EVOLUTION HEALTH

6 October 2020

Evolution Health (Life-Space Group) are pleased to engage in this consultation. The TGA have proposed the following changes to the 'Therapeutic Goods (Permissible Ingredients) Determination' ('the Determination') with effect from March 2021.

Proposed specific requirements

Magnesium is a mandatory component of this ingredient.

When used in medicines:

a) with an oral route of administration;
b) not indicated for laxative (or related) use; and
c) the maximum recommended daily dose for:

i. children aged between 1 and 3 years (inclusive) provides 65 mg or more total magnesium;
ii. children aged between 4 and 8 years (inclusive) provides 110 mg or more total magnesium; or
iii. individuals aged 9 years or older provides 250 mg or more total magnesium;

the following warning statements are required on the label:

'This product may have a laxative effect. Discontinue use if you develop diarrhoea (or words to that effect)'.
When used in medicines with an oral route of administration, the following warning is required on the label:

'Not suitable for infants under the age of twelve months' (or words to that effect).'

Discussion

Life-Space Group would like to raise our concerns with the proposed amendments on the grounds they are too restrictive and not in keeping with requirements for other permissible ingredients found in the determination. We also believe these proposed amendments are inconsistent with the available body of safety evidence and public health advice regarding nutritional guidelines which has been issued by multiple government authorities.

Implementation of a label statement warning consumers that an essential mineral like magnesium is not suitable for infants under twelve months is not in keeping with requirements for other similar permissible ingredients and could have other intended adverse implications. The Nutrient Reference Values, which are joint initiative of the Australian National Health and Medical Research Council (NHMRC), Australian Government Department of Health and Ageing and the New Zealand Ministry of Health (NZ MoH) specify an adequate intake (AI) for this nutrient of 75 mg / day for infants from 7 – 12 months of age. This value is accompanied by commentary that states:

The AI for 7-12 months was set by adding an estimate for magnesium from breast milk at this age to an estimate of intake from supplementary foods.

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This statement is an acknowledgement that infants begin to consume supplementary foods from this age and in some circumstances supplementation of intake would be warranted. Further, in implementing previous reforms, the TGA has clearly stated that consumers health knowledge is sub-optimal, so enforcing a label warning for a single essential nutrient like

magnesium is likely to signal to a consumer that magnesium is in some way harmful and could lead to unnecessary confusion. In some cases, parents might look to restrict their child's intake of magnesium with negative health outcomes. Should the TGA be wishing to limit administration of listed medicines to children under twelve months of age, then this should be a separate consultation as it has far reaching consequences, rather than implementation by stealth under the guise of a more insignificant and generalised consultation such as in this proposed change.

The proposed label warning threshold doses are excessively restrictive and could adversely impact consumers view of medicines. We are not against appropriate label statements to improve consumer use of medicines where there is a genuine rationale but we believe the proposed threshold doses are too low.

Adverse event evidence - European Scientific Committee on Food

The European Scientific Committee on Food (SCF), which the TGA has referred to in its ''Changes to the Permissible Ingredients Determination'' analysed data from studies on magnesium supplementation with doses ranging from 180 to 1095 mg elemental magnesium per day. No laxative effects were reported in children aged 4-12 years at up to 245 mg elemental magnesium per day (See **EFSA 2006, Table 3**).

Table 3. Mild diarrhoea induced by daily oral magnesium supplements

Total Mg Dose* (mg/day)	Diarrhoea (n)	Doses per day	Form	Subjects		Salt	Weeks	Ref.
				Mean age (range) (yr)	Gender			
180	0/130	3	Tablets	5.3-17.4	M, F	Asp. HCL#	3	1
245	0/112	2	Granules	8.1 (4-12)	M, F	Asp.HCL	3	2
245	0/181	2	Granules	4-12	M, F	Asp.HCL	3	3

Reference: 1 Classen et al (1986), 2 Schimatschek et al (1997), 3 Schimatschek et al (2001)

As doses of 245 mg of elemental magnesium did not produce diarrhoea in children between the ages of 4 and 17, it is unclear why the TGA is proposing an upper limit of 110 mg between the ages of 4 and 8 years to be the trigger for the proposed warning:

'This product may have a laxative effect. Discontinue use if you develop diarrhoea (or words to that effect)'.

Also, the fact that the National Health and Medical Research Council has issued a recommendation concerning the daily intake of magnesium for infants under the age of 12 months to avoid deficiency, provides justification for allowing this nutrient to be included in listed medicines intended for this population. Furthermore, the dose nominated to trigger a mandatory warning statement in children aged 1 years + would not even satisfy the recommended dietary intake for this age group which lends further validity to the conclusion that this threshold dose is too low.

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Adverse event evidence – Life-Space Group Pharmacovigilance searches

The Evolution Health pharmacovigilance team conducted clinical evidence searches using the Embase PV Wizard between September 2019 and April 2020 on three different forms of magnesium ingredients used in Pentavite and Life-space products. The magnesium citrate, and magnesium phosphate searches found a total of 393 articles. There were a total 86 safety signals generated, while instances of diarrhea or gastrointestinal distress were commonly found in adult populations, no cases of these effects were found in children aged 4 – 12 years, in agreement with the above SCF review.

The SCF 2006 report concluded that "As no data were available for children from 1 to 3 years, and since it was considered that extrapolation of the UL for older children and adults on the basis of body weight was inappropriate, no UL could be established for this age group".

Taking into account these two sources of safety surveillance, there is also no valid basis for the TGA extrapolating that a dose of 65mg for the 1-3 year age group, would pose the risk of a laxative effect.

National Health and Medical Research Council Guidelines

Children & adolescents (All)	**Recommended Dietary Intake (RDI) / Adequate intake (AI) of Magnesium**
7 – 12 mo	75 mg/day
1–3 yr	80 mg/day
4–8 yr	130 mg/day
9–13 yr	240 mg/day

Note: Breast milk volume of 0.6 L/day and the average magnesium concentration of breast milk of 34 mg/L gives a contribution of 20 mg/day from breast milk which is added to 55 mg/day from complementary foods.

Upper Limit Intake (UL) Magnesium	**Children & adolescents (All)**
7 – 12 months	Not established
1–3 yr	65 mg/day
4–8 yr	110 mg/day
9–13 yr	350 mg/day

NHMRC, when using diarrhoea as an endpoint, have set out that for children and adolescents 8 years and older and adults, a LOAEL of 360 mg of magnesium from non-food sources was established based on the results of Bashir et al (1993), supported by the findings of Fine et al (1991), Marken et al (1989) and Ricci et al (1991). It is, therefore unclear why the TGA is proposing an upper limit of 250 mg for the ages of 9 years and above to be the trigger for the proposed warning

The upper limits set for children 1 – 8 years by extrapolation on a body weight basis of 5 mg/kg/day meets most but not all the needs of those evaluated. Current bodyweight for children based on their age group, and this estimated 5 mg/kg/day provides us with a guide in identifying a suitable mean UL value for consumption. This value is an arbitrary amount as even the RDI is higher due to naturally occurring magnesium in food and the value is extrapolated. Further analysis was conducted to determine the recommended dose at which products intended to provide a laxative effect were effective.

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Clinically recommended laxative doses for Children

Recommended laxative dose 1

Blackmer (2010). Magnesium citrate ''Citroma''. Osmotic laxative. Oral: <6 y: 2-4 mL/kg/dose given once or divided. Each fl oz (30ml) contains: magnesium 290 mg. This would equate to at least a 290 mg dose of magnesium. See **Table 2 from this document - Medications commonly used for the management of constipation in children**.

TABLE 2. Medications commonly used for the management of constipation in children

Drug name	Brand name	Mechanism of action	Onset of action	Recommended dose	Adverse effects/ precautions/disadvantages
Glycerin	Colace; Fleet; Babylax	Osmotic laxative	15-30 min	**Rectal:** Neonates: 0.5 mL/kg/dose of rectal solution as enema <6 y: 1 infant suppository or 2-5 mL of rectal solution as enema >6 y: 1 adult suppository or 5-15 mL of rectal solution as enema	N/A
Magnesium citrate	Citroma	Osmotic laxative		**Oral:** <6 y: 2-4 mL/kg/dose given once or divided 6-12 y: 100-150 mL/dose given once or divided >12 y: 150-300 mL/dose given once or in divided doses OR 1-3 mL/kg/day	Risk of hypermagnesemia, hypophosphatemia, and secondary hypocalcemia Poor palatability
Magnesium hydroxide	Milk of Magnesia	Osmotic laxative		**Oral:*** <2 y: 0.5 mL/kg/dose 2-5 y: 5-15 mL/day once or divided 6-11 y: 15-30 mL/day once or divided >12 y: 30-60 mL/day once or divided OR 1-3 mL/kg/day divided BID	Risk of hypermagnesemia, hypophosphatemia or secondary hypocalcemia if overdosage and/or renal dysfunction; chalky taste

Reference: https://www.jpedhc.org/article/S0891-5245(10)00263-4/pdf

Recommended laxative dose 2

Biggs (2006). Oral magnesium citrate: 1 oz per year of child's age per day (maximum: 300 mL [10 oz]) for two or three days. For a three-year-old this equates to a dose of 870mg. Maximum dose equates to 2.9g. refer to **Table 5 found in 'Suggested Agents for Disimpaction in Infants and Children with Functional Constipation',** Biggs (2006).

TABLE 5

Suggested Agents for Disimpaction in Infants and Children with Functional Constipation

MEDICATIONS	*TREATMENT SIDE EFFECTS AND COMMENTS*
Oral magnesium citrate: 1 oz per year of child's age per day (maximum: 300 mL [10 oz]) for two or three days	Hypermagnesemia

Recommended laxative dose 3.

Clinical Guideline: evidence-based recommendations from ESPGHAN and NASPGHAN (Tabbers 2014)
We refer to **TABLE 6 in this document. Dosages of most frequently used oral and rectal laxatives**: of note is below:

Milk of magnesia (magnesium hydroxide)
2–5 y: 0.4–1.2 g/day, once or divided
6–11 y: 1.2–2.4 g/day, once or divided
12–18 y: 2.4–4.8 g/day, once or divided

Magnesium hydroxide $Mg(OH)_2$, so recommended elemental Magnesium dose range is between 166mg to 2000mg. This dose is much higher than the suggested dose proposed to cause laxation and diarrhea.

Recommended laxative dose 4

Magnesium citrate (Citrate of Magnesia, Citroma) is an OTC medicine that retains water in the intestines to relieve constipation. The medicine states the below instruction for use information:

Children 6 to under 12 years of age: Use 90 to 210 ml of magnesium citrate with a full glass of water; it may be taken as a single dose or divided doses.

Children 2 to under 6 years of age: Use 60 to 90 ml of magnesium citrate; it may be taken as a single dose or divided doses with a maximum dose of 90 ml in 24 hours.

Magnesium citrate solution contains 290 mg of magnesium and 80 mg of potassium per 1 fl oz (30 ml).
This dosing recommendation delivers between 580 and 2030mg of magnesium per dose, again much higher than the proposed dose suggested to risk diarrhea.

Summary

From the above recommendations it would appear that the minimum required dose to reliably induce laxation in children is 300 mg.

Conclusion

Our internal research, as noted in the previous sections covering adverse reactions on magnesium and diarrhoea indicates there was a lack of any osmotic laxative effect from magnesium found in the scientific research surveyed at a dose of 245mg elemental magnesium in children aged 4-17 years. Furthermore, extrapolating a dose of 65 mg for ages 1-3 years has been indicated to not be a valid approach for determining an appropriate threshold for this age group. Additionally, the threshold proposed for ages 9 years and above has been highlighted as inconsistent with the upper limit determined by the NHMRC which was determined using diarrhoea as an endpoint. Consequently, it is unclear why the TGA has selected the proposed threshold doses of elemental magnesium for the age groups discussed as it seems necessary that larger doses such as those recommended in clinical literature and product information sheets are needed to achieve the osmotic diarrhoea effect, which the TGA suggests occurs at much lower doses. It is very apparent that doses of over 300mg of

elemental magnesium will be more likely to induce a loosening of the stool or diarrhoea in children and therefore the threshold dosages suggested by the TGA which would trigger a label warning are too conservative and should better reflect the available clinical data.

We also reiterate that implementation of a label statement restricting administration of magnesium to children under twelve months of age is not in keeping with requirements for other similar permissible ingredients and could have other intended adverse implications.

References

Blackmer AB, Farrington AE. Constipation in the pediatric patient: an overview and pharmacologic considerations. J Pediatr Health Care. Nov-Dec 2010;24(6):385-99.

Biggs WS, Dery WH. Evaluation and treatment of constipation in infants and children. Am Fam Physician. 2006 Feb 1;73(3):469-77. Review.

EFSA. European Food Safety Authority. Tolerable Upper Intake Levels for Vitamins and Minerals - Magnesium 2006 [107-16]. Available from: http://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf

Fontana M, Bianchi C, Cataldo F, Conti Nibali S, Cucchiara S, Gobio Casali L, et al. Bowel frequency in healthy children. Acta Paediatr Scand 1989;78:682–4,

https://www.medicinenet.com/magnesium_citrate oral/article.htm#which_drugs_or_supplements_interact_with_magnesium_citrate
M M Tabbers, C DiLorenzo, M Y Berger, C Faure, M W Langendam, S Nurko, A Staiano, Y Vandenplas, M A Benninga, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; North American Society for Pediatric Gastroenterology. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014 Feb;58(2):258-74.

TGA. Consultation: Permissible ingredients annual changes 2020-21. Easily-dissociable magnesium salts and laxative effects. https://www.tga.gov.au/consultation/consultation-permissible-ingredients-annual-changes-2020-21

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