21 September 2016
EMA/PDCO/616910/2016
Inspections, Human Medicines Pharmacovigilance and Committees Division

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

14-16 September 2016

Opinions on paediatric investigation plans

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

- Macrogol 3350 / sodium sulfate / sodium chloride / potassium chloride / sodium ascorbate / ascorbic acid, EMEA-001705-PIP02-15, from Norgine Ltd., for bowel cleansing prior to clinical procedures;
- Humanised chimeric antibody with a humanised H chain and a chimeric (mouse V-domain, human C-domain) L chain against epidermal growth factor receptor conjugated to maleimidocaproyl monomethylauristatin F, EMEA-001732-PIP02-15, from AbbVie Ltd, for treatment of high-grade glioma;
- Birch pollen extract (Betula verrucosa), EMEA-001879-PIP01-15, from ALK Abelló A/S, for the treatment of allergic rhinitis / rhino-conjunctivitis;
- Monoclonal IgG1 anti-influenza A antibody, EMEA-001831-PIP01-15, from Roche Products Limited, for the treatment of influenza;
- Immunoglobulin G2, anti-(human α-calcitonin gene-related peptide/β-calcitonin gene-related peptide) (human-Mus musculus monoclonal TEV-48125 heavy chain), disulphide with human-Mus musculus monoclonal TEV-48125 light chain, dimer (fremanezumab), EMEA-001877-PIP01-15, from Teva Pharma GmbH, for the prevention of migraine headaches;
- 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 (Victoria lineage)/ Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Yamagata lineage), EMEA-001894-PIP01-15, from Seqirus GmbH, for the prevention of influenza infection.

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

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

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:

- Sirukumab, EMEA-001043-PIP02-16, from Janssen-Cilag International N.V., for the treatment of vasculitides;
- Allogeneic Mesenchymal Precursor Cells (rexlemestrocel-L), EMEA-001140-PIP02-15, from Mesoblast UK Limited, for the treatment of intervertebral disc disorder;
- Perindopril / amlodipine, EMEA-001968-PIP01-16, from ERREKAPPA EUROTERAPICI S.p.A., for the treatment of hypertension;
- Ciclosporin, EMEA-001998-PIP01-16, from Drug Delivery Solutions ApS, for the treatment of dry eye disease;
- Atorvastatin / Amlodipine, EMEA-002005-PIP01-16, from ELPEN Pharmaceutical Co. Inc, for the prevention of cardiovascular events in hypertension and diabetes mellitus type 2, treatment of concomitant angina and dyslipidaemia and treatment of concomitant hypertension and dyslipidaemia;
- Hydrochlorothiazide / Valsartan / Amlodipine, EMEA-002006-PIP01-16, from ELPEN Pharmaceutical Co. Inc, for the treatment of hypertension;
- Amlodipine / Candesartan, EMEA-002014-PIP01-16, from CIPROS S.r.l., for the treatment of Hypertension.

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:

- Mepolizumab, EMEA-000069-PIP04-13-M01, from GSK Trading Services Limited, for the treatment of vasculitides;
- dabigatran etexilate, EMEA-000081-PIP01-07-M09, from Boehringer Ingelheim International GmbH, for the prevention of thomboembolic events and preatment of thromboembolic events;
- ataluren, EMEA-000115-PIP01-07-M08, from PTC Therapeutics International, Limited, for the treatment of dystrophinopathy;
- ataluren, EMEA-000115-PIP02-09-M03, from PTC Therapeutics International, Limited, for the treatment of cystic fibrosis;

- Alipogene tiparvovec, EMEA-000292-PIP01-08-M03, from uniQure biopharma B.V., for the treatment of hyperchylomicronaemia;
- Human normal immunoglobulin, EMEA-000454-PIP01-08-M07, from Kedrion S.p.A., for the treatment of Primary Immunodeficiency (PID);
- Mirabegron, EMEA-000597-PIP02-10-M05, from Astellas Pharma Europe B.V., for the treatment of idiopathic overactive bladder;
- Mirabegron, EMEA-000597-PIP03-15-M02, from Astellas Pharma Europe B.V., for the treatment of neurogenic detrusor overactivity;
- Riociguat, EMEA-000718-PIP01-09-M06, from Bayer Pharma AG, for the treatment of pulmonary hypertension;
- serelaxin, EMEA-001168-PIP01-11-M03, from Novartis Europharm Limited, for the treatment of acute heart failure;
- Potassium (chloride) / magnesium (sulphate heptahydrate) / procaine (hydrochloride) / xylitol, EMEA-001171-PIP01-11-M01, from Swiss Cardio Technologies AG, for the cardioplegia;
- Human fibrinogen / human thrombin, EMEA-001340-PIP01-12-M02, from Mallinckrodt Pharmaceuticals, for the treatment of haemorrhage resulting from a surgical procedure;
- Sodium zirconium cyclosilicate, EMEA-001539-PIP01-13-M01, from ZS Pharma, Inc., for the treatment of hyperkalaemia;
- Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human betaA-T87Q-globin gene, EMEA-001665-PIP01-14-M01, from bluebird bio France, for the treatment of beta-thalassaemia;
- Eteplirsen, EMEA-001722-PIP01-14-M01, from Sarepta International C.V., for the treatment of Duchenne muscular dystrophy;
- Recombinant human nerve growth factor, EMEA-001729-PIP01-14-M01, from Dompé farmaceutici S.p.A., for the treatment of neurotrophic keratitis;
- Olaratumab, EMEA-001760-PIP01-15-M01, from Eli Lilly and Company Limited, for the treatment of soft tissue sarcoma and treatment of osteosarcoma.

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

- Tolvaptan, EMEA-001231-PIP02-13-M04, from Otsuka Pharmaceutical Europe Ltd., for the treatment of dilutional hyponatraemia and treatment of polycystic kidney disease.

Opinion on compliance check

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

- Rufinamide, EMEA-C-000709-PIP01-09-M05, from Eisai Limited, for the treatment of Lennox-Gastaut Syndrome.

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.

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 modification of a PIP adopted on 22 July 2016 for Linaclotide, EMEA-000927-PIP01-10-M03, from Allergan Pharmaceuticals International Limited, for the treatment of functional constipation, the PDCO adopted a revised positive opinion;

- Following the re-examination of the negative opinion on a PIP and a deferral adopted on 22 July 2016 for Angiotensin II, EMEA-001912-PIP01-15, from La Jolla Pharmaceutical Company, Inc., for the treatment of catecholamine-resistant hypotension associated with distributive shock, the PDCO recommended to maintain its 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.

Withdrawals

The PDCO noted that 5 applications were withdrawn during the late stages of the evaluation (30 days or less before completion of the procedure).

Interaction with the International Neonatal Consortium

Following the Second Scientific Workshop of the International Neonatal Consortium (INC) hosted at the EMA on 12-13 September 2016 the Critical Path Institute presented the approaches as a private-public partnership to design consortia to support development of medicines in the paediatric population specifically using the examples of INC as a "pre-competitive" space and the Pediatric Trial Consortium (PTC). INC is a multi-stakeholder consortium including families/parents, nurses, neonatologists, researchers, industry and regulatory bodies to advance development of neonates by working on specific deliverables in areas of highest unmet need. Deliverables are being worked on in specific work groups and face to face workshops. The PTC was presented and discussed also in view of ongoing European activities.

Other matters

At its meeting on 14 September, the Paediatric Committee (PDCO) voted to re-elect Dr Dirk Mentzer for a further 3-year mandate as Chair of the Committee.

The next meeting of the PDCO will be held on 12-14 October 2016.

– 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

Enquiries to: AskEMA
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/ask_ema_landing_page.jsp&mid=)