastine, EMEA-000347-PIP02-16-M01, from Faes Farma S.A., for the treatment of allergic conjunctivitis;
- Pevonedistat, EMEA-002117-PIP01-17-M01, from Takeda Pharma A/S, for the treatment of acute myeloid leukaemia (AML) and treatment of myelodysplastic syndromes (MDS);
- Avatrombopag (maleate), EMEA-001136-PIP01-11-M01, from Dova Pharmaceuticals Ireland Limited, for the treatment of idiopathic thrombocytopenic purpura and treatment of thrombocytopenic purpura secondary to liver disease;
- Fremanezumab, EMEA-001877-PIP01-15-M02, from Teva GmbH, for the prevention of migraine headaches;

- Sodium thiosulfate, EMEA-002147-PIP02-17-M01, from Fennec Pharmaceuticals, Inc., for the prevention of platinum-induced ototoxic hearing loss;
- Letermovir, EMEA-001631-PIP01-14-M04, from Merck Sharp & Dohme (Europe), Inc., for the prevention of cytomegalovirus infection (CMV);
- Lurasidone (hydrochloride), EMEA-001230-PIP01-11-M05, from AZIENDE CHIMICHE RIUNITE ANGELINI FRANCESCO - A.C.R.A.F. S.p.A., for the treatment of schizophrenia;
- Rivogenlecleucel, EMEA-001869-PIP01-15-M02, from Bellicum Pharma Ltd, for the adjunctive treatment in haematopoietic stem cell transplantation;
- Loxapine, EMEA-001115-PIP01-10-M07, from Ferrer Internacional, S.A., for the treatment of bipolar disorder and treatment of schizophrenia;
- Itacitinib, EMEA-002178-PIP01-17-M01, from Incyte Biosciences Distribution B.V, for the treatment of acute graft versus host disease;
- Dalbavancin, EMEA-000016-PIP01-07-M07, from Allergan Pharmaceuticals International Limited, for the treatment of acute bacterial skin and skin structure infections (ABSSSI);
- Volanesorsen , EMEA-001915-PIP01-15-M01, from Akcea Therapeutics, for the treatment of familial chylomicronemia syndrome;
- 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, EMEA-002369-PIP01-18-M01, from Celgene Europe B.V., for the treatment of mature B-cell neoplasms;
- Naloxegol, EMEA-001146-PIP01-11-M05, from Kyowa Kirin Pharmaceutical Development Limited, for the treatment of opioid-induced constipation;
- Apremilast, EMEA-000715-PIP05-13-M04, from Celgene Europe B.V., for the treatment of Behçet's disease;
- Ambrisentan, EMEA-000434-PIP01-08-M06, from Glaxo Group Limited, for the treatment of pulmonary arterial hypertension;
- Maralixibat chloride, EMEA-001475-PIP03-17-M01, from SFL Regulatory Services GmbH, for the treatment of progressive familial intrahepatic cholestasis (PFIC);
- Vonicog alfa, EMEA-001164-PIP01-11-M03, from Baxalta Innovations GmbH, for the treatment of von Willebrand disease;
- Rubidium Rb-82 chloride, EMEA-000882-PIP03-11-M04, from Jubilant DraxImage Inc., for the visualization of myocardial perfusion for diagnostic purposes;
- Crizanlizumab, EMEA-002141-PIP01-17-M02, from Novartis Europharm Limited, for the treatment of sickle cell disease;
- Bimekizumab, EMEA-002189-PIP01-17-M01, from UCB Biopharma SPRL, for the treatment of psoriasis;
- Beclometasone dipropionate/ formoterol fumarate dihydrate/ glycopyrronium bromide, EMEA-001875-PIP02-18-M01, from Chiesi Farmaceutici S.p.A., for the treatment of asthma.

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

- Avacopan, EMEA-002023-PIP01-16-M03, from ChemoCentryx Ireland Ltd., for the treatment of antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis;

Opinion on compliance check

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

- Asfotase alfa, EMEA-C-000987-PIP01-10-M04, from Alexion Europe S.A.S., for the treatment of hypophosphatasia;
- Decitabine, EMEA-C-000555-PIP01-09-M06, from Janssen-Cilag International NV, for the treatment of acute myeloid leukaemia.

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 9 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 12-15 November 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: 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

5. **Enquiries to: AskEMA**

   https://www.ema.europa.eu/en/about-us/contacts-european-medicines-agency