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Inspections, Human Medicines Pharmacovigilance and Committees Division

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

24-27 January 2017

Opinions on paediatric investigation plans

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

- Autologous CD34+ hematopoietic stem cells transduced ex vivo with EFS lentiviral vector encoding for the human adenosine deaminase gene, EMEA-001974-PIP01-16, from Pr Bobby Gaspar, for the treatment of severe combined immunodeficiency due to adenosine deaminase deficiency;
- Avelumab, EMEA-001849-PIP02-15, from Merck KGaA, for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms);
- Gadolinium, [α3,α6,α9-tris[3-[(2,3-dihydroxypropyl)amino]-3-oxopropyl]-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetato(3-)-κN3,κN6,κN9,κN15,κO3,κO6,κO9]-(P03277), EMEA-001949-PIP01-16, from GUERBET, for the detection and visualisation of areas with disruption of the blood brain barrier and/or abnormal vascularity for diagnostic purposes;
- Lamivudine / dolutegravir, EMEA-001940-PIP01-16, from ViiV Healthcare UK Limited, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection;
- Recombinant human alpha-glucosidase conjugated with multiple copies of synthetic bismannose-6-phosphate-tetra-mannose glycan, EMEA-001945-PIP01-16, from Genzyme Europe B.V., for the treatment of Pompe disease;
- Testosterone, EMEA-001529-PIP02-14, from Acerus Pharmaceuticals SRL, for the treatment of male hypogonadism;
- T-lymphocytes enriched leukocyte preparation depleted ex vivo of host host-alloreactive T cells using photodynamic treatment, EMEA-001980-PIP01-16, from Kiadis Pharma Netherlands B.V., for the adjunctive treatment in haematopoietic stem cell transplantation for a malignant disease;
- 8-chloro-5-methyl-1-[trans-4-(pyridin-2-yloxy)cyclohexyl]-5,6-dihydro-4H-[1,2,4]triazolo[4,3-

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a][1,4]benzodiazepine, EMEA-001918-PIP01-15, from Roche Registration Ltd, for the treatment of autism spectrum disorder.

The PDCO adopted an opinion(s) on the **refusal** of a PIP and a deferral for Somapacitan, EMEA-001469-PIP01-13, from Novo Nordisk A/S, for the treatment of growth hormone deficiency. For this medicine 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 and on the grounds that the specific medicinal product is likely to be unsafe.

The PDCO adopted an opinion(s) on the **refusal** of a PIP for Methylphenidate (hydrochloride), EMEA-002034-PIP01-16, from Mundipharma Research Limited, for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). For this medicine 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 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:

- atorvastatin (calcium) / ezetimibe, EMEA-002047-PIP01-16, from Midas Pharma GmbH, for the treatment of elevated cholesterol;
- alpelisib, EMEA-002016-PIP02-16, from Novartis Europharm Ltd, for the treatment of breast cancer;
- 5-(4-cyclopropyl-1H-imidazol-1-yl)-2-fluoro-N-(6-(4-isopropyl-4H-1,2,4- triazol-3-yl)pyridi-2-yl)-4-methylbenzamide, EMEA-001868-PIP02-16, from Gilead Sciences International Ltd., for the treatment of alcoholic hepatitis.

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:

- Ombitasvir / paritaprevir /ritonavir , EMEA-001440-PIP01-13-M01, from Abbvie Ltd, for the

treatment of chronic hepatitis C;

- cobimetinib, EMEA-001425-PIP01-13-M02, from Roche Registration Limited, for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue) with Ras, Raf or MEK pathway activation;
- dasabuvir (sodium monohydrate), EMEA-001439-PIP01-13-M01, from Abbvie Ltd, for the treatment of chronic hepatitis C;
- dupilumab, EMEA-001501-PIP01-13-M04, from Regeneron Pharmaceuticals, Inc, for the treatment of atopic dermatitis;
- Vericiguat, EMEA-001636-PIP01-14-M01, from Bayer Pharma AG, for the treatment of left ventricular failure;
- Naldemedine (tosylate), EMEA-001893-PIP01-15-M01, from Shionogi Limited, for the treatment of opioid-induced constipation (OIC).
- Vigabatrin, EMEA-000717-PIP02-13-M02, from ORPHELIA Pharma SA, for the treatment of epilepsy;
- mirabegron, EMEA-000597-PIP03-15-M03, from Astellas Pharma Europe B.V., for the treatment of neurogenic detrusor overactivity;
- Influenza virus surface antigens - A/turkey/Turkey/1/05 (H5N1), EMEA-000599-PIP01-09-M05, from Seqirus S.r.l., for the prevention of influenza;
- Fingolimod hydrochloride, EMEA-000087-PIP01-07-M05, from Novartis Europharm Limited, for the treatment of multiple sclerosis;
- Anidulafungin, EMEA-000469-PIP01-08-M07, from Pfizer Limited, for the treatment of invasive candidiasis;
- Conestat Alfa, EMEA-000367-PIP01-08-M06, from Pharming Group N.V., for the treatment of hereditary angioedema;
- Brivaracetam, EMEA-000332-PIP01-08-M11, from UCB Pharma S.A., for the treatment of epilepsy with partial onset seizures, treatment of neonatal seizures and treatment of paediatric epilepsy syndromes;
- Saxagliptin, EMEA-000200-PIP01-08-M07, from AstraZeneca AB, for the treatment of type 2 diabetes mellitus;
- Fidaxomicin, EMEA-000636-PIP01-09-M05, from Astellas Pharma Europe B.V., for the treatment of enterocolitis caused by Clostridium difficile;
- Tofacitinib, EMEA-000576-PIP01-09-M06, from Pfizer Limited, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis);
- Cobicistat, EMEA-000969-PIP01-10-M04, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus type-1 (HIV-1) infection;
- Treosulfan, EMEA-000883-PIP01-10-M03, from medac Gesellschaft für klinische Spezialpräparate mbH, for the conditioning treatment prior to haematopoietic progenitor cell transplantation;
- mepolizumab, EMEA-000069-PIP02-10-M07, from GSK Trading Services Limited, for the treatment of asthma;

- tazobactam / ceftolozane, EMEA-001142-PIP01-11-M02, from Merck Sharp & Dohme (Europe), Inc., for the treatment of abdominal and gastrointestinal infections and treatment of urinary tract infections;
- tafluprost, EMEA-001187-PIP01-11-M04, from Santen Oy, for the treatment of glaucoma;
- Tofacitinib, EMEA-000576-PIP02-11-M04, from Pfizer Limited, for the treatment of psoriasis;
- lacosamide, EMEA-000402-PIP02-11-M03, from UCB Pharma S.A., for the treatment of epilepsy with partial-onset seizures and treatment of generalised epilepsy and epileptic syndromes;
- ledipasvir / sofosbuvir, EMEA-001411-PIP01-12-M04, from Gilead Sciences International Ltd., for the treatment of chronic hepatitis C;
- avibactam / ceftazidime, EMEA-001313-PIP01-12-M05, from AstraZeneca AB, for the treatment of Gram-negative bacterial infections, treatment of intra-abdominal infections, treatment of pneumonia and treatment of urinary tract infections;
- Sirolimus, EMEA-001416-PIP01-12-M01, from Santen Incorporated, for the treatment of chronic non-infectious uveitis.

Opinion on compliance check

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

- Pneumococcal polysaccharide serotype 6B conjugated to Protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 23F conjugated to Protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 1 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 18C conjugated to tetanus toxoid / Pneumococcal polysaccharide serotype 19F conjugated to diphtheria toxoid / Pneumococcal polysaccharide serotype 7F conjugated to Protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 9V conjugated to Protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 14 conjugated to Protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 4 conjugated to Protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 5 conjugated to Protein D (derived from non-typeable Haemophilus influenzae) carrier protein, EMEA-C-000673-PIP01-09-M09, from GlaxoSmithKline Biologicals S.A., for the prevention of acute otitis media caused by non-typeable Haemophilus influenzae and prevention of diseases caused by streptococcus pneumoniae;
- Purified Pertussis Toxoid (PT) / Hepatitis B Surface Antigen, recombinant (HBsAg) / Purified Filamentous Haemagglutinin (FHA) / Inactivated Type 2 Poliovirus (MEF-1) / Haemophilus influenzae type b polysaccharide conjugated to tetanus protein / Inactivated Type 3 Poliovirus (Saukett) / Purified Diphtheria Toxoid / Inactivated Type 1 Poliovirus (Mahoney) / Purified Tetanus Toxoid, EMEA-C-001201-PIP01-11-M02, from Sanofi Pasteur, for the prevention of infections caused by Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis, poliovirus types 1, 2 and 3, prevention against invasive infections caused by Haemophilus influenzae type b and infection caused by hepatitis B virus.

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.

Withdrawals

The PDCO noted that 4 applications were withdrawn during the late stages of the evaluation (30 days or less before completion of the procedure).

Committee interactions

The coordinator of the paediatric rheumatology network PRINTO was invited to present PRINTO's activities to PDCO and discuss the network's experience and involvement in paediatric studies agreed in a PIP. The need for early interaction of academia with applicants was stressed to provide input to the PIP preparation, study protocol and eventually identification of sites and conduct of the clinical studies. While PRINTO over the past decades since its establishment has succeeded in increasing early interactions with industry, there is still a high need to improve and increase dialogue with regulators, in particular with PDCO to discuss important aspects of paediatric drug development, such as paediatric needs, study design, standard of care, etc. based on evolving knowledge and evidence. The committee supports increased interactions with academia and networks and suggested to use collaboration through Enpr-EMA.

Other matters

The PDCO welcomed the new alternate from France, Dominique Ploin.

The next meeting of the PDCO will be held on 21-24 February 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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