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Information for the package leaflet regarding lactose used as an excipient in medicinal products for human use

Draft

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Executive summary

This document has been written in the context of the revision of the Annex of the European Commission Guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (Annex, 2017 [3]; EC, 2018 [22]).

Lactose is a naturally occurring reducing disaccharide sugar used for manufacturing of drug products, vitamin preparations and sweeteners. It is found most notably in milk and is formed from galactose and glucose.

Lactose is widely used as a filler or diluent in tablets and capsules, in some parenteral formulations including corticosteroids and vaccines, and to give bulk to powders for dry powder inhalers.

Further it is used in the manufacture of some homeopathic products where lactose is commonly used as a vehicle for the manufacture of triturations.

Lactose is not considered to be toxic or harmful for healthy subjects. However, adverse effects might occur in patients with pre-existing conditions. Ingested lactose is hydrolysed by the enzyme lactase into its components, glucose and galactose, which are absorbed. If intestinal lactase activity is low or absent, undigested lactose may induce the symptoms of lactose intolerance. Further hydrolysation product galactose is a risk for patients suffering from hereditary galactosaemia. Both glucose and galactose may pose a risk to patients with hereditary glucose-galactose malabsorption. Patients with diabetes mellitus need to be made aware of medicines which contain significant amounts of glucose.

Lactose is commonly derived from cow's milk, and therefore may contain traces of cow's milk proteins which can cause serious allergic reactions in patients with cow's milk allergy.

Lactose is currently included in the Annex of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' dated 2017 but the information for the package leaflet relates only to the oral route of administration, and needs to be updated to include parenteral and inhaled products. The package leaflet wording in relation to the safety concerns hypersensitivity, galactosaemia, glucose-galactose malabsorption and diabetes mellitus has also been reviewed.

Proposal for updated information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Lactose	All	Zero	This medicine contains x mg of lactose in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.	This is equivalent to x/2 mg galactose and x/2 mg of glucose in each <dosage unit><unit volume>.
	Oral*, Inhalation	Zero	Lactose is a source of glucose and galactose. If you have one of the rare genetic disorders galactosaemia, or glucose-galactose intolerance or congenital lactase deficiency you must talk to your doctor or pharmacist before taking this medicine. <This medicine may contain traces of cow's milk proteins. If you are allergic to cow's milk, talk to your doctor or pharmacist before taking this medicine.>[1] <The small amount of lactose in each dose is unlikely to cause symptoms in adults with lactose intolerance.>[2]	Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary. [1] The text relating to cow's milk allergy is only required if the medicine contains lactose of bovine origin. Do not include this text if the medicine contains synthetic lactose free of cow's milk protein. [2] Use this Package Leaflet wording below the threshold of 400 mg per dose only. ** including oro-mucosal products that can be swallowed.*
		400 mg per dose	If your doctor has told you that you have an intolerance to lactose, talk to a doctor or a pharmacist before you take this medicine.	
	Oral	5 g per dose	If you have diabetes, you should take account of the amount of glucose in this medicine (x g	

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
			in each <dosage unit>).	
	Parenteral	Zero	< If you are allergic, or suspected to be allergic to cow's milk, you must not receive this medicine as it may contain trace amounts of cow's milk proteins.>[1]	[1] This text is required only if the medicine contains lactose of bovine origin. Do not include this text if the medicine contains synthetic lactose free of cow's milk protein.

Scientific background

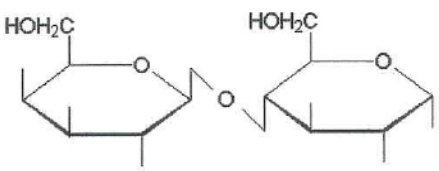
1. Characteristics

1.1. Category (function)

Lactose is a naturally occurring reducing disaccharide sugar used for manufacturing of drug products, vitamin preparations and sweeteners. It is found most notably in milk (occurring at levels between 1 and 7%) and is formed from galactose and glucose. Lactose is extracted from the whey of cow's milk (whey is the by-product from the production of cheese and casein).

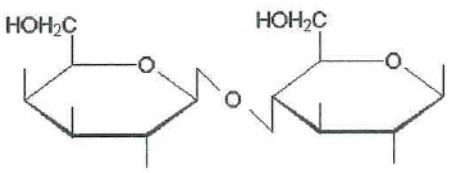
1.2. Physico-chemical Properties

Lactose consists of D-galactose and D-glucose fragments connected by a β-1-4 glycosidic bond. It has two isomeric forms (α and β) spontaneously passing from one into another due to mutarotation phenomenon. α- and β- forms differ in the conformation of the C^1 carbon in the glucopyranose fragment.



β-D-galactopyranosyl-4-α-D-glucopyranose

α-lactose



β-D-galactopyranosyl-4-β-D-glucopyranose

β-lactose

Lactose in the solid state occurs in crystalline forms (α-lactose monohydrate and α- and β-lactose anhydrous) or amorphous forms, which differ in their physico-chemical properties. In lactose anhydrous the β form typically predominates.

Amorphous lactose contains both the α- and β-forms. The crystalline forms are more hygroscopic and hard.

α-lactose monohydrate is obtained by crystallisation below 93.5°C. Shape of crystals (prism, rhombic etc.) depends on the crystallising conditions. Crystals formed are very hard and fragile.

β-lactose anhydrous is obtained by crystallisation above 93.5°C. The typical kite-form crystals are very small and soft. Due to low moisture content lactose anhydrous is suitable for the manufacturing of hydrophilic formulations with drug substance sensitive to moisture.

Molecular formula:	$C_{12}H_{22}O_{11}$. H_2O
	$C_{12}H_{22}O_{11}$
Molecular weight:	α-lactose monohydrate: 360.31 g/mol
	β-lactose anhydrous: 342.30 g/mol
Density (20 °C):	α-lactose monohydrate: 1.53 kg/l
	β-lactose anhydrous: 1.59 kg/l
Solubility:	freely but slowly soluble in water, practically insoluble in ethanol (96 per cent).

Currently there is no requirement specified in the two lactose monographs published by the European Pharmacopoeia (Ph. Eur), *Lactose monohydrate* and *Lactose,* to restrict the presence of or characterise and quantify the amounts of cow's milk proteins in lactose. The prescribed test for measurement of proteins and light-absorbing impurities allows for some impurities to be present. Therefore the prevalence of cow's milk proteins in lactose-containing products licensed in the EU is not quantified. It is assumed that they are likely to be present in most if not all products containing lactose.

1.3. Use in medicinal products

Functions in medicinal products formulations

Lactose is used as an inactive ingredient in various drug products.

α-lactose monohydrate is mostly used as a filler in tablets (because of poor flow characteristics it is often combined with free-flowing microcrystalline cellulose) and to a more limited extent in lyophilised products. Lactose is put into freeze-dried solution to increase volume and to promote cohesion. α-lactose monohydrate can also be sprayed onto a tablet to produce a shiny, hard coating, making the tablet easier to swallow. This form of lactose is also often used as a carrier of drug in inhalation devices. A carrier may be used for a dry powder inhaler (DPI) as a bulking agent to enhance reproducible dose metering. Regular shape and surface characteristics of lactose provide superior flow characteristics of drug-lactose mixtures in DPIs. However, every type of inhalation device has its own characteristics regarding both production and use by the patient; therefore, for every single combination of drug and DPI device, specific lactose, often with a narrow particle size distribution, is required. The quantity of lactose delivered per metered dose is typically in the low tens of milligrams range. The lactose component of each dose is essentially absorbed orally (Healy et al., 2014 [22]).

β-lactose anhydrous is mostly used in direct compression of tablet processes and as a filler in capsules.

Food

Lactose is the main sugar component of cow milk, and therefore contained in various amounts in dairy products (depending on processing methods) and products using dairy products during manufacture. Further it is introduced in various processed foods. It could be considered ubiquitously used in food processing. Since lactose can cause adverse events in patients with pre-existing conditions such as malabsorption, establishment of lactose thresholds in lactose intolerance and galactosaemia with regard to making a nutrition claim such as 'lactose free' was discussed by the European Food Safety Authority (EFSA). Furthermore, patients with diabetes should control their lactose intake because of its effect on the glucose level in blood.

A risk assessment on lactose thresholds in lactose intolerance and galactosaemia was discussed by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), leading to the publication of a Scientific Opinion in 2010 (EFSA, 2010 [17]). For infant and follow-on formula, 10 mg lactose/100 kcal was established as a safe threshold in galactosaemia. 10 mg lactose/100 g has been established as a threshold level for lactose-free food labelling in a number of EU states (DK, EE, FI, NO, SE).

2. Pharmaco-toxicological data

2.1. Toxicology

As lactose is a food component a limited quantity of published nonclinical toxicological data are available for lactose. Most of the studies were not primarily designed to assess the effects of lactose; lactose either formed part of a formulation or was used as a comparator product in those

investigations. No data has been reported for parenteral use. Furthermore, there are no juvenile toxicity studies available.

Baldrick and Bamford (1997) reviewed non–GLP studies in the rat, dog and/or primate following administration via the inhalation and dietary routes. The main findings reported in the rodent feeding studies were abdominal distension and diarrhoea which were considered to be due to non-specific effects associated with high dietary doses of lactose. Long term studies in rats with high dietary levels of lactose and related sugar and sugar alcohols resulted in pelvic nephrocalcinosis, adrenal medullary changes and Leydig cell tumours. The dietary imbalance resulting from these high doses cause physiological disturbances and an overload of metabolic processes particularly those involving calcium absorption. These changes at high dietary intakes of lactose are considered to be of little relevance for man under the normal conditions of use of the material as an excipient in pharmaceutical formulations. No adverse local effects to the lung have been demonstrated in the animal studies using the inhalation route (Baldrick and Bamford, 1997 [7]).

Table 1 Toxicity after single administration

Species	Route	Observations
Rats	Orally	Wise et al. (1984) [58]: Weanling or adult (9 week-old) rats were **fed diets containing 0, 250 or 500 g lactose/kg for 10 days**, after which the activities of six cecal microbial enzymes (azoreductase, beta-glucosidase, beta-glucuronidase, nitrate reductase, nitroreductase and urease) were determined. Result: Lactose caused cecal enlargement; Lactose increased total nitrate reductase and urease activities in both age groups, but decreased total azoreductase, beta-glucosidase, beta-glucuronidase and nitroreductase activities in weanlings.
Rats	Inhalation	De Jesus Valles et al. (2008) [15]: **Acute exposure of lactose inhalation,** lungs were excised and processed to determine several toxicity biomarkers Result: no toxic effect in pulmonary tissue.

Table 2 Toxicity after repeated administration

Species	Route	Observations
Rats	Orally	Hodgkinson et al. (1982) [26]: **Diets containing 30% by weight of waxy maize starch, lactose monohydrate, acetylated distarch phosphate (EEC No. 1414) or acetylated distarch adipate** (EEC No. 1422) were fed to weanling female Specified Pathogen-Free Sprague-Dawley rats for 1 yr and to similar 9-month-old rats for 34 wk. **Behaviour and general health** were unaffected by the different diets and there were no diet-related differences in food consumption. **main treatment-related changes** in rats on the three test diets were (1) cecal enlargement, (2) increased urinary excretion of calcium, (3) increased renal calcification as measured by chemical analysis of renal tissue obtained at autopsy and (4) increased medullary and pelvic nephrocalcinosis as assessed histopathologically.

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Rats	Orally	Wouterson (1987) [59]: Chronic Toxicity and Carcinogenicity of Lactitol in Rats: Comparison with Lactose. The lifetime study published in summary form here is described in much more detail by Sinkeldam et al (1992a) [48] – see below.
Rats	Orally	Sinkeldam et al. (1992a) [48] Sub-chronic and Chronic Toxicity/carcinogenicity feeding studies with lactitol in rats. In a comparative study investigating the sub-chronic and chronic toxicity of lactitol compared to lactose, weanling Wistar rats (n=10) fed diets containing 25% lactose for 13 weeks and a second group of rats aged 3 months fed diets with 25% lactose for 13 weeks showed the following effects in the lactose group: • No effect on mortality. • Cecal enlargement observed consistently. • Haematological parameters and urine composition - no treatment-related abnormalities. • Increased plasma alkaline phosphatase (AP) levels. A summary report of the lifetime study has been published earlier Wouterson (1987) [59]. In a lifetime toxicity/carcinogenicity study with in utero exposure, groups of 50 rats of each sex consumed diets with 0, 2, 5, or 10% lactitol, or 20% lactose for 130 weeks. Satellite groups of 10 rats per group received the same diet but were sacrificed after 53 weeks. The following effects were seen in the lactose group: • Statistically significant increase in bile duct hyperplasia. • Decrease in femur calcium content in terminated female rats. • Increased incidence of pelvic nephrocalcinosis, adrenomedullary proliferative changes and hyperplastic and neoplastic changes of Leydig cells. Authors note “since Leydig cell tumours occur in humans at an extremely low rate despite the ingestion of substantial amounts of lactose with ordinary meals, the observation made in rats lacks apparent relevance for man.”
Rats	Orally	De Groot AP et al. (1995) [14]: Effect of lactose on hyperplasia and neoplasia induction in adult mammals. 20% lactose diet unsupplemented or supplemented with 1% NH_4Cl or 2% $KHCO_3$, for at most 2.5 yr +control increased production in the large intestine of short-chain fatty acids (SCFA) resulting from increased fermentation of carbohydrate residues. Feeding lactose increased urinary calcium levels, the effect being enhanced by NH4Cl and reduced by $KHCO_3$. Lactose also tended to increase blood values of alkaline phosphatase and to decrease those for bicarbonate and base excess. These tendencies were generally more marked with NH4Cl, and less marked or absent with $KHCO_3$. In addition, rats fed lactose showed decreased severity of nephrosis, increased mineralisation and hyperplasia of the renal pelvic epithelium, and relatively high incidences of Leydig cell hyperplasia and neoplasia. The report suggests that the acidic end products

		of carbohydrate fermentation (SCFA) act as an acid load on the body.
Rats	Orally	Tischler et al. (1996) [53]: Effect of lactose on increased incidence of pheochromocytomas. This relationship is hypothesised to be based on altered Ca^{2+} homeostasis due to increased Ca^{2+} absorption or that the tumours occur secondarily to increased chromaffin cell turnover. Result: The data suggest that altered Ca^{2+} homeostasis may increase chromaffin cell proliferation and support the hypothesis that diets containing high concentrations of sugars and sugar alcohols cause pheochromocytomas in rats secondarily by this mechanism.
Rats	Orally	Liu et al. (2003) [28]: Metabolic **effects of glucose diet (CON), low lactose diet (10.5%, LLD), or a high lactose diet (41.9%, HLD)** in Long-Evans female rats, necropsy after 7 months. Results in HLD group: significantly lower body weights, significantly lower triglyceride and non-esterified fatty acid levels, serum glucose, insulin concentrations were lower than controls.

Genotoxicity

Some studies have been conducted into the genotoxic potential of lactose which are summarised below:

Lactose is the major carbohydrate in human and mammalian milk and its two monomers glucose and galactose are naturally occurring sugars that are not expected to be genotoxic. Some data on genotoxic potential of lactose has been identified. In an in vitro chromosome aberration assay lactose tested at concentrations up to 11.6 mg/ml did not reduce the mitotic activity nor induce chromosome aberrations in human lymphocytes cultured with or without the S-9 mix (Sinkeldam et al., 1992a [48]). Lactose (used as a control agent) was negative in sister-chromatid exchange assays both in vitro and in vivo in mice (Subramanyam et al., 1985 [51]).

Carcinogenicity

Long term feeding studies in rats have assessed the carcinogenic potential of lactose (Wouterson, 1987 [59]; Sinkeldam et al., 1992a [48]; de Groot AP et al 1995 [14]; Tischler et al., 1996 [53]: Table 2). As these studies were evaluating the use of lactose in the diet, very high doses were used (approximately 10,000 mg/kg). Notable findings included increased blood alkaline phosphate and urinary calcium, decreased pH of cecum contents and enlargement/increased weight of the cecum, and pelvic nephrocalcinosis of the kidneys. Notable neoplastic findings were increased hyperplasia and neoplasia (phaeochromocytomas) of the adrenal medulla and increased Leydig cell tumours.

Treatments causing carbohydrate malabsorption when rats are fed poorly digestible sugars (such as lactose) and sugar alcohols (such as lactitol) are associated with abnormalities in calcium homeostasis and in treatment-related adrenal medullary hyperplasia, and in some cases pheochromocytomas (Baer, 1988 [6]; Sinkeldam et al., 1992a [48]; De Groot et al. 1995 [14]; Tischler et al., 1996 [53]). In contrast to studies in rats, lactose did not induce pheochromocytomas in mice (Lynch et al. 1996 [30]). Agents causing carbohydrate malabsorption in humans have not been linked to an increased risk of pheochromocytomas (Baer, 1988 [6]) and the findings in the rat have been considered to have little relevance to humans (Tischler et al., 1996 [53]). Similarly, the increase in the incidence of Leydig cell hyperplasia and Leydig cell tumours observed when rats are fed lactose and related sugar alcohols (Woutersen, 1986 [59]; Sinkeldam et al., 1992a [48]; De Groot et al., 1995 [14]) is not seen in mice (Bar, 1992 [8]). In rats, many agents have been associated with Leydig cell tumours (Clegg et al.,

1997 [12]); however, these have not been associated with Leydig tumours in humans. This has been related to a number of physiological differences between rats and humans (Cook et al., 1999 [13]), including differences in the number of Leydig cell luteinising hormone (LH) and luteinising hormone-releasing hormone (LHRH) receptors.

It is generally considered that the relevance the rat adrenal medullary proliferative lesions and Leydig cell tumours are species-specific and related to chronic dietary imbalance resulting in physiological disturbances and an overload of the metabolic processes, and are not of relevance to humans.

Reproductive function toxicity

Studies on the reproductive toxicity of lactose are summarised in Table 3. Increased early and late resorptions were reported in mice, rats and rabbits (Beltrame et al., 1973 [9]; Pelagalli et al., 1971 [39]) at high administered doses 400 mg/kg to 25 g/kg. No effects were reported in the dam. Nevertheless there were discrepancies and/or lack of information available on these studies making the reliability of the findings questionable. A multigeneration study in rats (Sinkeldam et al., 1992b [49]) showed a reduction in litter parameters (e.g. slight reduction in the number of pups born alive, litter size at birth, viability index and pup weight for F0 and F1 offspring) which was considered to be secondary to maternal toxicity. No foetal effects were attributed to lactose. Studies in mice given 10,000 mg/kg lactose on days 8 to 12 of gestation revealed no maternal toxicity and no effects on litter size, body weight on days 1 and 3, or neonate survival (Seidenberg et al., 1986 [47]).

Table 3 Reproductive toxicity

Species	Route	Observations
Rat	Oral dietary	A study published in 1935 found that female rats fed 20% dietary lactose reproduced normally and had normal ovarian structures (Whitnah, 1935 [57])
Rat	Oral	Pelagalli et al, (1971) [39]†. Oral administration of 25 mg/kg* lactose to rats from day 4 to day 18 of pregnancy increased the number of resorptions and reduced the number and body weight of embryos removed on day 19 of gestation. *In a review by P. Baldrick and DG Bamford (1997 [7]) it is suggested that the 25 mg/kg is a typographical error and should state 25 g/kg (25,000 mg/kg); although this seems unlikely the reviewers had not been able to substantiate this. †Published in abstract form. Full details of the study are not available.
Mice, rat and rabbit	Oral	†Beltrame et al, (1973) [9]: **Maternal and Fetal Toxicity induced by lactose.** CFE-SPF rats, CF1-SPF mice and New Zealand rabbits were administered between 400 to 4000 mg/kg/day during organogenesis (GDs not specified) in single daily doses (rats and mice) or two half-daily doses (rabbits). Result: Lactose was well tolerated by pregnant rats and mice but caused high mortality in the pregnant rabbits. **Increased early and late resorptions were reported in all species tested**. However foetal development and viability were normal across all species. Increases in external and visceral major malformations or minor anomalies were reported, but stated to not be dose-related, and there were no effects

		on the skeleton. †Published in abstract form. Full details of the study are not available
Mice	Oral, gavage	Seidenberg et al. (1986) [47]: In this study pregnant ICR/SIM mice were administered 10,000 mg/kg lactose by oral intubation on days 8 to 12 of gestation. Results: No maternal toxicity and no effects on neonate survival, litter size and body weight on days 1 and 3.
Rat	Oral, dietary	Sinkeldam et al. (1992b) [49] conducted a multigeneration study in which Wistar rats were fed lactose (20% of diet) daily over three successive generations. Result: No adverse effects on fertility or reproductive performance. **Maternal toxicity characterised as low body weight, enlargement and increased weight of the caecum were noted**. **Foetal effects included a slight decrease in the number of pups born alive, litter size at birth, viability index and pup weight for F0 and F1 offspring were reported.** The reduction in litter parameters may have been secondary to the effects reported in the dams.

Local tolerance

No data found

Hypersensitivity

See clinical safety data.

2.2. Pharmaco- and toxicokinetics (in animals)

Animal kinetic data are not available in the literature except for the inhalation route

Inhalation

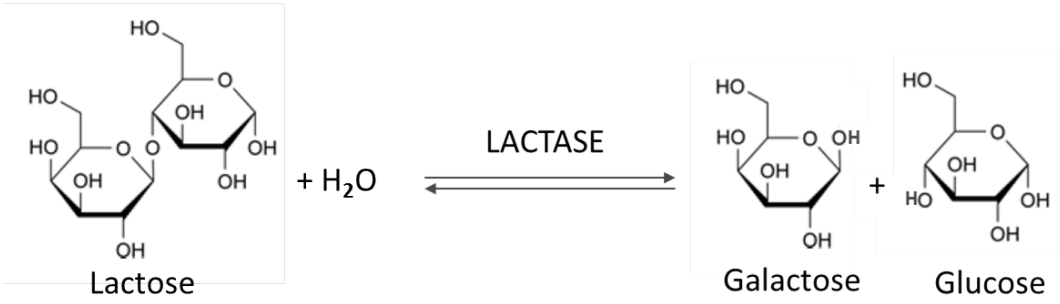
Studies performed in monkeys (*Macaca arctoides*) and rats (*Sprague-Dawley*) show that 14C lactose administered as a solution (water) intratracheally is rapidly absorbed into the systemic circulation of the rat and persists in the blood for at least 2 hours (Clark et al., 1974 [11]).

3. Pharmacokinetics (in humans)

3.1. ADME (absorption, distribution, metabolism, elimination)

Oral

Lactose is poorly absorbed orally. Ingested lactose is hydrolysed by the enzyme lactase in human small intestine into its monosaccharide components, glucose and galactose, which are absorbed. Only small amounts of intact lactose enter the systemic circulation via passive diffusion in the gut (Pimental et al., 2017 [41]).



Inhalation

When used as a carrier in dry powder inhalers, more than 98% of lactose settles in the oropharynx due to the large particle size (>50 µm) and is ingested (Nowak-Wegrzyn, 2002 [36]).

3.2. Interactions

Lactose is a reducing sugar and is therefore incompatible for formulation with primary and, to a lesser extent, secondary amines (for example amino acids, amphetamine, lisinopril) as a reaction occurs leading to brown-coloured condensation products (Penz & Zeleznik, 2017 [40]).

4. Clinical safety data

Lactose is a common food component and not considered to have a toxic effect in healthy individuals. Adverse effects are expected only in patients with pre-existing conditions of lactose or glucose-galactose malabsorption, galactosaemia, diabetes or hypersensitivities.

The EMA Biotechnology Working Party (BWP) concluded that the bovine spongiform encephalopathy (BSE) risk in finished pharmaceutical grade lactose is negligible (EMA, 2002 [19]; EC, 2011 [23]).

4.1. Hypersensitivity Reactions

Cases of allergic reactions including severe, life-threatening anaphylactic reactions have been reported in patients with allergies to cow's milk protein following treatment with medicinal products containing lactose with traces of cow's milk proteins present as an impurity. Reports from the literature and from spontaneous reporting have revealed cases, mainly in the paediatric population, following use of parenteral, and rarely inhaled or oral lactose-containing products which were attributed to the presence of cow's milk protein. These are reviewed below.

Cow's milk contains approximately 30-35 g of protein per litre – a mixture of serum (whey) proteins and caseins which may act as allergens. The serum proteins include alpha-lactoalbumin, beta-lactoglobulin, bovine serum albumin, bovine lactoferrin and bovine immunoglobulins. The casein proteins include alpha (s1)-casein, alpha (s2)-casein, beta casein, and kappa caseins. Two types of immunological/hypersensitivity reactions are triggered by cow's milk proteins, IgE-mediated immediate and non-IgE-mediated delayed reactions. Immediate hypersensitivity reactions usually manifest up to an hour after exposure and are facilitated by recognition of epitopes on the protein by the IgE antibody. The clinical manifestations include skin reactions (atopic dermatitis, urticaria), respiratory reactions (wheezing, bronchospasm) and systemic reactions (anaphylactic shock). Non-IgE-mediated reactions include food-protein-induced enterocolitis, proctocolitis and enteropathy syndromes, which primarily affect infants or young children (EFSA, 2014 [18]).

Children with severe milk allergy have been reported to experience acute allergic reactions following ingestion of food products containing >10 parts per million of total milk protein (1 mg /100 g; Nowak-Wegrzyn et al., 2004 [37]).

Estimates of the prevalence of cow's milk allergy vary widely across studies in different populations, and are dependent on the method of assessment (i.e. self-reporting versus sensitisation tests). Allergy can develop from the neonatal period but peaks during the first year of life, with prevalence declining as childhood progresses. In Europe, self-reported prevalence of cow's milk allergy ranged from 2% to 7.5% at one year of age. The prevalence of clinician-diagnosed disease was reported to be 1.8% at eight years of age in a Swedish study; in adults, self-reported prevalence ranged from 1.8% to 3.3%. Prevalence estimates based on clinical history plus a positive skin prick test were lower at 0.3% and 0.6% in Iceland and Sweden at 18 months of age, respectively (EFSA, 2014 [18]).

Parenteral medicines

Cases of severe allergic reactions to trace cow's milk protein in lactose-containing injectable methylprednisolone medicines were reviewed during an EU referral procedure (EMA, 2017 [20]). Cases were obtained from both literature and spontaneous reporting. In these cases, patients were being treated for an existing acute allergic reaction which was further exacerbated by the lactose-containing medicine. In some of the reported cases the adverse reaction was misinterpreted as a lack of therapeutic effect, leading to re-administration of methylprednisolone and subsequent worsening of the patient's clinical condition. Most cases occurred in patients under 12 years of age. Skin prick tests were conducted with a panel of corticosteroids in a number of these cases (e.g. Eda et al., 2009 [16], Savvatianos et al., 2011 [46]). Overall the results were consistent with the hypothesis that milk proteins in lactose caused the allergic reactions in patients with milk allergy, rather than methylprednisolone itself. In some cases traces of milk proteins were detected in samples of the implicated medicine using a highly sensitive ELISA assay (Savvatianos et al., 2011 [46]). It was considered that the initial allergic conditions, such as an asthma exacerbation, may have increased susceptibility to a further allergic reaction to cow's milk proteins in the lactose containing medicine. However, it cannot be ruled out that severe allergic reactions to parenterally-administered cow's milk protein could occur in the absence of a pre-existing allergic state. At the conclusion of the referral procedure, marketing authorisation holders of lactose-containing injectable methylprednisolone products were required to reformulate their products to remove lactose, with a contraindication to use in patients with cow's milk allergy introduced as an interim measure (EMA, 2017 [20]). In the light of this, a contraindication to use in patients with cow's milk allergy is recommended for lactose-containing parenteral medicines, with a threshold dose of zero.

Inhaled medicines

Lactose is commonly used in dry powder inhalers (DPI) as a carrier to improve flow characteristics and aerosolisation performance. The lactose particles are typically 50-100 µm in diameter and are deposited in the mouth or the back of the throat during inhalation, following separation of the active ingredient (Healy et al., 2014 [22]). In terms of lactose exposure therefore, the dose can be considered as being delivered orally, although some exposure to the airways may occur.

Nowak-Wegrzyn et al. (2002) [36] investigated a range of DPIs for milk protein content. Milk proteins were detected in all tested DPIs. Whey proteins were present at much higher concentrations than casein or whole milk protein, consistent with the method of lactose purification. The authors noted that food allergen inhalation can induce acute bronchospasm in food allergic patients, and that in addition to a local lung effect, systemic allergic reactions might result from milk protein absorption from lung mucous membranes or ingestion of swallowed lactose from DPIs.

One case of hypersensitivity in an adult and a number of cases in children have been reported following inhalation from DPIs containing lactose carrier. In the adult case (Morisset, 2006 [34]) a woman allergic to milk presented with several atopic dermatitis and asthma exacerbations following prescription of a formoterol dry powder inhaler. Skin prick and IgE testing was positive for cow's milk. A bronchial challenge with lactose induced bronchospasm, rhinitis and exacerbation of asthma. Nowak-Wegrzyn et al. (2004) [37] describe an 8 year old boy with severe milk allergy and asthma who experienced chest tightness immediately following three inhalations of Advair Diskus (salmeterol/fluticasone DPI containing lactose) despite several months of successful use. A subsequent supervised inhalation challenge induced chest tightness, dramatic decline in FEV_1 and hypotension, treated with adrenaline. Sa et al. (2011) [45] report on a 10 year old boy with asthma and cow's milk allergy who experienced urticaria around the lips and bronchospasm following treatment with a lactose-containing fluticasone DPI. In a case described by Robles and Motheral (2014) [43] a 9 year old boy with a history of milk allergy was admitted to hospital with an exacerbation of asthma and experienced chest tightness and a prolonged hospital stay after receiving 1 dose of lactose-containing Advair Diskus DPI. He had no adverse reaction to the lactose-free Advair Diskus HFA. Robles and Motheral conclude that lactose-containing inhaled medications should not be administered to patients with milk protein allergies. Morikawa et al. (2016) [33] describe a 6 year old girl with milk allergy and persistent asthma who suffered an anaphylactic reaction following inhalation of Inavir (laminamivir octanoate hydrate) to treat an influenza infection. A subsequent skin-prick test showed a positive reaction for the lactose excipient but negative for laninamivir; the milk protein beta-lactoglobulin was detected in the excipient. The authors noted that patients with influenza may be at higher risk due to increased airway hypersensitivity. A further case in association with laminamivir is reported by Yamaide et al. (2016) [60]. In this case, a 9 year old boy with severe milk allergy and asthma treated with a fluticasone/salmeterol DPI experienced chest tightness, shortness of breath and wheeze immediately after inhalation of laminamivir. Skin-prick testing was positive for lactose but not laminamivir. His DPI was subsequently changed to a metered dose inhaler. Maini et al. (2017) [31] discuss a case in which a 17 year old male with cow's milk allergy was treated with a lactose-containing fluticasone/salmeterol inhaler without problems, but experienced tongue and lip swelling and chest tightness following a trial with an albuterol DPI training device which contained lactose only. A further case is described by Andrade et al. (2017) [2] who report that an 8 year old boy with cow's milk allergy experienced lingual and labial pruritus with oxygen desaturation following challenge with a lactose-containing budesonide DPI. In this case, further investigation via mass spectrometry found no trace of cow's milk protein contamination in the medicine but several galactose-derived oligosaccharide residues with suspected allergenic potential were detected.

Some DPIs, such as Symbicort Turbohaler (budesonide/formoterol; Astra Zeneca, 2017 [4]) include an explicit reference to cow's milk protein in the 'hypersensitivity to the active substance or any of the excipients' contraindication in section 4.3 of the SmPC. However, many other products do not.

In contrast, Spiegel and Anolik (2010) [50] reviewed 278 milk allergic patients from a pool of 8418 with asthma. 21 used the lactose-containing DPIs Advair Diskus or Asmanex. No reactions attributable to milk protein were identified. The authors suggest that this may have been because the milk protein contamination was too low, and/or the patients had been fortunate not to be dispensed batches with higher degrees of contamination. They further state that milk protein reactions to DPIs are rare, and that 'watchful vigilance' rather than avoidance of such medications is appropriate. Kelso (2014) [27] reviewed food allergens in medications, including lactose in DPIs, and concluded that medicines should not be routinely withheld from patients who have particular food allergies because the vast majority will tolerate them without problems. Clinical guidelines also vary. The British Society for Allergy and Clinical Immunology (BSACI) note in their guideline on milk allergy that removal of milk proteins from

pharmaceutical grade lactose is an efficient process, and allergic reactions are thus highly unlikely in most milk allergic individuals (Luyt et al., 2014 [29]). However, the Drug Allergy Committee of the Spanish Society of Allergology and Clinical Immunology recommend that patients with severe cow's milk allergy should be treated only with medicines containing lactose which is not of animal origin (particularly intravenous medicines, but also other routes; Audicana Berasategui et al., 2011 [5]).

Severe hypersensitivity reactions to trace milk proteins in lactose-containing DPIs appear to be reported less frequently than reactions to parenteral medicines. However, no safe threshold dose of inhaled milk protein has been established. Acute allergic reactions have been reported in children with severe milk allergy following ingestion of food products containing >10 parts per million of total milk protein (Nowak-Wegrzyn et al., 2004 [37]). The EMA Pharmacovigilance Working Party (PhVWP) reviewed lactose in powder for inhalation in 2008; a small number of reports of hypersensitivity reactions involving patients with a history of milk allergy were noted, and it was concluded that the threshold inhaled dose of lactose for patients with milk allergy should be zero. Given the uncertainty regarding a safe threshold for inhalation of lactose in patients with cow's milk allergy, a threshold dose of zero has also been adopted in this guideline. However, given the small number of documented cases of hypersensitivity relative to the number of DPI on the market, and evidence that some DPI are used by patients with known cow's milk allergy without ill effect, a 'talk to your doctor or pharmacist' warning in the package leaflet is proposed, rather than a 'do not use' statement.

Oral medicines

Several cases of hypersensitivity reactions to oral lactose-containing medicines have been reported. Two adult asthmatics developed bronchospasm from lactose-based placebo tablets, confirmed by positive double-blind challenges (Zeiss, 1976 [61]; Van Assendelft, 1984 [55]). In the case described by van Assendelft, the patient had lactose intolerance and the author speculates that they may have reacted to one of the metabolic products of colonic bacterial digestion of lactose. Rosenhall (1982 [44]) describes a blinded study in asthma patients in which oral lactose (used as a placebo control) elicited asthma symptoms on 10 occasions. However, when patients were re-challenged without being deprived of their morning medication the symptoms did not reoccur, making interpretation uncertain; as noted by Rosenhall, omission of treatment and repeated forced expiratory manoeuvres can in themselves provoke asthma symptoms in susceptible patients. Tsuruta et al. (2005 [54]) describe a case of a 54 year old woman who experienced an erythematous rash on her eyelids after trials of several different lactose-containing medicines. She had experienced a similar reaction to ingestion of dairy products, and an oral challenge test confirmed reaction to lactose. The precise mechanism of such fixed eruptions is unknown, but they are considered to be an allergic reaction or genetic disorder. In this case, other family members had lactose intolerance. It is unclear whether this case represents a reaction to lactose itself or to trace cow's milk proteins.

Cases of anaphylactic reactions to orally administered lactose-containing medicines have also been noted via EU pharmacovigilance procedures. Given the uncertainty regarding a safe threshold for ingestion of lactose in patients with cow's milk allergy, a threshold dose of zero has been adopted in this guideline, in line with the recommendation for parenteral and inhaled products. However, given the small number of documented cases of hypersensitivity relative to the very large number of lactose-containing medicines on the market, a 'talk to your doctor or pharmacist' warning in the package leaflet is proposed, rather than a 'do not use' statement.

4.2. Lactose malabsorption / intolerance

Ingested lactose is normally hydrolysed by the lactase enzyme on the microvillus membrane of enterocytes. It is split into glucose and galactose, which are rapidly absorbed within the small

intestine. Disruption of this process can lead to an increased osmotic load from undigested lactose, causing lactose malabsorption and thus symptoms of intolerance; symptoms are variable but can include abdominal pain, bloating, flatulence, nausea and diarrhoea. Lactose malabsorption can be either genetically determined (primary lactase deficiency) or acquired as a consequence of other diseases which damage the intestinal epithelium such as coeliac disease. Primary lactase deficiency may be a result of congenital lactase deficiency – a severe form of the disease in which lactase activity is very low or absent from birth – or lactase non-persistence, caused by the down-regulation of lactase after weaning (EFSA 2010 [17]). Both these primary forms of lactose malabsorption are inherited in an autosomal recessive manner (Canani et al 2016 [10]).

Congenital lactase deficiency is very rare, with only a few cases documented in the world. The prevalence of lactase non-persistence varies widely; in Europe prevalence in adults varies from 15% to 70%. The post-weaning fall in lactase activity generally occurs between 2 and 5 years of age (Canani et al., 2016 [10]).

A number of studies have attempted to determine a threshold for lactose intake which will trigger symptoms in lactose-intolerant patients. These were reviewed in relation to food by the EFSA Panel on dietetic products, nutrition and allergies. They noted the great variation in individual tolerances, with symptoms of lactose intolerance described after intake of less than 6 g of lactose in some subjects. Noiles et al. (2010 [35]) note that some individuals have been reported to experience symptoms with as little as 100 mg. However, the Panel concluded that the vast majority of patients with lactose malabsorption will tolerate up to 12 g of lactose as a single dose with no or minor symptoms (EFSA 2010 [17]).

Montalto et al conducted a randomised, cross-over, double-blind, controlled study to investigate whether low dose lactose in medicines increased breath hydrogen excretion or gastrointestinal symptoms. 77 patients with confirmed lactose malabsorption underwent two hydrogen breath tests with 400 mg of lactose and 400 mg of placebo. No significant differences in breath hydrogen excretion or severity of symptoms was seen with 400 mg of lactose compared to placebo, suggesting that medicines with 400 mg of lactose or less could be used safely in patients with malabsorption (Montalto et al., 2008 [32]).

Based on the above studies, a threshold of 400 mg of lactose per dosage unit is considered to be a safe threshold for the vast majority of patients with lactose malabsorption. It should be noted however that ingestion of multiple doses of some medicines, particularly if taking more than one lactose-containing medicine, could result in a total daily dose of lactose of more than 10 g (Noiles et al., 2010 [35]). The amount of lactose per dosage unit should therefore be stated clearly in the product information.

4.3. Galactosaemia

Galactose is metabolised predominantly via a sequence of reactions known as the Leloir pathway. Deficiency of any of the three enzymes which catalyse this pathway can lead to congenital galactosaemia, with the presentation and prognosis varying according to the enzyme affected. The most severe form is classical galactosaemia, resulting from a deficiency of galactose-1-phosphate uridylyl-transferase (GALT) and affecting approximately 1 in 30,000 to 1 in 60,000 live births. Symptoms include vomiting, diarrhoea, cataracts, hepatomegaly and E. coli sepsis, and can lead to neonatal death. Long term complications may include speech and cognitive disabilities, primary or premature ovarian failure, ataxic neurologic disease, delayed growth, and decreased bone density. Other variants of galactosaemia are caused by deficiency in galactokinase (GALK) or UDP-galactose-4-epimerase (GALE). For all types of galactosaemia, a galactose-restricted diet is the mainstay of

treatment (Fridovich-Keil, 2006 [24]). Dietary lactose elimination, so far as possible, is therefore necessary.

The EFSA Panel on dietetic products, nutrition and allergies reviewed appropriate thresholds for lactose in infant and follow-on formula milk labelled as 'lactose-free'. They note that in some infants 100 mg of lactose per day has been found to sustain mild jaundice and failure to thrive. Acceptable galactose intakes for patients with severe galactosaemia, based on data from European treatment centres, are considered to be: infants 50–200 mg, toddlers 150–200 mg, school children 200–300 mg, adolescents 250–400 mg and adults 300–500 mg of galactose per day. One milligram of lactose contributes 0.5 mg of galactose, so even small amounts of lactose contribute significantly to daily intake for patients with galactosaemia. Based on assumed daily energy intake, the Panel endorsed the criterion of ≤10 mg lactose/100 kcal for labelling infant and follow-on formulae as "lactose-free" and suitable for use in galactosaemia. For example, assuming an energy intake of 600 kcal in milk per day for an infant, this criterion would give a maximum galactose intake of 6 x 10 mg/2 = 30 mg of galactose, within the daily limit of 50–200 mg (EFSA, 2010 [17]). Even small additional quantities of lactose in medication could contribute very significantly to daily galactose intake. Given this, a conservative threshold is warranted for warnings related to galactosaemia, and a threshold of zero is considered appropriate for all routes of administration.

4.4. Glucose-galactose malabsorption

Congenital glucose-galactose malabsorption (GGM) is a very rare autosomal recessive disease, with only approximately 200 affected individuals known worldwide. It results from a defect in the SLC5A1 gene, which codes for an intestinal brush border Na+/glucose co-transporter. GGM presents with onset of severe, watery acidic diarrhoea from birth and is life-threatening if not treated. Treatment is via a low glucose-galactose diet, including fructose-based formula (Rafeey and Golzar, 2007 [42]; Canani et al., 2016 [10]). Some tolerance of glucose and galactose may develop over time, and children with GGM may be able to add limited amounts of carbohydrate to their diet as they get older (Abad-Sinden et al., 1997 [1]). Given the importance of glucose and galactose avoidance, particularly in young children, a threshold of zero is considered appropriate for warnings related to glucose-galactose malabsorption for the oral route of administration. Given that lactose delivered via inhaled medicines is essentially absorbed orally, the warning should also apply to the inhaled route.

4.5. Diabetes mellitus

In lactase-sufficient patients, ingested lactose is metabolised in the gut to glucose and galactose prior to absorption. Each gram of lactose will yield 0.5 g of each monosaccharide. The glucose released can therefore contribute to the overall glucose intake of the patient, which may be significant in patients with diabetes mellitus, a disorder of glucose metabolism. The galactose component has only a small effect on plasma glucose levels, probably as a result of hepatic conversion of galactose to glucose. However, galactose has a significant effect on insulin release, with one study in patients with Type 2 diabetes finding that ingestion of 50 g of lactose resulted in an insulin area response 85% of that following ingestion of 50 g of glucose (Ercan et al., 1993 [21]; O'Hara et al., 2014 [38]) found that ingestion of 40 g of galactose significantly increased plasma insulin levels compared to placebo. Intravenously administered lactose is rapidly excreted into the urine, with no significant increase in plasma glucose (Weser et al., 1967 [56]).

It is important for patients with diabetes mellitus to be aware of their glucose intake in order to manage their condition appropriately, and they should therefore be alerted if a medicine contains a

significant quantity of lactose. The 5 g threshold for oral medicines from the 2017 guideline has been maintained, with a minor update to the wording.

5. Safety information relevant for the package leaflet

Summary of concerns

Lactose is not considered to be toxic or harmful for healthy subjects. However, adverse effects might occur in patients with pre-existing conditions of malabsorption, galactosaemia, diabetes or hypersensitivities.

Ingested lactose is hydrolysed by the gut enzyme lactase into its components, glucose and galactose, which are absorbed. If lactase activity is low or absent, undigested lactose may induce the symptoms of lactose intolerance. The threshold dose which produces symptoms varies greatly in individuals with lactose intolerance. In a blinded, randomised, placebo-controlled study, a dose of 400 mg of lactose was found not to induce symptoms in participants (Montalto, 2014 [32]); a review by EFSA (2010) [17] suggested that in fact most patients will tolerate doses of 6–12 g per day. A threshold of 400 mg lactose per dose has conservatively been set for inclusion of a warning in the package leaflet of oral products.

Glucose-galactose malabsorption is a very rare, potentially life-threatening inherited condition treated via a low glucose-galactose diet. A threshold of zero is considered appropriate for warnings related to glucose-galactose malabsorption for the oral route of administration. Given that lactose delivered via inhaled medicines is essentially absorbed orally, the warning should also apply to the inhaled route. Galactosaemia is a rare, serious genetic disorder of galactose metabolism managed via a galactose-restricted diet, with elimination of dietary lactose as far as possible. Given this, a conservative threshold is warranted for warnings related to galactosaemia, and a threshold of zero is considered appropriate for both oral and inhaled routes of administration.

It is important for patients with diabetes mellitus to be aware of their glucose intake in order to manage their condition appropriately. Each gram of lactose ingested yields 0.5 g of glucose. A warning relating to diabetes mellitus is recommended for products exceeding the 5 g lactose threshold for oral medicines in the 2017 guidelines, and this threshold has been maintained.

Pharmaceutical grade lactose may contain traces of milk proteins. There is evidence for serious allergic reactions occurring in milk-allergic patients exposed to lactose-containing medicines, particularly intravenously-administered products. A zero threshold is therefore proposed for warnings relating to milk-allergic patients.

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Annex 1 - Information in the package leaflet before revision (as per 2017 Guideline)

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Lactose	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SmPC proposal: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
		5 g	Contains x g lactose (x/2 g glucose and x/2 g galactose) per dose. This should be taken into account in patients with diabetes mellitus.	