



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2015
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Human Medicines Research and Development Support

Response to public comments received on the 'Inventory of paediatric therapeutic needs - Gastroenterology' (EMA/PDCO/43828/2015 Corr.1)

Start of public consultation	8 May 2015
End of consultation (deadline for comments)	6 July 2015

Comments received from:

Name of organisation or individual

- (1) European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
- (2) European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)
- (3) Helmut Küster, MD, Chief, Neonatology, University Children's Hospital Göttingen, Germany



1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
(1)	EUCOPE welcomes the opportunity to comment on the Guideline on <i>Inventory of paediatric therapeutic needs Gastroenterology</i> prepared by EMA.	n/a
(3)	Laxatives used to prevent meconium ileus Data on PK, PD, efficacy and safety in newborns, especially very low birth weight infants with a birth weight <1500g Data on long-term safety.	<i>Not included in the Inventory:</i> Products to address medical needs specific to pre-term and term neonates will be included in a separate "Inventory of paediatric needs Neonatology" which is currently in preparation. For consistency therefore also the needs related to neonatal colitis identified for sirolimus and tacrolimus have been removed from the Gastroenterology Inventory.
(3)	Ursodeoxycholic acid after long-term parenteral nutrition Data on PK, PD, efficacy and safety in newborns Data on long-term safety.	<i>Not included in the Inventory:</i> Products for medical needs specific to pre-term and term neonates will be included in a separate "Inventory of paediatric needs Neonatology" which is currently in preparation. For consistency therefore also the needs related to neonatal colitis identified for sirolimus and tacrolimus have been removed from the Gastroenterology Inventory.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Categories	(1)	<p>Comment:</p> <p>The categories suggested do not include a category for bowel preparations. KLEAN-PREP is not listed but registered in France in paediatric population.</p> <p>Proposed change: Include KLEAN-PREP</p>	<p><i>Not included in the Inventory:</i></p> <p>As this product is already authorised in the paediatric population, there are no research or regulatory gaps that need to be addressed and would warrant inclusion in the Inventory.</p>
Laxatives	(1)	<p>Comments:</p> <p>Under the category of laxatives there is <i>Bisacodyl</i> listed. However MOVICOL paediatric is not included.</p> <p>Proposed change: Include MOVICOL</p>	<p><i>Not included in the Inventory:</i></p> <p>As this product is already authorised in the paediatric population, there are no research or regulatory gaps that need to be addressed and would warrant inclusion in the Inventory.</p>
Suggest addition to “Antiemetics” section (Page 2 of document)	(2)	<p>Comment and rationale: Despite prolonged use of Metoclopramide in paediatrics there remain limited data. A recent study (Ericson et al, JPGN Mar 21 2015) carried out in almost 900,00 infants suggested that it was associated with increased risk of adverse events compared to erythromycin. The authors concluded that “Studies are needed to confirm safety and effectiveness of both drugs in infants”</p> <p>Proposed change (if any): addition of: Metoclopramide - safety and effectiveness data in paediatric age including infants</p>	<p><i>Not included in the Inventory:</i></p> <p>The PDCO re-endorsed their view expressed in 2008 in the “Assessment of paediatric needs gastroenterology”¹ which concluded that the paediatric needs for metoclopramide are already covered and identified no need for further paediatric data.</p> <p>In addition, PDCO considered the Article 31 referral procedure on metoclopramide-containing medicines in 2013², which came to the following conclusion on paediatric use:</p>

¹ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004059.pdf

² http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Metoclopramide-containing_medicines/human_referral_000349.jsp&mid=WC0b01ac05805c516f

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>“(..) metoclopramide should only be authorised for short-term use (up to 5 days), that it should not be used in children below 1 year of age and that in children over 1 year of age it should only be used as a second-choice treatment (after other treatments have been considered or tried) for the prevention of delayed nausea and vomiting after chemotherapy and for the treatment of post-operative nausea and vomiting.”</p> <p>Therefore metoclopramide has not been included in the Inventory.</p>
Suggest addition to “Laxatives” section (Page 2 of document)	(2)	<p>Comment and rationale: Currently, no data of Prucalopride in children for slow transit constipation and other motility disorders in children (e.g. chronic intestinal pseudoobstruction). Available data in children limited to functional constipation (not slow transit) suggests limited efficacy. Existing adult data suggests drug may be useful in this group of disorders</p> <p>Proposed change (if any): addition of: Prucalopride - data on efficacy, optimal dosing and safety use for slow transit constipation and other motility disorders in children (e.g. chronic intestinal pseudoobstruction).</p>	<p><i>Included in the Inventory:</i></p> <p>As suggested, prucalopride has been included in the Inventory with the identified needs of “Data on PK, efficacy and safety for motility disorders in children (e.g. chronic intestinal pseudoobstruction)”.</p> <p>Of note, a PIP for prucalopride succinate has been completed in the condition of “Treatment of chronic constipation”.</p>

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Suggest addition to "Motility drugs" section (Page 2 of document)	(2)	<p>Comment and rationale: Recent review by Mt-Isa et al (Mt-Isa S, Tomlin S, Sutcliffe A, Underwood M, Williamson P, Croft NM, Ashby D. Prokinetics prescribing in paediatrics: evidence on cisapride, domperidone, and metoclopramide. J Pediatr Gastroenterol Nutr. 2015 Apr;60(4):508-14.) found that prescriptions of domperidone increased 10-fold, mainly following the withdrawal of cisapride in 2000. Despite this increase no new safety signals were identified and dramatic changes in prescribing despite the lack of good-quality supporting evidence. This would "support the development of suitable powered clinical studies"</p> <p>Proposed change (if any): addition of: Domperidone - Data on efficacy and safety in gastro-oesophageal reflux and gastrointestinal stasis</p>	<p><i>Not included in the Inventory:</i></p> <p>The PDCO re-endorsed their view expressed in 2008 in the Assessment of paediatric needs gastroenterology³ which concluded that the paediatric needs for domperidone are already covered and identified no need for further paediatric data.</p> <p>In addition, PDCO considered the Article 31 referral procedure for domperidone in 2014⁴, which concluded that the use of domperidone-containing medicines should be restricted and domperidone should only be used to relieve symptoms of nausea and vomiting, with restrictions in doses and length of treatment and careful adjustment by the patient's weight where available for use in children.</p> <p>Therefore domperidone has not been included in the Inventory.</p>
Suggest addition to "Biological agents – immune-modulators" section (Page 2 of document)	(2)	<p>Comment and rationale: Many biologicals (infliximab, adalimumab, ustekinumab, vedolizumab, Smad7antisense and biosimilars already tested or approved for adult IBD but little if any data in children</p> <p>Proposed change (if any): addition of: biologicals (infliximab, adalimumab, ustekinumab, vedolizumab, Smad7antisense and biosimilars –</p>	<p><i>Not included in Inventory:</i></p> <p>The need for data on these products in paediatric IBD is agreed in principle. However, for adalimumab, infliximab, ustekinumab and vedolizumab, this need has already been addressed in Paediatric Investigation Plans (PIPs) that have been agreed in the</p>

³ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004059.pdf

⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Domperidone-containing_medicines/human_referral_prac_000021.jsp&mid=WC0b01ac05805c516f

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		<p>(i) data on PK/PD, efficacy and safety + optimal (personalised) use in pediatric IBD. Including dosage in remission, relapse or weaning.</p> <p>(ii) data on the pros and cons of combination therapy (biosimilars and immunomodulator) in pediatric IBD.</p>	<p>"Treatment of ulcerative colitis" and/or "Treatment of Crohn's disease". As explained in the Notes included in the Gastroenterology Inventory, products with an agreed PIP in the condition of interest are not included in the list.</p> <p>In addition, the Inventory aims to identify the needs for 'existing' medicinal products; therefore, products that are not yet authorised (such as Smad7 antisense and biosimilars) are not included.</p>
Suggest addition of new section entitled "Eosinophilic oesophagitis"	(2)	<p>Comment and rationale: limited data in children for the use of swallowed topical steroids for the treatment of eosinophilic oesophagitis that has failed to respond to elimination diets</p> <p>Proposed change (if any): addition of: swallowed topical steroids ("oral viscous" budesonide, swallowed fluticasone): data on PK, efficacy and safety for eosinophilic oesophagitis</p>	<p><i>Included in the Inventory:</i></p> <p>As suggested, swallowed topical steroids have been included in the Inventory with the identified needs of "Data on PK, efficacy and safety for eosinophilic oesophagitis".</p>
Suggested addition of new section entitled "Probiotics"	(2)	<p>Comment and rationale: Rapidly increasing use and study of probiotics for a variety of paediatric disorders. Emerging data of its efficacy but need for further high quality studies</p>	<p><i>Not included in Inventory:</i></p> <p>Several double-blind, placebo-controlled, randomised trials of <i>Lactobacillus reuteri</i> in the treatment of infant colic are available⁵ and a meta-analysis is ongoing⁶.</p>

⁵ Chau K, Lau E, Greenberg S, Jacobson S, Yazdani-Brojeni P, Verma N, Koren G: Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating *Lactobacillus reuteri* DSM 17938. J Pediatr. 2015 Jan; 166(1): 74-8

Savino F, Ceratto S, Poggi E, Cartosio ME, Cordero di Montezemolo L, Giannattasio A: Preventive effects of oral probiotic on infantile colic: a prospective, randomised, blinded, controlled trial using *Lactobacillus reuteri* DSM 17938. Benef Microbes. 2015 Jan 1; 6(3):245-51

Sung V, Hiscock H, Tang MLK, Mensah FK, Nation ML, Satzke C, Heine RG, Stock A, Barr RG, Wake M: Treating infant colic with the probiotic *Lactobacillus reuteri*: double blind, placebo controlled randomised trial. BMJ 2014; 348:g2107

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): addition of: Lactobacillus reuteri - Data on optimal dosing, efficacy and safety for use in infantile colic	Therefore the PDCO considered that there is no need for additional data in this indication.
Page 4 under section entitled "Proton pump inhibitors"	(2)	<p>Comment and rationale: limited studies in premature babies, newborns and young infants. Also limited literature on long-term effects of PPI usage in children. Also limited data on long-term effects of PPIs in children (respiratory/digestive infections, iron, Vitamin D)</p> <p>Proposed change (if any): addition of: Data on optimal dosing, efficacy and safety for use of PPIs in premature babies, newborns and young infants. Data on long-term safety and effects of PPIs in children.</p>	<p><i>Not included in Inventory:</i></p> <p>Studies with proton pump inhibitors have been conducted in all age ranges from premature neonates to adolescents, therefore the PDCO considered that there is no need for additional data in this indication.</p>

⁶ Sung V, Cabana MD, D'Amico F, Deshpande G, Dupont C, Indrio F, Mentula S, Partty A, Savino F, Szajewska H, Tancredi D: Lactobacillus reuteri DSM 17938 for managing infant colic: protocol for an individual participant data meta-analysis. *BMJ Open*. 2014 Dec 4; 4(12):e006475.