Specialised milks marketed for infants with allergies in the UK

Information for health professionals

January 2021

FIRST STEPS NUTRITION TRUST

Specialised milks marketed for infants with allergies in the UK. Information for health professionals. January 2021

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This resource is provided for information only and individual advice on diet and health should always be sought from appropriate health professionals. We have attempted to provide accurate information on the composition of specialised infant milks sold in the UK for infants with allergies in this report and do so in good faith. However, composition, names and claims may change, so please refer to the specific manufacturers for up-to-date information. *When referencing this document please refer to the website for the most recent version*

Acknowledgements

We would like to thank the Scottish Government for a financial contribution to the updating of this work. Thanks are due to Sarah Weston, Dr Helen Crawley, Dr Vicky Sibson, Bahar Ghodsian, Debra Davidson, Alison Holmes, Caroline King, Anita MacDonald, Karen Mackay, June McMahon, Colin Michie and the Royal College of Paediatrics and Child Health, Jessica Williams, Gillian Weaver, and the Unicef UK Baby Friendly Initiative, who have added useful comments to this or earlier iterations of reports on specialised infant milks. We would like to thank all those working for infant milk companies who provided information about their specialised milk products for this edition.

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First Steps Nutrition Trust is a charity which provides evidence-based and independent information and support for good nutrition from pre-conception to five years of age.

For information about infant milks sold over the counter in the UK see www.infantmilkinfo.org

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1 Introduction

Breastfeeding and breastmilk

This report is about specialised milks marketed for infants with food allergies.

First Steps Nutrition Trust strongly supports international and national recommendations that every mother in the UK should be supported to breastfeed her baby exclusively for the first six months of his or her life, and to breastfeed alongside the introduction of solid foods at about 6 months for at least one year, and for as long after that as the mother chooses.

1.1 Who is this report for?

One of the most widely used specialised infant milk categories is milks designed for use when an infant has a hypersensitive reaction to a food component. This report looks at products marketed in the UK for infants with food allergies.

First Steps Nutrition Trust strongly supports greater investment to support women to breastfeed through the Unicef UK Baby Friendly Initiative accreditation scheme in maternity, neonatal, university and community settings. All those who work within Unicef UK Baby Friendly accredited settings must carefully consider their role in the protection of infant and young child health by respecting the WHO *International Code of Marketing of Breast-milk Substitutes* and subsequent World Health Assembly resolutions designed to protect the health of all infants, young children and their families. As part of this commitment it is important that health workers can access independent information about infant milks rather than relying on manufacturer information. This report has been written to provide that independent information.

Working within the WHO Code does not mean that health professionals cannot obtain up-to-date information about products. We strongly encourage health workers to be critical when they are presented with information from sales representatives or in advertising, to work together to ensure they can interpret clinical studies presented as evidence, and to consider setting up multi-disciplinary groups to manage information presented to them about specialised milks.

A useful guide for health workers, *Working within the International Code of Marketing of Breast-milk Substitutes: A guide for health workers,* can be downloaded from Unicef UK Baby Friendly Initiative at https://www.unicef.org.uk/babyfriendly/wp-content/uploads/sites/2/2016/10/Working-within-The-Code-Guide-for-Health-Workers.pdf

A resource for dietitians on how they can work within the WHO Code can be accessed at: https://www.firststepsnutrition.org/working-within-the-who-code

The information in this report is not designed to replace specialist medical and professional support and care from a clinical team.

The aim is to provide an overview of products available and key information about these products, and to investigate some of the claims made in the context of what else is known or recommended by independent scientific bodies. We hope it will stimulate discussion and encourage health workers who require information about products to be *active* in obtaining the information they need from commercial companies, and not be *passive* recipients of marketing information.

Terminology

There are a number of names and terms used for infant milks. Some people call them 'breastmilk substitutes', while others prefer the term 'artificial milks' or 'formula milks'. The term 'breastmilk substitute' refers to all products that are marketed in a way which suggests they should replace breastfeeding, even if the product is not suitable for that purpose. This may include infant milk, baby foods, gruel, tea, juice, bottles, teats/nipples and related equipment. For clarity we use the following terms throughout this report:

What do we mean by infant milk?

We use the term 'infant milk' as an umbrella term for all milk-based or milk substitute based drinks provided commercially for infants.

What do we mean by infant formula?

We use the term 'infant formula' to mean a food that can meet all an infant's nutritional needs during the first six months of life and which complies with the regulations for infant formula.

What do we mean by specialised infant milk?

We use the term 'specialised infant milk' to mean a product which can meet all of the nutritional needs of infants as a breastmilk substitute in the first six months of life, and which complies with the regulations for infant foods for special medical purposes.

Information for health professionals on infant milks available to buy over the counter in the UK can be found at www.infantmilkinfo.org and more detailed information on the components of infant milks, claims made and the safety of products can be found at www.firststepsnutrition.org/infant-milks-health-workers.

1.2 Appropriate prescribing

In the current economic climate, it is important for NHS organisations to ensure that foods for special medical purposes such as specialised infant formulas are appropriately prescribed. Between 2006 and 2016, prescriptions of specialist infant milks for infants with cows' milk allergy increased by nearly 500% from 105,029 to over 600,000 a year (PrescQIPP, 2016) while NHS spending on these products increased by nearly 700% from £8.1m to over £60m annually (NHS Digital, 2017). The increased prescribing and spend on these products have been suggested as being due to industry influence on over-diagnosis and evidence for this was outlined by Chris van Tulleken in an article in the BMJ in December 2018 (van Tulleken, 2018).

Reasons for the increase in spend were also investigated by the NHS London Procurement Partnership (LPP)[1], a London-based NHS initiative which collaborates with NHS organisations and social enterprises to deliver savings and improvements to enhance patient care.

In London the reasons for the increase in spend were suggested as:

- The increasing cost and range of paediatric specialised nutrition products
- Inequities in dietetic provision across London which mean that infants/children may be started on an inappropriate feed for a prolonged period
- Greater focus on allergy and training by companies that sell specialised formula, leading to greater, but sometimes misdiagnosed, identification of cows' milk allergy
- Poor communication between the acute and public health/GP sectors of the NHS, leading to inappropriate prescription
- Inappropriate use of a product as a first-line infant milk
- Wastage from over-prescribing, and
- Parental reluctance to change products.

As different NHS Trusts have different dietetic and GP service provision, so prescribing guidelines will vary by Trust, but in many places they have been produced by individual clinical commissioning groups (CCGs). The London Procurement Partnership (LPP) has produced unsponsored GP guides to help support GP decision-making with regards to re-challenging children with allergies, outlining appropriate prescribing volumes per month, providing templates to make sure that prescribing of specialised nutrition products contains all essential information (e.g. anthropometry, product name, unit size, daily dose, monthly volume, prescribing goal, and plans for review), and lists current prices of these products.

The LPP recommends five ways to address spend on specialised nutrition products:

1. Understanding local prescribing and cost data by liaising with medicines management teams.
2. Understanding local dietetic capacity and their referral criteria into primary, secondary and tertiary organisations.

[1] For further information on the London Procurement Partnership and (after registering) to access its annual report, data analysis and GP guides and prescribing templates, see the LPP website http://www.lpp.nhs.uk/. This requires an NHS account.

3. Implementing appropriate prescribing initiatives to reflect local priorities, e.g. developing local feeding guidance, and auditing high-spending GP practices using Scriptswitch software.
4. Collecting outcome (clinical, experience, financial) and output data.
5. Sharing data with GP practices, dietetic departments and CCGs.

1.3 Specialised milks prescribed for infants with food allergy

One of the most widely used specialised infant milks categories covers milks designed for use when an infant has a hypersensitive reaction to a food component. This can be an immediate IgE mediated allergic reaction or a delayed non IgE mediated food allergy, and infants can have single or multiple food allergies.

It is estimated that the lifetime self-reported prevalence of allergy to common foods in Europe ranges from 0.1 to 6.0% (Nwaru et al, 2014). Although food allergies are more common in children than adults many children outgrow their allergies during infancy and childhood. Food allergies are caused by the immune system handling harmless proteins in certain foods as a threat. The immune system releases a number of chemicals, which trigger an allergic reaction. The most common types of food allergy in infants and children are: hen's egg, cows' milk, peanut, soy, wheat and fish.

NICE guidelines on food allergy in children (CG 116, 2011) outline common symptoms and assessment procedures for diagnosis. As the impact of being diagnosed with a food allergy can lead to a significantly reduced quality of life, it is vital, wherever possible, that normal physiological feeding continues with removal of the suspected allergens to protect the feeding experience as an infant develops.

An infant's allergic reaction may be life threatening and, in these cases, treatment needs to be clear, accurate and delivered as quickly and safely as possible to reduce risk of further reactions and co-morbidities. The risks of giving formula to a breastfed baby however may result in a higher incidence of allergy, and more severe allergy, so changing feeding regimes should be done with caution and support. In addition, cows' milk allergy can be over-diagnosed among children with food allergy symptoms. A study of 381 infants exhibiting a possible adverse reaction to cows' milk found that 243 of them (64%) were mislabelled with a cows' milk allergy (Elizur et al, 2013). Almost 30% of infants with mislabelled reactions presented within the first month of life, and nearly half presented in the first two months, compared with only 9% and 20% of infants with IgE-confirmed cows' milk allergy. Misdiagnosis was most common in the first few months of life where infants had atopic dermatitis and where parents were more highly educated. Most infants with cows' milk allergy will have symptoms affecting a number of organ systems and not just the skin and better parental and physician awareness of the importance of objectively diagnosing milk allergy is required to avoid mislabelling of infants as being allergic to cows' milk.

NICE clinical knowledge summary on cows' milk allergy management (NICE Cows' milk allergy CKS, 2015) provides guidance on how to manage suspected or diagnosed cows' milk allergy. The first line of support is to encourage continued breastfeeding for breastfed babies and to advise the mother to exclude cows' milk from her diet and to consider

prescribing a daily supplement of 1000 mg of calcium and 10 micrograms of vitamin D to the mother to prevent nutritional deficiencies.

Where infants are mixed fed or exclusively formula fed then an extensively hydrolysed formula is tolerated by the majority of infants and children (90%) with cows' milk allergy. These formula (often called hypoallergenic formula) are based on cows' milk but the protein is broken down into smaller peptides that are less well recognised by the immune system. For the very few infants with severe allergy or multiple food allergies an infant formula which contains fully broken down proteins in the form of amino acids (amino acid based formula) should be used.

It is important to note that soya protein–based formulas, partially hydrolysed infant formula, hydrolysed pre-term formula or infant formula made from goats' milk are ***not*** suitable breastmilk substitutes for cows' milk allergy treatment.

Many healthcare professionals who are involved in research and practice, or who sit on expert groups looking at diagnosis and management of food allergies in infancy, work with breastmilk substitute companies, and so there is considerable conflict of interest in this area of infant nutrition (van Tulleken, 2018). Care therefore needs to be taken when reviewing papers and guidelines from organisations and individuals where there may be conflict of interest. Health professionals should, wherever possible, use information that is conflict of interest free, and avoid any training offered in this area which is sponsored by breastmilk substitute companies.

1.4 Making up specialised milks safely

UK policy on how to make up powdered infant milks safely states that at least 1 litre of fresh water from the cold tap should be boiled in a kettle. Previously boiled water should not be used. The boiled water should be left to cool for no more than 30 minutes. These two steps should ensure that the water used to reconstitute the feed is at a temperature above 70°, which will kill most of the pathogenic micro-organisms that may be present in powdered formula milk (Food Standards Agency, 2005; NHS, 2011; Crawley, Westland and Sibson, 2020). In 2013, following concern over some manufacturers suggesting that their products be reconstituted at temperatures below 70°C, the Department of Health reiterated its position on the safe preparation of powdered infant and follow-on formula milks and also stated that:

"... we want to be clear that all standard, non-specialised infant formula and follow-on formulas, including those containing probiotics, should be prepared in-line with current best practice, regardless of the presence of any contrary instructions on the product, in order to minimise the risk of infection." (Department of Health, 2013)

The reconstitution of specialised milks marketed as foods for special medical purposes are however not subject to these recommendations and instructions are allowed to be given that they may be reconstituted at lower temperatures. Guidance is designed to ensure that feeds are reconstituted with water at a temperature of at least 70°C. Not following this guidance puts vulnerable infants (e.g. preterm, low-birthweight, immunocompromised infants) with special medical needs at a greater risk of microbiological contamination, as powdered feeds are not sterile and may contain harmful bacteria such as *Cronobacter*

sakazakii (Crawley, Westland and Sibson, 2020). However, it is the opinion of the regulators at the UK competent authorities that, as an FSMP will be used under 'medical supervision', a risk assessment can be made on an individual basis. We believe this needs further review and recommend that safety is a primary consideration when using any infant milk. This position has been re-iterated in BDA guidance for the preparation and handling of specialised feeds for infants in UK hospital settings, which sets out the conditions under which some infant milks may be reconstituted at temperatures lower than 70°C. The guidelines can be accessed at: www.bda.uk.com/regionsgroups/groups/paediatric/sfu_guidelines

Table 1 shows specialised milks for infants with food allergies that are marketed as foods for special medical purposes where reconstitution is recommended at temperatures below 70°C or where instructions for reconstitution fail to specify both the volume of water to be boiled and minimum cooling time. It gives the rationale for the lower temperatures where this has been stated by the manufacturer. Some of the manufacturers we have contacted have offered no rationale for either recommending lower reconstitution temperatures, or for failing to recommend a specific volume of water to be boiled to maintain a temperature of over 70ºC for reconstitution.

TABLE 1. Specialised milks for infants with food allergies where reconstitution is recommended by manufacturers at temperatures below 70°C, and the rationale for lower temperatures

Category	Manufacturer/ Product	Instruction	Rationale
Extensively hydrolysed peptide-based infant milks suitable from birth	Abbott Nutrition Similac Alimentum	Boil fresh tap water, and allow to cool for no more than 30 minutes.	None given
	Aptamil Pepti Syneo	Boil fresh water for five minutes or until an electric kettle switches off. Pour the required amount of water into the sterilised bottle, cover the bottle with the cap and cool down to room temperature	To preserve the *Bifidobacterium breve* M-16V
	Mead Johnson Nutramigen 1 with LGG	Boil fresh water, cool down to room temperature.	To preserve the probiotic bacteria
	SMA Althéra	Boil drinking (tap) water. Allow to cool for no more than 30 minutes.	None given
Extensively hydrolysed peptide-based infant milks with medium chain triglycerides, suitable from birth	Aptamil Pepti-junior	Boil freshly run water. Leave kettle to cool for 30 minutes	None given
	Mead Johnson Pregestimil LIPIL	Boil fresh water. Cool for no longer than 30 minutes.	None given

Category	Manufacturer/ Product	Instruction	Rationale
Extensively hydrolysed peptide-based infant milks suitable from 6 months	Mead Johnson Nutramigen 2 with LGG[1]	Boil fresh water, cool down to room temperature.	To preserve the probiotic bacteria
Amino-acid based infant milks for non-metabolic disorders, suitable from birth	Abbott Nutrition Similac Elecare	Boil fresh tap water, and allow to cool for no more than 30 minutes.	None given
	Mead Johnson Nutramigen Puramino	Boil fresh water. Cool for no longer than 30 minutes.	None given
	Nutricia Neocate LCP	Boil fresh water, and cool for at least 30 minutes so that it feels warm to the wrist.	None given
	Nutricia Neocate Syneo	Boil fresh water for 5 minutes, pour the required amount of water into the sterilised bottle, and cool down to room temperature.	To preserve the *Bifidobacterium breve* M-16V
	SMA Alfamino	Boil drinking (tap) water. Allow to cool for no more than 30 minutes.	None given

1.5 Cost of specialised milks for infants with food allergy

The cost of specialised milks marketed for infants with food allergies varies and there is a wide price range. To enable a clearer understanding of price we have compared the cost of infant milks per 100ml of infant milk as consumed (see Table 2). We searched the British National Formulary (BNF) for Children, which is updated on a monthly basis, and took high street prices for products not listed. It should be noted that some products listed on manufacturer websites are missing from the BNF for Children and some products included in that report have been discontinued. To act as a comparison to these prices, main brands of cows' milk based powdered infant formula for use in term babies cost between 9p and 25p per 100ml.

TABLE 2. The cost of specialised milks marketed for infants with allergies

Prices are correct as of December 2020.

Category	Infant milks in this category	Price per unit (£)	December 2020 BNFC price unless otherwise stated*	Package weight/ volume	Cost per 100ml formula (£)
Soy protein based infant formula suitable from birth	SMA Wysoy	£13.00	Boots	800g	£0.20
Extensively hydrolysed peptide-based infant milks suitable from birth	Abbott Nutrition Similac Alimentum	£10.01	✓	400g	£0.35
	Aptamil Pepti 1	£9.87	✓	400g	£0.34
	Aptamil Pepti 1	£9.87	✓	400g	£0.34
	Aptamil Pepti Syneo	£10.65	MIMS	400g	£0.37
	Mead Johnson Nutramigen 1 with LGG	£11.21	✓	400g	£0.37
	SMA Althéra	£9.06	✓	450g	£0.30
Extensively hydrolysed peptide-based infant milks with medium chain triglycerides, suitable from birth	Aptamil Pepti-junior	£14.03	✓	450g	£0.42
	Mead Johnson Pregestimil LIPIL	£12.43	✓	400g	£0.42
	Nutricia Infatrini Peptisorb	£3.92	✓	200ml	£1.96
Extensively hydrolysed peptide-based milks suitable from 6 months	Aptamil Pepti 2	£9.41	✓	400g	£0.32
	Mead Johnson Nutramigen 2 with LGG	£11.21	✓	400g	£0.37
Amino-acid based infant milks for non-metabolic disorders, suitable from birth	Abbott Nutrition Similac EleCare	£28.08	MIMS	400g	£0.91
	Mead Johnson Nutramigen Puramino	£22.98	✓	400g	£0.78
	Nutricia Neocate LCP	£22.98	✓	400g	£0.79
	Nutricia Neocate Syneo	£24.82	✓	400g	£0.91
	SMA Alfamino	£22.98	✓	400g	£0.79

* Information taken from the British National Formulary for Children, Boots the Chemist or from the manufacturer's website unless otherwise specified, correct as of December 2020.

2 Specialised milks for infants with food allergy available in the UK

Information in this report has been taken from website information or promotional material designed for health professionals or from conversations with consumer care lines or company staff. Whilst every attempt is made to give up-to-date information, it is advisable to check the dates of current data cards and refer to company websites to see if there has been any reformulation. Table 3 outlines specialised infant milks for infants with food allergy available in the UK. All of the products outlined here are available on prescription with the exception of Wysoy which can be purchased over the counter. It is included here as in some rare cases it may be suggested as an option for children with cows' milk allergy.

TABLE 3. Specialised milks for infants with food allergy available in the UK

Category	Names of infant milks included in this category
Soya protein based infant formula suitable from birth	SMA Wysoy
Extensively hydrolysed peptide-based infant milks suitable from birth	Abbott Nutrition Similac Alimentum Aptamil Pepti 1 Aptamil Pepti Syneo Mead Johnson Nutramigen 1 with LGG SMA Althéra
Extensively hydrolysed peptide-based infant milks with medium chain triglycerides as the main fat source, suitable from birth	Aptamil Pepti-junior Mead Johnson Pregestimil LIPIL Nutricia Infatrini Peptisorb
Extensively hydrolysed peptide-based milks suitable from 6 months	Aptamil Pepti 2 Mead Johnson Nutramigen 2 with LGG
Amino-acid based infant milks for non-metabolic disorders, suitable from birth	Abbott Nutrition EleCare Mead Johnson Nutramigen Puramino Nutricia Neocate LCP Nutricia Neocate Syneo SMA Alfamino

2.1 Infant milks suitable for specific population groups

Specialised infant milk for vegetarians

Vegetarians avoid all meat and fish products and usually avoid ingredients that are sourced from slaughtered animals, such as gelatine and rennet. Whilst there is no legal definition of the term vegetarian, the Food Standards Agency identifies the legislation relevant to the use of the term and other legislation relevant to ingredient listing of animal products and provides advice on labelling foods as 'suitable for vegetarians' or 'vegetarian'. Additionally, the Vegetarian Society defines a vegetarian as: *"Someone who lives on a diet of grains, pulses, nuts, seeds, vegetables and fruits with, or without, the use of dairy products and eggs. A vegetarian does not eat any meat, poultry, game, fish, shellfish or by-products of slaughter.*" The Food Standards Agency guidance suggests that the term vegetarian should not be applied to foods that are, or are made from or with the aid of, products derived from animals that have died or have been slaughtered, or animals that die as a result of being eaten.

Specialised infant milks derived from cows' milk are generally not suitable for vegetarians due to the inclusion of fish oils and/or the use of the animal-derived enzyme rennet during the production process. Rennet, a by-product of animal slaughter, is used to separate curds from whey and, although vegetarian alternatives are available, manufacturers of infant milk do not typically use them. Infant milks derived from pork or meat protein or using pork enzymes during the manufacturing process (even though this this may not be present on the final foodstuff) are not suitable for vegetarians. Not all manufacturers label formula milks as to their suitability for vegetarians.

Specialised infant milk for vegans

Vegans avoid all products derived from animals and the vitamin D in infant milks is derived from animal products. Where a vegan mother requests or requires a top up or replacement for her own breastmilk for one or more infants in a neonatal unit then wherever possible donor human milk should be the first line of treatment. For more information on feeding vegan infants see the resource *Eating well for vegan infants and under-5's* at www.firststepsnutrition.org/eating-well-infants-new-mums.

Halal and kosher specialised infant milk

Many specialised infant milks have sought approval for use by communities who require halal products. Many of those who choose a kosher diet will use specialised infant milks that are vegetarian or halal approved.

The term halal or 'permissible' can be applied both to ingredients and to the manufacturing process. The approval process tends to give halal approval status to the factory or production facility to indicate that it has been inspected and approved to produce halal food, rather than to the product itself, so infant milks of the same brand which do not contain any haram or 'forbidden' ingredients may not all be halal approved (even if only the container size differs) if they have been made in different production facilities. It is important that this is checked for each milk if it is a concern to the family seeking advice. We have asked for

the halal status of all products but have not been provided with this information for a number of products and have assumed that it is not halal approved unless we have been specifically told it is.

Table 4 shows which specialised infant milks are suitable for vegetarians and vegans, and which are halal approved as at December 2020.

TABLE 4. Specialised milks for infants with food allergies suitable for vegetarians, vegans and those wishing to use halal products

Category of infant milk	Name of infant milk	Suitable for vegetarians	Suitable for vegans	Halal approved
Soya protein based infant formula suitable from birth	SMA Wysoy	✓		✓
Extensively hydrolysed peptide-based infant milks suitable from birth	Abbott Nutrition Similac Alimentum			
	Aptamil Pepti 1			
	Aptamil Pepti Syneo			
	Mead Johnson Nutramigen 1 with LGG			
	SMA Althéra			
Extensively hydrolysed peptide-based infant milks with medium chain triglycerides, suitable from birth	Aptamil Pepti-junior			
	Mead Johnson Pregestimil LIPIL			
	Nutricia Infatrini Peptisorb			
Extensively hydrolysed peptide-based milks suitable from 6 months	Aptamil Pepti 2			
	Nutramigen 2 with LGG			
Amino-acid based infant milks for non-metabolic disorders, suitable from birth	Abbott Nutrition EleCare	✓		✓
	Mead Johnson Nutramigen Puramino			✓
	Nutricia Neocate LCP	✓		✓
	Nutricia Neocate Syneo	✓		✓
	SMA Alfamino			

Note: Formulations can change, so check with manufacturer.

2.2 Soya protein-based infant formula suitable from birth

Key points

Soya protein-based infant formula uses protein from soya beans, and the carbohydrate source is maltodextrin. It contains no animal protein or lactose.

Concerns have been raised over the potential allergenic effect of soya protein-based formula in infants at high risk of atopy and over the effects that the phyto-oestrogens present in soy protein-based formula might have on future reproductive health.

Soya protein-based infant formula have been shown to support normal growth and development in healthy term infants, the Chief Medical Officer has recommended that soya protein-based formula should not be routinely used for infants under 6 months of age who have cows' milk allergy or intolerance.

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that the high levels of phyto-oestrogens present in soya protein-based milks posed a potential risk to the future reproductive health of infants (Committee on Toxicity, 2003).

The carbohydrate source in soya protein-based infant formula is maltodextrin rather than lactose so infants may need attentive mouth care as maltodextrin is associated with demineralisation of enamel (Rezende and Hashizume, 2018). Parents and carers using soya protein-based infant formula are advised to avoid prolonged contact of milk feeds with their baby's teeth and ensure that they clean their baby's teeth after the last feed at night.

The NHS recommend that soya protein-based infant formula should only ever be used if it has been recommended or prescribed by a health visitor or GP, and then only from 6 months. Parents and carers should always seek medical advice before feeding their infant soya protein-based infant formula.

Soya protein-based infant formula combine protein from soya beans with water, vegetable oils, maltodextrin and vitamins and minerals.

The amino-acid profile of soya protein is deficient in sulphur-containing amino acids, and soya protein-based formula must therefore be fortified with the sulphur-containing amino acid L-methionine. Soya protein based infant formula are available both over the counter and by prescription and may be used from birth. They have sometimes been used for children who require an alternative to cows' milk based infant milks because they have an allergy or intolerance to cows' milk, or because they have a specific condition such as galactosaemia or galactokinase deficiency.

In a systematic review of clinical studies examining measures of infant health and development and comparing soy protein based infant formula with cows' milk protein based infant formula and/or human milk, Mendez et al (2002) concluded that modern soya protein

based formula supplemented with methionine support normal growth and development in healthy term infants during the first year of life.

Soya protein-based infant formulas have often been used as an alternative to cows' milk protein based infant milks in children with cows' milk allergy. In a review of trials comparing the effect of prolonged feeding of soya protein-based infant formula and of cows' milk protein based infant formula, meta-analysis found no significant difference in childhood asthma incidence, childhood eczema incidence or childhood rhinitis. The authors concluded that soya protein-based formula cannot be recommended for allergy prevention or food intolerance in infants at high risk of atopy (Osborn and Sinn, 2006).

It is recognised that a proportion of children with cows' milk allergy are also allergic to soya protein. The Chief Medical Officer has recommended that soya protein based infant formula should not be used as the first line of treatment for infants under 6 months of age who have cows' milk allergy as this is the period when they are most likely to become sensitised to soy protein (Chief Medical Officer, 2004). ESPGHAN recommends that soya protein-based infant formula should not be used for infants under 6 months of age and that the use of therapeutic milks based on extensively hydrolysed proteins (or amino-acid preparations if hydrolysates are not tolerated) should be preferred to the use of soya protein-based formula in the treatment of cows' milk allergy (Agostoni et al, 2006).

Soya protein-based infant formula contain much higher levels of phyto-oestrogens than formula based on cows' milk protein. Setchell et al (1998) estimated that infants aged 1 to 4 months who were fed soya protein-based formula would receive 6-12mg/kg of body weight of phyto-oestrogens per day, compared to 0.7-1.4mg/kg of body weight per day for adults consuming soya protein-based products. There has been very little research into the effects of consumption of phyto-oestrogens from soy protein-based formula in very young infants. However, research in animals suggests that phyto-oestrogens can have detrimental effects on reproductive function, immune function and carcinogenesis.

In a review of the scientific evidence on soya protein-based formula, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that the high levels of phyto-oestrogens present in soya protein-based formula posed a potential risk to the future reproductive health of infants (Committee on Toxicity, 2003). A longitudinal study looking at 283 infants exclusively given soya protein-based formula from birth suggests that girls may display different vaginal and uterine development in line with exogenous oestrogen exposure (Adgent et al, 2018). The impact this may have on development is yet to be established.

COT concluded that the available studies have produced conflicting results, and while the balance of evidence from these does not suggest important adverse effects of soy infant formula on reproductive development, they are too limited to provide strong reassurance of safety and that there is no scientific basis for changing the current government advice – namely, that there is no substantive medical need for, nor health benefit arising from the use of soya-based infant formula, and that it should be used only in exceptional circumstances to ensure adequate nutrition (Committee On Toxicity, 2013).

In 2019 COT provided a discussion paper on the use of soya drinks for infants from 6 months of age and children aged 1-4 years and updated the evidence base on potential risks

associated with soya intake on development. This can be reviewed at tox201965discussionpaperonsoyadrink_0.pdf (food.gov.uk)

Wysoy is the only soya protein based infant formula available on the UK market. The carbohydrate source in Wysoy is maltodextrin rather than lactose so infants may need attentive mouth care as maltodextrin is associated with demineralisation of enamel (Rezende and Hashizume, 2018). Parents and carers using soya protein-based infant formula are advised to avoid prolonged contact of milk feeds with their baby's teeth and ensure that they clean their baby's teeth after the last feed at night.

The required composition of soya protein-based infant formula is different to that of cows' milk-based formula for a number of micronutrients including iron and phosphorus due to differences in bioavailability. Soya protein-based formula are suitable for vegetarians but not for vegans.

The NHS recommend that soya protein-based infant formula should only ever be used if it has been recommended or prescribed by a health visitor or GP, and then only from 6 months (NHS, 2019).

The nutritional composition of soya protein-based infant formula suitable from birth

The nutritional composition and ingredients in SMA Wysoy, the only soya protein-based product on the market, are given in Table 5.

TABLE 5. The nutritional composition of soya protein based infant formula suitable from birth

Nutrients per 100ml	SMA Wysoy
MACRONUTRIENTS	
Energy kcal	67
Protein g	1.8
Carbohydrate g	6.8
- of which lactose	0
Carbohydrate source	Maltodextrin
Fat g	3.6
Fat source	Palm, coconut, soya, sunflower and rapeseed oils
Added LCPs ARA	✓
DHA	✓
LCP source	Fungal/algal oils (vegetable source)
MICRONUTRIENTS	
VITAMINS	
Vitamin A µg-RE	64
Vitamin C mg	12
Vitamin E mg	0.78
Vitamin D µg	1.5
Vitamin K µg	6.5
Thiamin (B_1) µg	50
Riboflavin (B_2) µg	130
Niacin µg	700
Vitamin B_6 µg	70
Vitamin B_{12} µg	0.2
Folate µg-DFE	15.2
Biotin µg	2.3
Pantothenic acid µg	440
MINERALS	
Calcium mg	68
Chloride mg	47
Copper µg	50
Iodine µg	14
Iron mg	0.65
Magnesium mg	7.6
Manganese µg	20
Phosphorus mg	50
Potassium mg	82
Selenium µg	2.5
Sodium mg	22
Zinc mg	0.52
ADDED INGREDIENTS	
Structured vegetable oils	×
Prebiotics	×
Nucleotides	×
Inositol	×
Taurine	✓

Nutrients per 100ml	SMA Wysoy
Choline	✓
Added antioxidants	✓
Contains soya	✓
Contains fish oil	×
Suitable for vegetarians	✓
Halal approved	✓
Osmolality mOsm/kg H_20	133

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid

2.3 Extensively hydrolysed peptide-based infant milks suitable from birth

Key points

Extensively hydrolysed infant milks are marketed primarily to be used in the dietary management of mild to moderate cows' milk allergy. Some products are also marketed to manage multiple allergies, gastroenterological disorders such as malabsorption, inflammatory bowel disorder and short bowel syndrome, prolonged diarrhoea and cystic fibrosis. Infant milks that are also prescribed for infants with malabsorption have a proportion of their fat content as medium chain triglycerides.

Breastfeeding is the optimal way to feed a baby with cows' milk allergy. Currently, maternal elimination of all cows' milk protein foods and fluids is recommended with adequate calcium and vitamin D supplementation to meet the mother's nutritional requirements during breastfeeding. NICE clinical guidelines on the management and treatment of cows' milk allergy provide clinical guidance on treatment of both suspected and confirmed cows' milk allergy (National Institute for Health and Care Excellence, 2015).

This group of infant milks contains proteins which have been extensively broken down or hydrolysed. The hydrolysis process uses pork enzymes.

The use of high-profile health professionals working in allergy to promote brands is common in this area. When making clinical decisions, healthcare professionals should take note of whether guidelines or guides are sponsored by infant milk companies and should look for independent information wherever possible.

Breastfeeding remains the best way to feed an infant with IgE or non IgE mediated cows' milk allergy. Greater clinical success and cost savings can be made to the NHS by supporting breastfeeding wherever possible, and when clinically indicated, rather than immediately prescribing extensively hydrolysed infant milks. It is important also to safeguard the best interests of mixed fed infants, and successful breastfeeding will be achieved with skilled diet history taking and successful maternal elimination of cows' milk protein containing foods and fluids. In exclusively breastfed babies**,** the June 2015 NICE clinical knowledge summary on management of cows' milk allergy in infants advises breastfeeding mothers who exclude all dairy products from their diet to take a daily supplement of 1,000mg of calcium and 10 micrograms of vitamin D to prevent nutritional deficiencies (National Institute for Health and Care Excellence, 2015).

In the UK, NICE guidelines are available for the diagnosis and management of food allergy in children and young people (National Institute for Health and Clinical Excellence, 2011) and additional support is available through the NICE clinical knowledge summary on confirmed cows' milk allergy highlighted above. UK guidelines for managing cows' milk allergy in primary care known as the iMAP guidelines have recently been rewritten with independent support (Fox et al, 2019) and information on this is available at https://doi.org/10.1186/s13601-019-0281-8

This updated guidance is available through the GP Infant Feeding Network website www.gpifn.org/imap. The updated guidance better supports breastfeeding and aims to reduce the over-diagnosis of cows' milk allergy that has been linked to previous versions of this guidance (van Tulleken, 2018).

ESPGHAN and an international working group which itself was funded by Nutricia, have published guidelines on the diagnosis and management of cows' milk allergy, depending upon whether infants are breastfed or infant milk fed (Koletzko et al, 2012; Vandenplas et al, 2007). They both recommend an extensively hydrolysed infant milk with proven efficacy in appropriate clinical trials. ESPGHAN note that, despite American and European guidelines recommending that extensively hydrolysed infant milks are tested in elimination challenge tests under double blind placebo controlled conditions in order to ensure, with 95% confidence, that they do not provoke allergic reactions in 90% of infants or children with diagnosed cows' milk allergy, this has not been undertaken by all manufacturers (Høst et al, 1999). It is noted that a small percentage of infants and children diagnosed with cows' milk allergy who are given an extensively hydrolysed infant milk will continue to exhibit symptoms and may require a trial of an amino-acid based (elemental) infant milk.

Hydrolysed infant milks are heavily marketed to health professionals using allergy specialist dietitians and physicians via conferences, learning events and infant milk company branded recipe guides, parent guides, case studies, frequently asked questions and feeding tips. It is important that health professionals ignore marketing materials and consider the composition of each product, making independent assessments of evidence presented.

Specialised milks marketed for infants with food allergies

There are eight different extensively hydrolysed peptide-based infant milks suitable from birth and all are approved by the Advisory Board for Prescribable Substances. All of the infant milks are powdered with the exception of Infatrini Peptisorb which is a ready-to-feed liquid. Extensively hydrolysed milks have been divided into two groups to allow some comparison of products based on whether they have MCT as the main fat source.

Extensively hydrolysed milks marketed primarily for use in the treatment of cows' milk allergy which do not contain medium chain triglycerides as the main fat source:

- Abbott Nutrition Alimentum
- Aptamil Pepti 1 (contains lactose)
- Aptamil Pepti Syneo (contains lactose)
- Mead Johnson Nutramigen 1 with LGG
- SMA Althéra (contains lactose).

Extensively hydrolysed milks marketed for severe and multiple allergies, disaccharide and whole protein allergy requiring peptide or amino-acid and which have medium chain triglycerides as the main fat source:

- Aptamil Pepti-junior
- Mead Johnson Pregestimil LIPIL
- Nutricia Infatrini Peptisorb

Nutricia Infatrini Peptisorb is an extensively hydrolysed infant milk marketed for disease-related malnutrition, malabsorption, inflammatory bowel disease, short bowel syndrome and whole protein allergy. It has a significantly higher energy content than other milks in this category.

All of the extensively hydrolysed infant milks suitable from birth comply with UK regulations for foods for special medical purposes. Current compositional regulations can be found at www.infantmilkinfo.org. There are no extensively hydrolysed infant milks suitable for vegetarians or vegans, or which are halal approved. All of this group of specialised infant milks are based on cows' milk protein.

Nutritional composition

This group of infant milks are composed of extensively hydrolysed proteins, fats, added vitamins, minerals and trace elements. They differ from infant formula in that they are processed to extensively, but not completely, break down the casein and whey present in the cows' milk protein using a combination of heat, enzymes (to break polypeptide chains), hydrostatic pressure and ultrafiltration. The hydrolysis of proteins is achieved using pork enzymes.

Infant milks with a molecular weight of <3,000 Da (daltons) can be categorised as hypoallergenic and hence considered suitable for use in the management of infants with cows' milk allergy. The molecular weight distribution of peptides within extensively hydrolysed milks varies. For example, SMA Althéra claim that 99.3% of their peptides are <1,000 Da. In Similac Alimentum, 99% of the peptides are reported to be <1,500 Da.

Unlike infant formulas which contain carbohydrate mainly in the form of lactose, this group of infant milks contain carbohydrate mainly in the form of maltodextrin or dried glucose syrup.

All of these products are milk-based. Aptamil Pepti 1, Aptamil Pepti-junior, Aptamil Pepti Syneo, Nutricia Infatrini Peptisorb and SMA Althéra are whey-based infant milks, whereas Abbott Nutrition Similac Alimentum, Mead Johnson Nutramigen 1 with LGG and Pregestimil LIPIL are casein-based infant milks.

A number of these infant milks contain added medium chain triglycerides (MCTs). MCTs are triglycerides with a chain length of 8-10 carbon atoms, e.g. C:8 to C:10. These types of fats are shorter than long chain triglycerides (LCTs), are relatively soluble in water and are hydrolysed faster during digestion and absorption than LCTs. They are also metabolised using a different pathway to LCTs and enter the body via the portal venous system rather than the lymphatic system. MCTs are used therapeutically in infant milks for individuals with maldigestion, malabsorption and other gastroenterological conditions, such as short bowel syndrome.

Of the milks with added medium chain trigylcerides, 50% of the fat in Aptamil Pepti-junior, 52% of the fat in Nutricia Infatrini Peptisorb and 55% of the fat in Mead Johnson Pregestimil LIPIL are from MCTs.

Manufacturer product claims and evidence given to support them

One of the difficulties in reviewing evidence presented on the efficacy and use of infant milks marketed for management of cows' milk allergy and other allergies in infants, is that many of those who do research in this area, or who write clinical guidelines, are also employed or funded by the baby feeding industry. We have looked at some of the evidence currently being used to support the claims made for some extensively hydrolysed infant milks, and we hope that awareness of how data is presented to health professionals will stimulate a more critical approach when reviewing advertising in this area. Reviews of advertising in the print media of some specialised infant milks can also be found in the publications '*Scientific and Factual?' A review of breastmilk substitute advertising to health professionals' (2016) and* '*Scientific and Factual?' A further review of breastmilk substitute advertising to health professionals (2019)*, available at www.firststepsnutrition.org/reviews-of-claims. Not all specialised milks are advertised in the health professional literature so we have focused here on those that commonly are.

Abbott Nutrition Alimentum

In advertising in the March 2016 edition of Complete Nutrition, the marketing campaign for this product focussed on an emotional advert showing a mother and infant sleeping, with very little text. They claim that the milk has proven efficacy and support this claim with one study from 1991 that looked at the safety of a casein hydrolysate infant milk, which does not qualify as a study of efficacy of outcome (Sampson et al, 1991), and one study quoting data that is 'on file'. A further claim that the product is well tolerated is based on a small methodologically challenged Abbott-funded non-randomised prospective study of 25 4 month old infants with cows' milk allergy on a 15-day trial of Similac Alimentum, with parent-reported outcomes (Borschel & Baggs, 2015). Overall, 50% of parents said they were very satisfied and 50% were somewhat satisfied with the study formula. The third claim made is that the formula is free of palm oil and palm olein and that this supports calcium absorption and bone mineralisation. This is supported with one reference to a study by Koo et al (2006). However, this review has been criticised as there was no breastfed reference group and there is known to be a large variation in normal bone mineral content in infants, which in itself may have no clinical significance. In the EU there are rules that govern the fatty acid composition of milks and it is the individual fatty acid profile rather than the source of fatty acids that is regulated. A more detailed review of this advertisement can be found in '*Scientific and Factual?' A review of breastmilk substitute advertising to health professionals*, available at https://www.firststepsnutrition.org/reviews-of-claims.

Abbott Nutrition have now added the oligosaccharide 2'-Fucosyllactose (2'-FL) to both their Alimentum and EleCare infant milks. Both brands feature in Abbott's September 2020 advertising in an e-shot from the healthcare professional journal Complete Nutrition. This advertisement suggests that both Alimentum and EleCare with 2'-FL support symptom resolution, help support the immune needs of formula-fed infants with cows' milk allergy and are trusted by parents and healthcare professionals. A review of the advertisement and the evidence used in support of these statements can be found in section 2.5 of this report, under the header 'Abbott EleCare'.

Nutricia Aptamil Pepti 1

In their 2018 print advertising campaign in professional journals that we have previously reviewed in *'Scientific and Factual?' A further review of breastmilk substitute advertising to health professionals*, (available at https://www.firststepsnutrition.org/reviews-of-claims) Nutricia claimed that Aptamil Pepti is "*the UK's most palatable extensively hydrolysed formula*". They support this claim by referencing a Nutricia-funded study. The research report referenced is unobtainable, however, a paper published by the same author outlining this work references a taste test carried out on extensively hydrolysed formula on the UK market. The study reported that Pepti 1 was ranked as most palatable by 77% of participants and that the health care professionals in the study expected that good palatability would result in better acceptance. It was acknowledged that this does not prove that there is any link between health care professional taste preference and child preferences for the same formula (Maslin et al, 2018). The study participants were dietitians and GPs who all had prior experience of treating an infant with cows' milk allergy, were recruited by market research agencies from their healthcare professional registers and 98% of whom had prior awareness of Aptamil Pepti 1. The study was funded by Nutricia.

The 2018 advertisement for Pepti 1 also suggested that it is *"The 1st step in the effective management of cows' milk allergy is extensively hydrolysed formula"* in any infant. The main body of the advertisement omits the fact that extensively hydrolysed formula is only the first line of treatment of CMA in infants who are formula-fed or mixed fed. The iMAP guideline is used in support of this suggestion, however, the guideline recommends a trial of an extensively hydrolysed formula only for infants who are formula-fed or mixed-fed (Venter et al, 2017).

Aptamil Pepti Syneo

Aptamil Pepti Syneo is a whey based extensively hydrolysed formula containing synbiotics which are a combination of galacto- and fructo-oligosaccharides (GOS/FOS) and the live bacteria *Bifidobacterium breve* M-16V. Media marketing in the December 2020 issue of Network Health Digest claims that the oligosaccharides and probiotic in Aptamil Pepti Syneo work synergistically. This claim is not substantiated by published clinical trials, furthermore, none of the clinical trials referenced in this marketing compare Aptamil Pepti with both oligosaccharides and probiotics added to the same formula with either prebiotics only or probiotics only, therefore this claim is unsubstantiated. Further claims made are that compared to the same extensively hydrolysed formula without synbiotics, Aptamil Pepti Syneo supports improved symptom management, and lists the following benefits:

- Reduction in abdominal discomfort and wind
- Reduction in atopic dermatitis severity
- Reduction in constipation and dry stools

All of these claims, including the initial claim that Aptamil Pepti Syneo supports improved symptom management, are supported by reference to either a twelve week randomised controlled trial in infants with atopic dermatitis, or to poster presentations from an as yet unpublished four week split arm study.

The claim that Aptamil Syneo has been shown to reduce atopic dermatitis severity is supported by reference to a Nutricia sponsored, double-blinded, placebo-controlled multi-centre trial including 90 infants with atopic dermatitis fed with either Aptamil Pepti Syneo or the same formula without synbiotics (Aptamil Pepti), over 12 weeks. It is interesting that this study reported no significant differences in the extent and severity of atopic dermatitis between the symbiotic and non-synbiotic groups. The marketing material has a small footnote to say that this finding relates to a subgroup of 48 infants with IgE associated atopic dermatitis where those who received the synbiotic formula had a significantly greater reduction in SCORAD score after 12 weeks than infants who received the non-synbiotic formula. It is however important to note that the report from this trial draws attention to the fact that it was not powered to determine whether synbiotic treatment is effective in the subgroup of patients with IgE-associated atopic dermatitis (van der Aa et al, 2010). The only other reference used to substantiate this claim is a poster presentation (Browne et al, 2019) from an as yet unpublished study.

The claim that the product has been shown to reduce constipation and dry stools is also substantiated by reference to a poster presentation (Atwal et al, 2020) from an as yet unpublished study and to the clinical trial by van der Aa et al., 2010 outlined above. This trial also reported that in the group receiving infant formula with synbiotics, faecal consistency was significantly softer, fewer children had episodes of dry stools and parents reported less constipation during the intervention period. The claim for a reduction in abdominal discomfort and wind is supported only by reference to the poster presentation by Atwal et al, 2020.

Nutricia also claim that Aptamil Pepti Syneo '*modulates the gut microbiota to support long term health and immunity'*. The clinical trial by van der Aa et al, 2010 is used to support only the first part of this claim – that Aptamil Pepti Syneo '*modulates the gut microbiota'*. Four further references are given to substantiate the second part of this claim, that Aptamil Pepti Syneo 'supports long term health and immunity'. Putting together the first and second claims in one statement suggests that the evidence referred to shows that the claimed benefits are the result of modulation of the gut microbiota. Two of the references given to support these claims are Nutricia review articles and two are clinical trials. Neither of the clinical trials referenced examine cause and effect over the long term for the consumption of Aptamil Pepti Syneo.

The first of these clinical trials is a follow-up to the van der Aa (2010) double-blinded, placebo-controlled multi-centre trial looking at the development of asthma-like symptoms as determined by parental report 1 year after the initial twelve week intervention (Van der Aa et al, 2011). Specifically, parents were asked to report wheezing, a concept that can often be misunderstood parents, and this was not confirmed by the investigators. The trial reported that frequent wheezing and wheezing and/or noisy/rattly breathing apart from colds were significantly less prevalent in the synbiotic group than in the placebo group. Wheezing apart from colds did not differ significantly between the two groups. Significantly fewer children in the synbiotic group than in the placebo group used asthma medication at time of follow-up. There were significantly less new users of asthma medication in the synbiotic than in the placebo group. At follow-up the percentage of children with elevated specific IgE against the presence of a cat was significantly lower in the synbiotic group than in the placebo group and the number of children with elevated specific IgE against cat presence at follow-

up, that did not have elevated cat-IgE at baseline, was 0 out of 29 in the synbiotic group and 5 out of 33 (15.2%, none of these 5 children had cats in the home) in the placebo group (van der Aa et al, 2011).

The primary focus of the second clinical trial referenced was growth and tolerance. Hypo-allergenicity was a secondary outcome, evaluated in a subset of 30 infants with cows' milk allergy aged 0 to 3 years (Harvey et al, 2014). Furthermore, the product being evaluated was an amino acid formula, Neocate Syneo, rather than the new Aptamil Pepti Syneo. The study provided 95% confidence that at least 90% of infants and children with cows' milk allergy would have no reaction to Neocate Syneo, thus demonstrating the hypoallergenicity of Neocate-Syneo in infants and children with documented cows' milk allergy. These outcomes cannot however be reliably extrapolated to Aptamil Pepti Syneo.

SMA Althéra (Nestlé)

The 2018 advertising campaign in the December 2018/January 2019 edition of the health professional journal *'Complete Nutrition'* implied that Althéra shows better clinical outcomes for symptoms resolution than other brands because it has a greater level of hydrolysis and consistently lower allergenic potential than other brands. This claim is based on the theory that the smaller Dalton size and low residual β-lactoglobulin present in Althéra, result in a product with a less allergenic profile, which therefore suggests that it may result in better clinical outcomes. The only clinical trial used to support this claim compared Nestlé Althéra with an amino acid-based formula. This small clinical trial including 65 infants aged between 6 and 12 months showed that infants with cows' milk allergy tolerated the Althéra formula milk to the same extent as the amino acid formula tested and showed similar outcomes in terms of skin, gastrointestinal and respiratory tract symptoms of allergy as infants fed the amino acid formula (Niggemann et al, 2007). The trial did not suggest that Althéra has a consistently low allergenic profile in terms of its protein profile across batches and did not compare the outcomes achieved with Althéra compared to other extensively hydrolysed formula milks.

A more detailed review of this advertisement can be found in '*Scientific and Factual?' A further review of breastmilk substitute advertising to health professionals*, available at https://www.firststepsnutrition.org/reviews-of-claims.

Current marketing for Nestlé Althéra on the company website for healthcare professionals – www.smahcp.co.uk makes the statements *'positive gut microbiota modulation'* and '*preferred taste vs casein extensively hydrolysed formulas*' in relation to Althéra. References for the claims on taste are given as data on file at Abbott and a study from Vandenplas et al (2013) which aimed to determine whether a whey or casein hydrolysate is the best option for treatment of cows' milk allergy, and which showed that both were equally effective. The reference given to support the claim for positive gut microbiota modulation is one paper from Francavilla et al (2012) which investigated the impact of lactose on the composition of the gut microbiota in infants with cows' milk allergy, reporting that the presence of lactose increased the total faecal counts of Lactobacillus/Bifidobacterium and decreasing that of Bacteroides/Clostridia. The small study compared two products both from Nestlé and there are several limitations with the study. Several extensively hydrolysed formula contain lactose so this is not a defining feature of this product.

Mead Johnson Nutramigen 1 with LGG

Mead Johnson's extensively hydrolysed formula, Nutramigen LIPIL 1, was reformulated in 2015 to include a "unique probiotic", *Lactobacillus rhamnosus* GG (LGG). They claimed that it '*is clinically proven to relieve cows' milk allergy symptoms affecting the skin and gastrointestinal tract'* and we reviewed this advert in the 2016 publication '*Scientific and Factual? A review of breastmilk substitute marketing to healthcare professionals'* which can be accessed at www.firststepsnutrition.org/reviews-of-claims. EFSA stated that there is no benefit in adding probiotics to infant formula or follow-on formula (EFSA, 2014). Mead Johnson claim that this formula is clinically proven to accelerate tolerance to cows' milk. The 2015 advertising campaign in the health professional literature used the slogan "*The express route to the end of cows' milk allergy"*. This claim was based on data from a non-randomised prospective trial among Italian infants aged 1-12 months with cows' milk allergy who were already treated and free of symptoms and who were non-randomised to one of five treatment groups for 12 months to look at acquisition of tolerance to cows' milk (Canani et al, 2013). Two of the study arms used an extensively hydrolysed whey-based formula, one formula with LGG, one soya formula, one amino-acid based formula, and one a hydrolysed rice formula. The duration and exclusivity of breastfeeding between groups was not reported other than the proportion of infants per group breastfed for two months or more.

One of the main findings of the study was that infants with IgE mediated cows' milk allergy were less likely than those with non-IgE mediated allergy to achieve tolerance after 12 months. The group receiving Nutramigen with LGG had the lowest rate of IgE mediated allergy. There were differences in the brand of infant milk consumed in each of the treatment groups. For example, within the amino acid-based formula group (n=33), three different brands of formula were consumed, but in the largest group (n=71), extensively hydrolysed casein-based formula with LGG, only Nutramigen with LGG was consumed. Differences between brands may therefore have been masked, as brands were grouped according to category. The trial notably lacked a breastfeeding reference group to explore the effect of normal feeding on tolerance to cows' milk protein. As approximately half of infants with cow's milk allergy are known to outgrow this allergy at around 12 months, this may well also confound any conclusions regarding tolerance.

The authors concluded that the rate of acquiring oral tolerance was higher in the groups having either of the extensively hydrolysed formula and this was augmented by the addition of LGG, however, the study contains a large number of variables that could have impacted on the outcomes. Mead Johnson claimed in their advertising that this milk is *'proven to have an average efficacy of 99%'* but in a footnote say that this claim actually refers to a different extensively hydrolysed product which does not have probiotics added. Again they also caveat the claims *'the only extensively hydrolysed formula clinically proven to accelerate time to tolerance*' and *'8 out of 10 infants are tolerant to cows' milk after 12 months use"* with the admission that these data come from the Canani et al, 2013 study reported above that compared an extensively hydrolysed formula with infant groups given soy, amino-acid and rice hydrolysate formula. Mead Johnson also claim that this is '*the world's leading CMA formula*' with evidence for this *'on file'*.

The 2018 advertising campaign in the health professional literature continues to use the 2015 claims and includes a further statement *'Help give her the ability to protect herself from future allergic manifestations'.* We reviewed this advertising in the 2019 report *'Scientific and Factual? A further review of breastmilk substitute advertising to healthcare professionals'* which can be accessed at www.firststepsnutrition.org/reviews-of-claims. The study used to support this implied claim is a clinical trial part sponsored by Mead Johnson, carried out between 2008 and 2014 (Canani et al, 2017). The infants included in the trial were aged between 1 and 12 months with a median age of 5 months, and the follow-up period was 36 months. Only infants with proven IgE mediated cows' milk allergy were included in the trial. Infants were randomised to receive either Nutramigen extensively hydrolysed formula with no probiotic or Nutramigen extensively hydrolysed formula with the probiotic *Lactobacillis rhamnosus* GG (LGG). Allergic manifestations and other food allergies were recorded at baseline and at 12 months, 24 months and 36 months. Skin prick tests and double-blinded, placebo-controlled food challenge tests were also performed at these visits to determine tolerance acquisition. The trial reported an absolute risk difference of -0.23 of any allergic manifestation during 36 months for Nutramigen with LGG compared to Nutramigen without probiotic. This means that, compared with extensively hydrolysed formula without probiotics, four subjects needed to be treated with extensively hydrolysed formula with probiotic for 36 months to prevent at least one allergic manifestation.

As highlighted previously, this trial relates only to children with IgE mediated cows' milk allergy. It is not clear from the trial data if the Nutramigen milks with LGG currently marketed are those used in the trial. No details of the duration or exclusivity of breastfeeding was provided except for the proportion of babies breastfed for more than two months, and there was no breastfed reference group. Parents were not blinded to the infant milk their child received and they recorded the amount of milk consumed daily. Health problems and allergic symptoms were recorded by structured interviews with parents. The interviews occurred at 12-month intervals or more frequently in individual children if advised by the GP. Although dietitians were employed to give advice on the cows' milk exclusion diet, the trial report did not appear to record compliance with the diet.

Mead Johnson have also provided financial support for studies in Europe and the US that estimate the cost savings of using their Nutramigen extensively hydrolysed formula products with LGG in comparison to extensively hydrolysed formula products without LGG. The UK study by Guest and Singh, 2019 uses data on clinical outcomes from the previously mentioned Canani et al, 2017 study. Estimates of associated healthcare resource costs were derived from interviews with four UK GPs experienced in the management of patients with cows' milk allergy according to their local clinical protocol and NICE guidance (NICE, 2011). The data collected was used to populate a predictive statistical model that estimated the potential savings in healthcare costs that would be made by using extensively hydrolysed formula with LGG compared to extensively hydrolysed formula without LGG as the first line of treatment in infants with IgE mediated cows' milk allergy. The original study had a follow-up period of three years and the predictive model extrapolated potential savings to five years. This study reported that cost savings would be made on the basis of greater acquisition of tolerance and reduced allergic manifestations in infants fed Nutramigen LGG compared to those fed Nutramigen without LGG. No other brands were compared in the study. Nutramigen without LGG is no longer available in the UK and the

study does not provide any evidence that Nutramigen with LGG is any more cost effective than extensively hydrolysed formula from other manufacturers.

The study has some major limitations including that the base data was taken from a study with some methodological limitations, as outlined previously. In addition, data on resource use came from only four GPs in different UK locations. Local treatment protocols may vary and so it is not certain that the costs used were typical of other areas in the UK. The study fails to mention that breastfeeding remains the best way to feed an infant with IgE or non IgE mediated cows' milk allergy. Greater clinical success and cost savings can be made to the NHS by supporting breastfeeding wherever possible, and when clinically indicated.
As this milk contains the probiotic *Lactobacillus rhamnosus GG,* instructions for making up this powdered infant milk include the use of cold water. This has caused some concern among health professionals, who recognise the risk associated with making powdered infant milk up with water at temperatures below 70^{o}C. The Food Standards Agency and the Department of Health regulators agreed, in a restricted correspondence and data review in 2015, that the milk can be sold in the UK with these instructions for making up the milk but suggesting that claims for efficacy of this product contradict most other scientific reviews.

Safety of use

Infants receiving extensively hydrolysed infant milks may need attentive mouth care as some of the added sugars found in some of these infant milks are associated with the demineralisation of enamel (Rezende and Hashizume, 2018).

The manufacturers of Aptamil Pepti-junior advise that Pepti-junior should not be used at full strength initially in infants with severe gut damage, but do not give evidence supporting this recommendation. Instead, they recommend starting at half strength, working up to full strength in 2-3 days.

As there is so much marketing and promotion of products in this area, it is particularly important that health professionals know how to work within the WHO Code and to refer to recognised clinical guidance if suitable local prescribing guidance is not provided.

The nutritional composition of extensively hydrolysed peptide-based infant milks suitable from birth

Table 6 shows the nutritional composition of extensively hydrolysed infant milks which do not have medium chain triglycerides added as the main fat source, and Table 7 shows the composition of extensively hydrolysed infant milks with medium chain triglycerides as the main fat source.

TABLE 6. The nutritional composition of extensively hydrolysed (peptide-based) infant milks suitable from birth

Nutrients per 100ml	Abbott Nutrition Similac Alimentum	Aptamil Pepti 1	Aptamil Pepti Syneo	Mead Johnson Nutramigen 1 with LGG	SMA Althéra
INDICATIONS	Cows' milk allergy and other conditions where extensively hydrolysed formula is indicated	Cows' milk allergy	Cow's milk allergy	Cows' milk allergy	Cows' milk allergy and/or multiple food protein allergies
MACRONUTRIENT					
Energy kcal	68	66	66	68	67
Protein g	1.9	1.6	1.6	1.9	1.6
Protein source	Milk	Milk	Milk	Milk	Milk
Whey:casein ratio	0:100	100:0	100:0	0:100	100:0
Carbohydrate g	6.6	7.1	7.1	7.4	7.3
– of which lactose g	0	2.9	2.89	0	3.7
Carbohydrate source	Maltodextrin, sucrose, modified starch	Maltodextrin, lactose, oligosaccharides	Maltodextrin, lactose, oligosaccharides	Glucose syrup, modified corn starch	Lactose, maltodextrin
Fat g	3.8	3.4	3.4	3.4	3.4
Fat source	High oleic safflower, MCT from palm kernel, coconut, soya and single cell oils	Palm, coconut, rapeseed, high oleic sunflower, sunflower, single cell and fish oils	Palm, coconut, rapeseed, high oleic sunflower, sunflower, single cell and fish oils	Palm olein, coconut, soya, high oleic sunflower and single cell oils	Sunflower, rapeseed, coconut and single cell oils
Added LCPs ARA	✓	✓	✓	✓	✓
DHA	✓	✓	✓	✓	✓
LCP source	Fungal/algal oils (vegetable source)	Fish oil, fungal oils (vegetable source)	Fish oil, fungal oils (vegetable source)	Fungal/algal oils (vegetable source)	Fungal/algal oils (vegetable source)
MICRONUTRIENTS					
VITAMINS					
Vitamin A µg-RE	61	58	58	61	66
Vitamin C mg	8.5	9.1	9.1	8.1	11
Vitamin E mg	1.4	1.2	1.2	0.61	1.8
Vitamin D µg	1.7	1.7	1.7	1.68	1.6
Vitamin K µg	8.8	NK	4.4	8.7	5.9
Thiamin (B_1) µg	50	70	70	54	67
Riboflavin (B_2) µg	70	140	140	61	130

Nutrients per 100ml	Abbott Nutrition Similac Alimentum	Aptamil Pepti 1	Aptamil Pepti Syneo	Mead Johnson Nutramigen 1 with LGG	SMA Althéra
Niacin µg (mg NE)	710 (1.2)	870	880	(0.67)	920 (1.6)
Vitamin B_6 µg	40	NK	45	40	53
Vitamin B_{12} µg	0.2	0.16	0.16	0.2	0.18
Folic acid µg	10		8.8		
Folate µg DFE		15		18.2	16
Biotin µg	3.0	1.9	1.9	2.0	1.6
Pantothenic acid µg	510	NK	574	340	440
MINERALS					
Calcium mg	71	61	61	76	70
Chloride mg	54	51	51	65	53
Copper µg	50	52	52	51	54
Iodine µg	13	NK	13	15.5	16
Iron mg	1.22	0.54	0.54	1.2	0.66
Magnesium mg	5.1	5.0	5.0	5.0	5.9
Manganese µg	10	8.0	8.0	17	9.0
Phosphorus mg	44	35	35	52	46
Potassium mg	71	87	87	82	80
Selenium µg	2.7	NK	3.0	2.4	3.3
Sodium mg	30	20.8	20.9	32	25
Zinc mg	0.51	0.66	0.66	0.47	0.66
ADDED INGREDIENTS					
Prebiotics	✓	✓	✓	×	×
Probiotics	×	×	✓	✓	×
Nucleotides	×	✓	✓	×	×
Inositol	✓	✓	✓	✓	✓
Taurine	✓	✓	✓	✓	✓
Choline	✓	✓	✓	✓	✓
L-carnitine	✓	✓	✓	✓	✓
Added antioxidants	✓	✓	✓	✓	✓
Contains soya	✓	×	×	✓	×
Contains fish oil	×	✓	✓	×	×
Suitable for vegetarians	×	×	×	×	×
Halal approved	×	×	×	×	×
Osmolality mOsm/kg	290	280	280	280	290

ARA = arachidonic acid
DHA = docosahexaenoic acid
LCP = long chain polyunsaturated fatty acid
NA = not applicable
NK = not known

TABLE 7. The nutritional composition of extensively hydrolysed (peptide-based) infant milks with medium chain triglycerides as the main fat source, suitable from birth

Nutrients per 100ml	Aptamil Pepti-junior	Mead Johnson Pregestimil LIPIL	Nutricia Infatrini Peptisorb
INDICATIONS	Malabsorption from conditions such as short bowel syndrome, liver disease, chronic diarrhoea, post gastrointestinal surgery, feed intolerance	Allergy, fat malabsorption, maldigestion	Short bowel syndrome, malabsorption, inflammatory bowel disease, bowel fistulae, disease-related malnutrition, whole protein intolerance
MACRONUTRIENTS			
Energy kcal	66	68	100
Protein g	1.8	1.9	2.6
Protein source	Milk	Milk	Milk
Whey:casein ratio	100:0	0:100	100:0
Carbohydrate g	7.2	6.9	10.2
– of which lactose g	0.05	0	<0.1
Carbohydrate source	Glucose syrup, maltodextrin	Glucose syrup, modified corn starch	Glucose syrup, maltodextrin,
Fat g	3.4	3.8	5.4
Fat source	MCTs from coconut and palm oil, rapeseed, sunflower, palm, high oleic sunflower oil, fish and single cell oils	MCTs from coconut oil, soya, high oleic sunflower oil and single cell oils	MCTs from coconut and palm oil, corn, rapeseed, sunflower, fish and single cell oils
With medium chain triglyceride oils (%)	✓(50)	✓ (55)	✓ (52)
Added LCPs ARA	✓	✓	✓
DHA	✓	✓	✓
LCP source	Fish oil, fungal oils (vegetable source)	Fungal/algal oils (vegetable source)	Fish oil, fungal/algal oils (vegetable source)
MICRONUTRIENTS			
VITAMINS			
Vitamin A µg-RE	59	77	88
Vitamin C mg	9.3	13	14
Vitamin E mg	1.2	1.81	2.7
Vitamin D µg	1.7	1.25	2.4
Vitamin K µg	4.4	8.1	6.7
Thiamin (B_1) µg	70	54	150
Riboflavin (B_2) µg	140	61	200
Niacin µg (mg NE)	430	0.68	800 (1.67)
Vitamin B_6 µg	50	41	110

Nutrients per 100ml	Aptamil Pepti-junior	Mead Johnson Pregestimil LIPIL	Nutricia Infatrini Peptisorb
Vitamin B_{12} µg	0.16	0.2	0.30
Folic acid µg		10.8	
Folate µg DFE	14		26.7
Biotin µg	1.7	2.0	4.0
Pantothenic acid µg	540	340	800
MINERALS			
Calcium mg	76	78	90
Chloride mg	43	58	75
Copper µg	53	51	75
Iodine µg	13	14.2	19
Iron mg	0.72	1.22	1.2
Magnesium mg	5.1	7.5	9.0
Manganese µg	3.0	41	6.0
Phosphorus mg	47	51	45
Potassium mg	75	74	111
Selenium µg	2.9	1.49	3.75
Sodium mg	21.7	29	37
Zinc mg	0.67	0.68	0.8
ADDED INGREDIENTS			
Structured vegetable oils (beta-palmitate)	×	×	×
Prebiotics	×	×	×
Nucleotides	✓	×	✓
Inositol	✓	✓	✓
Taurine	✓	✓	✓
Choline	✓	✓	✓
Added antioxidants	✓	✓	✓
Contains soya	×	✓	×
Contains fish oil	✓	×	✓
Suitable for vegetarians	×	×	×
Halal approved	×	×	×
Osmolality mOsm/kg	210	280	350

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
NA = not applicable NK = not known

2.4 Extensively hydrolysed peptide-based infant milks suitable from 6 months

Key points

Specialised infant milks marketed in the UK for infants aged 6 to 12 months are also often referred to as follow-on specialised milks. These milks are not needed as an extensively hydrolysed milk suitable from birth can be used throughout the first year.

There are two follow-on versions of extensively hydrolysed infant formula: Aptamil Pepti 2 and Nutramigen 2 with LGG. There does not appear to be any advantage in having a follow-on version of these milks and there may be potential risks from higher and different carbohydrate ingredients.

We encourage manufacturers of follow-on or stage 2 specialised milks to clarify the purpose, composition and ingredients of these milks.

Specialised infant milks marketed for infants aged 6 to 12 months are available in the UK for infants with cows' milk allergy. As these are marketed for those over 6 months, they may be referred to as specialised follow-on formula or specialised 'stage 2' milks. Companies often justify the presence of these milks on the market by saying that they can help meet infants' increasing iron requirements after six months. However, current UK infant feeding guidelines recommend that, after 6 months of age, additional iron requirements should be met by including iron-rich complementary foods in the diet. If an infant is not breastfed and has a medical condition, such as cows' milk allergy, so is unable to have a first formula milk, it is usually most appropriate for them to have a specialised infant milk suitable from birth until 12 months of age.

Specialised infant milks for those aged 6 to 12 months fall under the same regulations as those for under six months, the Regulation on Foods for Specific Groups (FSG) (609/2013). As both the stage 1 and stage 2 specialised milks fall under the same regulations and, in general, follow-on milks are deemed unnecessary, the purpose of these stage 2 specialist milks is questionable.

There are currently two specialised infant milks in the UK marketed for infants aged 6-12 months: Aptamil Pepti 2 (produced by Nutricia) and Nutramigen 2 with LGG (produced by Mead Johnson). Both are extensively hydrolysed cows' milk based and suitable for infants with cows' milk allergy. They are available on prescription and both state that the product should only be used under medical supervision. Both milks comply with EC regulations for foods for special medical purposes. Neither are suitable for vegetarians or vegans or are halal approved.

Aptamil Pepti 2 is a whey-based powder formula. The main carbohydrate source in Aptamil Pepti 2 is maltodextrin rather than lactose. Nutramigen 2 with LGG contains no lactose and the carbohydrate content (which is higher than in Nutramigen 1 LGG) is from glucose syrup, fructose and modified corn starch. Maltodextrin is associated with demineralisation of enamel (Rezende and Hashizume, 2018). There are health concerns about the addition of

maltodextrin and other added sugars into foods marketed for infants, including potential programming of sweeter taste preferences from a very early age, dental decay and long-term chronic diseases.

Nutricia state on their website that '*Aptamil Pepti 2 supports a restricted, cows' milk-free weaning diet for babies over 6 months, and includes extra calcium, vitamin D and iron*.' Despite this statement, there is no increase in Vitamin D between Aptamil Pepti 1 and Pepti 2, both products contain 1.7ug/100ml. Nutramigen 1 LGG and Nutramigen 2 LGG also have the same vitamin D content.

Nutramigen 2 LGG contains less iron than Nutramigen 1 LGG (1.08mg/100ml compared to 1.2mg) which is odd considering that additional iron in products is often given as a rationale for follow-on milk products. Aptamil Pepti 2 contains 1mg iron/100ml compared to 0.54mg in Pepti 1. EFSA (2014) in its Scientific opinion on the essential composition of infant and follow-on formulae suggested that follow-on formula should have a higher minimum (target) iron content than infant formula and current regulations on the compositional requirements for infant formula and follow-on formula reflect these recommendations. Both Aptamil Pepti 1 and Nutramigen 1 with LGG meet the higher target for iron required for specialised follow-on formula and are therefore, by EFSA criteria, appropriate throughout the first year. The increase in an infant's micronutrient requirements from the age of 6 months can therefore be met by continuing the use of extensively hydrolysed infant milks suitable from birth throughout the first year alongside the introduction of solids.

Concerns have been raised about the higher iron content of follow-on milks as there is some evidence that excessive iron intakes may result in a reduced uptake of other trace metals and the oxidation of lipids (Aggett et al, 2002). Studies among iron replete toddlers have shown adverse effects on cognitive outcomes and growth for infants with high iron intakes (Lozoff et al, 2011, Idjradinata et al, 1994.) A large UK trial of nearly 500 infants and toddlers given follow-on formula between 9 and 18 months of age found that there were no developmental or growth advantages in children given iron-supplemented follow-on formula (Morley et al, 1999).

Nutricia state Aptamil Pepti 2 is the only extensively hydrolysed formula containing oligosaccharides. According to EFSA, 2014 oligosaccharides have not been shown to be a necessary addition to infant formula or follow-on formula (EFSA, 2014). Nutramigen 2 LGG contains probiotics and claims to be '*an age-adapted, casein-based extensively hydrolysed formula developed for the dietary management of infants with mild to moderate cow's milk allergy'.* A number of claims are made about the product but it is not clear how it has been 'age-adapted' as the iron content is lower than Nutramigen 1 LGG. A claim is made that its '*Specifically developed taste profile helps acceptance by infants from 6 months onwards'* but no explanation or evidence is given to support this claim.

The nutritional composition of extensively hydrolysed (peptide-based) infant milks marketed as suitable from birth

The nutritional composition and ingredients of extensively hydrolysed infant milks marketed as suitable from 6 months are given in Table 8.

TABLE 8. The nutritional composition of extensively hydrolysed (peptide-based) infant milks marketed as suitable from birth

Nutrients per 100ml	Aptamil Pepti 2	Mead Johnson Nutramigen 2 with LGG
INDICATIONS	Cows' milk allergy	Cows' milk allergy
MACRONUTRIENT		
Energy kcal	68	68
Protein g	1.6	1.7
Protein source	Milk	Milk
Whey:casein ratio	100:0	0:100
Carbohydrate g	7.8	7.7
– of which lactose g	3.0	0
Carbohydrate source	Maltodextrin, lactose oligosaccharides	Glucose syrup, fructose, modified corn starch
Fat g	3.2	3.4
Fat source	Palm oil, coconut oil, rapeseed oil, high oleic sunflower oil, sunflower oil, single cell oil and fish oil	Palm olein, coconut, soya, high oleic sunflower oil, single cell oils
Added LCPs ARA	✓	✓
DHA	✓	✓
LCP source	Fish oil, fungal oils (vegetable source)	Fungal and algal oils (vegetable source)
MICRONUTRIENTS		
VITAMINS		
Vitamin A µg-RE	60	65
Vitamin C mg	8.5	7.4
Vitamin E mg	1.2	0.67
Vitamin D µg	1.7	1.7
Vitamin K µg	4.5	5.4
Thiamin (B_1) µg	70	65
Riboflavin (B_2) µg	140	84
Niacin µg (mg NE)	920	1040
Vitamin B_6 µg	NS	87
Vitamin B_{12} µg	0.16	0.14
Folate µg DFE	14	13.5
Biotin µg	1.8	1.41
Pantothenic acid µg	NS	500

Nutrients per 100ml	Aptamil Pepti 2	Mead Johnson Nutramigen 2 with LGG
MINERALS		
Calcium mg	79	81
Chloride mg	53	47
Copper µg	53	50
Iodine µg	NS	15.5
Iron mg	1.0	1.08
Magnesium mg	7.6	8.1
Manganese µg	7.0	20
Phosphorus mg	49	47
Potassium mg	90	94
Selenium µg	NS	2.4
Sodium mg	22	24
Zinc mg	0.68	0.74
ADDED INGREDIENTS		
Prebiotics	✓	×
Probiotics	×	✓
Nucleotides	✓	×
Inositol	✓	✓
Taurine	✓	✓
Choline	✓	✓
L-carnitine	✓	✓
Added antioxidants	✓	✓
Contains soya	×	×
Contains fish oil	✓	×
Suitable for vegetarians	×	×
Halal approved	×	×
Osmolality mOsm/kg	NS	NS

NS – Not stated

2.5 Amino-acid based infant milks suitable from birth

Key points

Amino-acid based infant milks contain protein in the form of individual amino acids and are marketed to be used in the dietary management of more severe cows' milk allergy or multiple allergies. Amino-acid based infant milks are unlike other hypoallergenic infant milks in that they contain amino acids which are synthetically derived, as opposed to peptides originating from cows' milk, meat or soya as found in extensively hydrolysed formula.

These milks are about three times more expensive than extensively hydrolysed formula meaning that more appropriate prescribing could generate considerable cost savings to the NHS.

Breastfeeding is the optimal way to feed a baby with cows' milk allergy. Currently, maternal elimination of cows' milk protein foods and fluids is recommended with adequate calcium and vitamin D supplementation to meet the mother's nutritional requirements during breastfeeding.

Amino-acid based infant milks are lactose-free and contain maltodextrin or dried glucose syrup as the main carbohydrate source, meaning that oral care is particularly important for infants given these products.

The use of high-profile health professionals working in allergy to promote brands which make these products is common. When making clinical decisions, healthcare professionals should take note of whether guidelines or guides produced by healthcare professionals are sponsored by infant milk companies and should look for independent information wherever possible.

Amino-acid based infant milks are unlike other hypoallergenic infant milks in that they contain amino acids which are synthetically derived, as opposed to peptides originating from cows' milk as found in extensively hydrolysed formula.

It is recommended that infants with more severe cows' milk allergy or multiple food allergy require breastfeeding mothers to have maternal dietary restriction of the identified allergens and/or the use of an amino-acid based infant milk.

As of December 2014, the EU Food Information for Consumers (EUFIC) Regulation came into force requiring 14 allergens on the regulatory list to be labelled on pre-packed foods, which includes infant milk. These are:

- celery (and celeriac)
- cereals containing gluten
- crustaceans, e.g. prawns, crabs, lobster, crayfish
- eggs
- fish
- lupin

- milk
- molluscs, e.g. clams, mussels, squid
- mustard
- nuts, e.g. almonds, walnuts, pecans, Brazil nuts
- peanuts
- sesame
- soybeans
- sulphur dioxide, a preservative found in some dried fruit.

This should be beneficial to those who want to continue to breastfeed but who may need to follow an exclusion diet of some kind, and full dietetic support should always be given for mothers to do this. Additional support will be needed so that breastfeeding women can manage their breastmilk supply if they have to have a period of expressing milk as they adopt dietary restrictions.

The Health Improvement Network (THIN) database holds data on 6 million anonymised UK patients entered by GPs and this has been found to be representative of the UK population. A Mead Johnson funded study of 295 of these records examined the cost-effectiveness of giving infants under 1 year of age an extensively hydrolysed infant milk compared with an amino-acid based infant milk as a first-line treatment for cows' milk allergy. It found no significant differences in clinical outcomes between the two groups but did find a significant difference in 12-monthly cost to the NHS of £1,853 vs £3,161 per infant for the extensively hydrolysed and amino-acid based infant milks respectively (Taylor et al, 2012). The authors conclude that, in the absence of good-quality data demonstrating the superiority of one infant milk over another, in many cases it would be both cheaper and as effective to opt for extensively hydrolysed infant milks.

A systematic review, undertaken in 2007 by Hill et al, examined the efficacy of amino-acid based infant milks in relieving symptoms of cows' milk allergy (Hill et al, 2007). They found six published randomised controlled trials, three of which were of good quality. Hill et al concluded that there was evidence of growth and tolerance of amino-acid based infant milks when compared with extensively hydrolysed infant milks but noted a limited evidence base arising from small sample sizes, use of different infant milks, no evidence of alternatives to amino-acid based infant milks being used, and multiple outcomes which were often inconsistently reported.

A German study compared safety and efficacy of an extensively hydrolysed formula compared with an amino-acid based formula in a small industry-funded prospective randomised controlled study with 65 infants with cows' milk allergy (Niggemann et al, 2007). The authors reported that growth and tolerance were the same when infants were given either milk, as were gastrointestinal symptoms and respiratory tract symptoms of allergy. A slight decrease in eczema was noted for infants fed the amino-acid based formula, but those on extensively hydrolysed formula had fewer episodes of vomiting and softer stools.

There is a considerable literature on the diagnosis and management of cows' milk and other food allergy in infancy, and we appreciate that we have only presented a few examples here. The management of any individual child requires expert clinical decision-making.

Milks currently marketed

There are five amino-acid based infant formulas for non-metabolic disorders available in the UK:

- Abbott Nutrition EleCare
- Mead Johnson Nutramigen Puramino
- Nutricia Neocate LCP
- Nutricia Neocate Syneo
- SMA Alfamino.

All of these infant formulas are manufactured in a powdered format and are available on prescription. The greatest increase in spend on paediatric prescribable infant milks since 2006 has been in the hypoallergenic infant formula market.[2] In the current economic climate, clinical commissioning groups are reviewing ways to manage this by creating prescribing guidelines to ensure that these products are not used inappropriately or for longer than necessary.

Nutritional Composition

These group of infant milks are nutritionally complete. They differ from infant formula in that the protein source is free amino acids rather than milk protein.

Unlike infant formula which contain carbohydrate mainly in the form of lactose, this group of infant milks contain carbohydrate mainly in the form of maltodextrin or dried glucose syrup and do not contain lactose. They contain added vitamins, minerals and trace elements.

Manufacturers claims and information given to support them

Both Nutricia Neocate LCP and Neocate Syneo make reference to *"fast, effective*" resolution of symptoms in 3-14 days in a small trial of 25 infants who were given Neocate LCP for two weeks after symptoms did not resolve with a casein-based extensively hydrolysed infant milk. The study authors reported that symptom resolution was observed in 22 of the 25 subjects following a challenge with the casein-based infant milk after that period (Vanderhoof et al, 1997). A second small study referenced (de Boissieu et al, 1997) reported on 13 infants in France who had shown allergic symptoms to an extensively hydrolysed formula but tolerated an amino-acid based formula. Neocate Syneo was not given to infants in either study despite both being referenced in their promotion to health professionals.

Print advertising in 2015 claimed that Neocate LCP was the "*Number 1 amino acid formula in the UK"* for which no evidence was given, and that it had superior palatability, with the evidence for this 'on file'. It also claimed that this milk "*Enables growth"*, referring to the Niggemann et al study which showed equal growth and tolerance when either an amino-acid based or extensively hydrolysed formula is given (Niggemann et al, 2007), and a study by Isolauri et al (1995) which again showed that both extensively hydrolysed and amino-acid based formula led to adequate growth in infants with cows' milk allergy. The authors suggested that extensively hydrolysed formulas are safe and effective for most infants with

2 Data from LPP website http://www.lpp.nhs.uk/. Access requires an NHS account.

cows' milk allergy, but that an amino-acid based formula may be preferable for infants with multiple food allergies. The print advert also claimed that this product has an "*Optimal nutrient profile"* but simply references the current EU and Codex standards for foods for special medical purposes which do not specify an optimum profile, simply the range of values acceptable in law.

Nutricia Neocate Syneo has a similar nutritional composition to Neocate LCP but contains a prebiotic strain of fructo-oligosaccharides and a probiotic *Bifidobacterium breve* M-16V. Nutricia claim that Neocate Syneo can *"help rebalance gut microbiota dysbiosis".* We discussed print advertising for Neocate Syneo in the 2019 report '*Scientific and Factual? A further review of breastmilk substitute advertising'* which can be accessed at www.firststepsnutrition.org/reviews-of-claims. They reference two papers for this claim which were both funded by Nutricia. The first of which studied three groups of infants: a healthy exclusively breastfed group, a control group (who were given Neocate LCP) and a test group who were given Neocate LCP with added *Bifidobacterium breve* and a blend of fructo-oligosaccharides (Candy et al, 2017). The milk given to the test group was similar to Neocate Syneo but not identical. The infants in the test and control arm both had *"suspected"* cows' milk allergy and were given the formula for 8 weeks, during which time their cows' milk allergy may have resolved independently of the formula they were given. The infants in all three groups came from a range of different countries and were aged between 1.2 to 14.2 months old. There were also twice as many caesarean-delivered babies in the control group than the test group. All of these factors were likely to affect their gut microbiota (Phillips, 2009; Odamaki, 2016; Wen & Duffy, 2017) and may have confounded the outcomes.

The study showed a shift in the faecal microbiota of infants on the milk containing pre- and probiotics (synbiotics) towards that of the breastfed infants but no change in gastrointestinal symptoms between the test and control group. They did not study gut microbiota directly but instead extrapolated the change in faecal microbiota to assume a shift in gut microbiota. In their promotion to health professionals, Nutricia also refer to a similar study (Burks et al, 2015) which looked at self-reported stool characteristics in those given a milk similar to Neocate Syneo. 81 out of 110 of the infants on either formula experienced an adverse event. The researchers found a similar decrease in symptoms for those taking an amino acid-based formula both with and without pre- and probiotics, suggesting that these added ingredients may not have any additional benefit. This corresponds with an ESPGHAN review in 2014 stating that there is *"insufficient data to recommend the routine use of probiotic- and/ or prebiotic supplemented formulae"* while EFSA (2014) found *"no evidence that the addition of prebiotics, probiotics or synbiotics to infant formula has any benefits to health in term infants".*

Nutramigen Puramino

Puramino contains 33% medium chain triglycerides. Mead Johnson's current online marketing for Puramino claims *'proven fast and effective in managing cow's milk allergy symptoms'* quoting two references. The first by Burks et al (2008) didn't include a milk with medium triglyceride oil so is therefore not directly comparable, and the second study by Vanderhoof et al (2016) funded by Mead Johnson compared an extensively hydrolysed formula with an amino-acid based formula where infants had not responded to the extensively hydrolysed formula. This was an observational, nonrandomized study with a the

relatively small sample size and simply showed efficacy for an amino-acid based formula in infants with more complex allergy. Little additional support is given for the claims made, with references provided for the absorption of MCT relating simply to these fats and not related to this infant milk.

Abbott Elecare

Abbott EleCare is the most recent amino-acid based infant formula to be introduced to the UK market. The carbohydrate sources in EleCare are maltodextrin, modified corn starch and oligosaccharides including 2' Fucosyllactose (2'-FL). Abbott state in their 2020/2021 media advertising for EleCare:

'*help support the immune system in the gut and beyond*' and '*contains 2'-FL HMO which has proven benefits for the gut and systemic immune responses*'.

These implied claims are supported by reference to studies from their own clinical trial which enrolled 402 healthy term infants by the fifth day of life. The primary outcome of the first study was growth and tolerance in infants fed 1 of 3 isocaloric formula. Each contained galacto-oligosaccharides and 2 test formulas contained 2'-FL at either 0.02g/100ml or 0.1g/100ml. No significant differences in growth parameters were reported between the formula groups however, some similarities in rates of absorption of 2'-FL at trial day 42 between healthy infants who were either breastfed or fed one of the formula supplemented with 2'-FL, were reported. These similarities were no longer apparent at day 119 and no clinical advantage was shown for the addition of 2'-FL (Marriage et al 2015).

In a further study from this clinical trial, Geohring et al (2016) examined the effects of feeding formula supplemented with 2'-FL on biomarkers of immune function at 6 weeks of age. Few differences between the feeding groups and no clinical advantages were reported. Out of 10 circulating plasma inflammatory cytokines tested, only 5 (50%) were significantly higher in the group fed the control formula containing only galacto-oligosaccharides (GOS) compared to the test formula groups who were fed formula supplemented with the same total concentration of oligosaccharides as the control formula, but with different proportions of GOS replaced by 2'-FL. Similarly, when viral induced cytokine response was tested, concentrations of these cytokines did not differ between the control group and the test formula groups with the exception that the concentration of 5 out of 10 of the cytokines tested was lower for infants fed the formula with a lower concentration of 2'-FL compared to infants fed the control formula. Only one difference was found between all groups for all cytokines when the supernatant from phytohaemagglutinin-stimulated peripheral blood mononuclear cells was tested. No significant differences were reported for any circulating lymphocyte cell populations between the control group and either of the 2'-FL–supplemented groups.

The composition of the infant formulas used in the clinical trial was very different to that of EleCare. The infant formulas used in the clinical trial were based on standard, non-hydrolysed infant formula whereas EleCare is an amino acid based infant formula. Furthermore, whilst the test formulas contained 0.24g oligosaccharide per 100ml made up from both GOS and 2'-FL, EleCare contains 0.02g/100ml 2'-FL and does not contain added GOS.

A review article by Abbott (Reverri et al, 2018) is also used in support of claims around gut health and the immune response. However, this adds little to the clinical evidence base as it summarises the studies by Marriage et al, 2015 and Goehring et al, 2016 previously listed, and includes a further randomized double-blinded controlled tolerance trial which has not been published in a peer-reviewed publication, and which uses a test formula based on whole milk proteins rather than the amino base used in Elecare (Kajzer et al, 2016). The remaining studies in this review article include a small prospective single arm tolerance study of 59 healthy infants reported by parents to be very fussy or extremely fussy. As the test formula they were switched to was a low lactose, partially hydrolysed formula with 2'-FL, the reported improvements in tolerance cannot be extrapolated to EleCare with 2'-FL which is based on amino acids.

Reverri et al 2018 also present post-hoc analysis of adverse events from the clinical trial data reported by Marriage et al. They reported that the formula with 2'-FL was associated with significantly fewer parent reported respiratory tract infections compared to the control formula. It is important to note that identifying differences in respiratory tract infections between groups was not the primary outcome of the study which may not have been powered to identify these differences.

Abbott also imply that EleCare with 2'-FL supports '*healthy growth and symptom resolution'*. They support these implied claims with evidence drawn from 4 clinical trials, however, none of the four used EleCare with 2'-FL as the test formula (Borschel et al, 2013, Borschel et al 2014a, Borschel et al, 2014b, Sicherer et al, 2001). Sicherer et al, 2001 examined the hypoallergenicity of EleCare without 2'-FL in a group of children aged between 6 and 17.5 months, the results cannot therefore be reliably extrapolated to infants using EleCare with 2'-FL. The remaining 3 studies by Borschel et al report that EleCare without 2'-FL supports normal growth in infants. This is not surprising as EleCare conforms to current UK compositional regulations for the composition of specialised infant milks. Borschel et al 2014a reports that when infants experiencing chronic diarrhoea switched to EleCare improvements in stooling patterns were observed. Borschel et al, 2014b reported that from the beginning of the study to study exit, paediatrician reported symptom scores for infants with presumptive food-induced proctocolitis were significantly reduced when infants switched from their current formula (not an amino acid formula) to EleCare.

Abbott also state that their EleCare formula with 2'-FL is '*trusted by parents and healthcare professionals'*. This statement is based on data referred to in their marketing as 'RTI research Abbott EleCare No. 1 Dr Recommended. Final results 2019' which Abbott have shared with us. The research, commissioned by Abbott to establish which amino-acid formula gastroenterologists recommended most, reported that 70% of paediatric gastroenterologists (n=375) responding to a questionnaire recommend EleCare significantly more often than Neocate or any other brand for infants aged 0-12 months. No reasons why this is the case are offered, there may therefore be other factors such as price influencing recommendations. It is also important to remember that this is a US based survey and so was undertaken in an infant milk landscape where Abbott have a much more dominant market presence. Infant milk marketing and promotion are not restricted in the US as they are in Europe and the UK, therefore participants may already have been exposed to significant levels of promotional activity from the big brands.

Abbott draw on the results of a survey emailed to 1,995 parents/carers of EleCare consumers, to support their claim that Elecare with 2'-FL is trusted by parents. Of 1995 parents mailed, 175 parents of infant consumers of EleCare responded. Parents reported that 80% of the infants in the study experienced 2 or more symptoms, for example, vomiting, diarrhoea, blood in stools and spit-up prior to initiating EleCare. Of these parents 96% reported that they were satisfied or very satisfied with EleCare. As with the survey of gastroenterologists, it is unclear how much promotional activity and conflict of interest was involved in the study. Furthermore, it is important to note that this survey was not a bench marking exercise against other available amino-acid based formula milks and that it relates to EleCare and not to EleCare with 2'FL.

Despite providing a long list of references to support the implied claims made, none of the clinical trials listed relate to EleCare with 2'-FL and most not even to an amino acid based infant milk. Others refer to clinical trials conducted with child rather than infant consumers. Those that suggest a role for 2'-FL in immune system support are based on secondary outcomes and post-hoc analysis. There is currently insufficient information to support suggestions of a health benefit for the addition of artificially created HMOs to infant milks.

Abbott also claim that EleCare is the best value hypoallergenic formula of its kind. We have conducted our own cost analysis of specialised infant milks for cows' milk allergy and have found brands that cost less per 100ml of reconstituted formula (see table 1).

Safety of use

Most of this group of infant formulas contain dried glucose syrup as the main carbohydrate source, meaning that dental care is particularly important for individuals being given these products.

In recent years evidence has emerged suggesting a link between use of Neocate and the development of rickets and other types of metabolic bone disease (Abulebda et al, 2017; Gonzalez Ballesteros et al, 2017; Uday et al, 2018). This appears to be particularly common in children using Neocate rather than other elemental formulas (Creo et al, 2018). Many of the published studies exploring this had small sample sizes. However, one of the larger studies, compromising of 102 children who were receiving Neocate via a tube, found up to 23% of them had a form of metabolic bone disease (Creo et al, 2018). Another study identified fifty-one children across 17 institutions who had hypophosphatemia associated with elemental formula (most of whom were on Neocate). Skeletal radiographs demonstrated that 94% of these children had rickets, fractures or undermineralisation (Gonzalez Ballesteros et al 2017).

These studies suspected the cause to be deficient dietary supply or decreased gastrointestinal absorption of phosphate (Ang et al, 2018; Uday et al, 2018). These cases improved with supplemental phosphate or changing to a different elemental formula. However, in some cases, this treatment led to subsequent hypocalcaemia (Gonzalez Ballesteros et al, 2017; Akhtar Ali et al, 2019).

It is important to note that most of these cases were identified prior to October 2017 when Nutricia began adding dipotassium hydrogen phosphate to Neocate, however, Nutricia still advise routine monitoring of micronutrients and, in particular phosphate, for those on

Neocate. Further research is needed to re-assess whether the safety of Neocate has improved.

The risks of the addition of probiotics to infant milks, such as Neocate Syneo, is not yet established. However, the Norwegian Food Safety Authority in 2014[3] has stated that a daily supply of a *"monoculture"* in *"large quantities over a prolonged period of time to age groups where the intestinal flora is still developing may therefore have unknown, but possible long-lasting adverse effects".* There is however a known risk from bacterial contamination if powdered infant milks are made up with water at a temperature below 70C (see www.firststepsnutrition.org/making-infant-milk-safely)

The nutritional composition of amino-acid based infant milks suitable from birth

The nutritional composition and ingredients of amino-acid based infant milks marketed for non-metabolic disorders, suitable from birth are given in Table 9.

[3] https://www.mattilsynet.no/language/english/food_and_water/Food_for_specific_Groups__FSG_/foods_for_infants_and_young_children_containing_probiotics.16873

TABLE 9. The nutritional composition of amino-acid based infant milks suitable from birth

Nutrients per 100ml	Abbott Nutrition Similac EleCare	Mead Johnson Nutramigen Puramino	Nutricia Neocate LCP	Nutricia Neocate Syneo	SMA Alfamino
INDICATIONS	Cows' milk allergy, severe and/or multiple food allergies, other conditions where amino acid based formula is indicated	Severe cows' milk allergy and multiple food allergy	Cows' milk allergy, multiple food protein allergies, and other conditions where an amino acid based diet is recommended	Cows' milk allergy, multiple food protein allergies and other conditions where an amino acid-based diet is recommended	Cows' milk allergy and multiple food allergy other conditions where amino acid based formula is indicated
MACRONUTRIENTS					
Energy kcal	68	68	67	68	66
Protein g	1.8	1.9	1.8	1.9	1.8
Protein source	Amino acids	Amino acids	Amino acids	Amino acids	Amino acids
Carbohydrate g	7.2	6.9	7.1	7.2	7.5
– of which lactose g	0	0	0	0	0
Carbohydrate source	Maltodextrin, modified corn starch, oligosaccharides	Glucose syrup, modified tapioca starch	Dried glucose syrup	Dried glucose syrup, oligosaccharides	Glucose syrup, starch
Fat g	3.3	3.7	3.5	3.4	3.3
Fat source	High oleic safflower oil, MCTs from palm kernel oil, coconut oil, soy oil, and single cell oils	High oleic sunflower, MCTs from coconut, palm kernel, soya and single cell oils	High oleic sunflower, coconut, rapeseed, sunflower and single cell oils	MCTs from coconut and/or palm oil,, high oleic sunflower oil, rapeseed oil, sunflower oil, and single cell oils	Sunflower, rapeseed, structured palm and single cell oils
– as medium chain triglyceride oils %	33	33	4	33	24
Added LCPs ARA	✓	✓	✓	✓	✓
DHA	✓	✓	✓	✓	✓
LCP source	Fungal/algal oils	Fungal/algal oils	Fungal/algal oils	Fungal/algal oils	Fungal/algal oils
MICRONUTRIENTS					
VITAMINS					
Vitamin A µg-RE	60	57	58	60	66
Vitamin C mg	8.5	6.4	7.1	7.3	11
Vitamin E mg	1.4	0.61	1.48	1.37	1.5
Vitamin D µg	1.69	1.63	1.6	1.64	1.7
Vitamin K µg	8.8	6.1	6.0	6.2	6.0

Nutrients per 100ml	Abbott Nutrition Similac EleCare	Mead Johnson Nutramigen Puramino	Nutricia Neocate LCP	Nutricia Neocate Syneo	SMA Alfamino
Thiamin (B_1) µg	100	40	80	80	68
Riboflavin (B_2) µg	70	54	80	80	130
Niacin µg (mg NE)	(0.47)	(0.63)	(1.27)	570 (1.33)	930 (1.6)
Vitamin B_6 µg	60	50	60	70	53
Vitamin B_{12} µg	0.17	0.12	0.19	0.19	0.2
Folic acid µg	10				
Folate µg DFE		11.4	15.4	15.8	17
Biotin µg	2.8	1.6	2.6	2.7	1.6
Pantothenic acid µg	410	380	410	420	440
MINERALS					
Calcium mg	78	76	77.1	79.2	70
Chloride mg	54	60	53	54.4	56
Copper µg	50	50	57	58	57
Iodine µg	12.2	13.5	14	14.3	15
Iron mg	1.0	1.0	1.0	1.0	0.66
Magnesium mg	5.7	8.1	7.0	7.2	6.0
Manganese µg	50	11	7.0	7.0	9.0
Phosphorus mg	51	44	50.2	51.5	47
Potassium mg	72	96	72.9	74.8	76
Selenium µg	2.7	2.4	2.5	2.6	3.4
Sodium mg	30	22	29.3	30.0	26
Zinc mg	0.54	0.61	0.73	0.75	0.66
ADDED INGREDIENTS					
Structured vegetable oils (beta-palmitate)	×	×	×	×	✓
Prebiotics	✓	×	×	✓	×
Probiotics	×	×	×	✓	×
Nucleotides	×	×	✓	✓	×
Inositol	✓	✓	✓	✓	✓
Taurine	✓	✓	✓	✓	✓
Choline	✓	✓	✓	✓	✓
L-carnitine	✓	✓	✓	✓	✓
Added antioxidants	✓	✓	✓	✓	✓
Contains soya	✓	✓	×	×	×
Contains fish oil	×	×	×	×	×
Suitable for vegetarians	✓	×	✓	✓	×
Halal approved	✓	✓	✓	✓	NS
Osmolality mOsm/kg	300	350	340	360	327

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
MCT = medium chain triglycerides NK = not known

5 Companies marketing milks for infants with food allergy

Abbott Nutrition
Infant milks produced:
- *Similac Alimentum*
- *Similac EleCare*

Abbott Nutrition
Abbott House
Vanwall Business Park
Vanwall Road
Maidenhead
Berkshire SL6 4XE
T: 01628 773 355
www.abbottnutrition.co.uk

Aptamil
Infant milks produced:
- *Aptamil Pepti 1*
- *Aptamil Pepti 2*
- *Aptamil Pepti Syneo*
- *Aptamil Pepti-junior*

Aptamil
Newmarket House
Newmarket Avenue
White Horse Business Park
Trowbridge
Wiltshire BA14 0XQ
T: 0800 996 1000
www.eln.nutricia.co.uk

Mead Johnson Nutrition UK Ltd
Infant milks produced:
- *Nutramigen 1 with LGG*
- *Nutramigen 2 with LGG*
- *Nutramigen Puramino*
- *Pregestimil LIPIL*

Mead Johnson Nutrition UK Ltd
c/o Reckitt Benckiser
Wellcroft House
Wellcroft Road
Slough SL1 4AQ
T: 01895 230575
www.nutramigen.co.uk

Nutricia Ltd
Infant milks produced:

- *Neocate LCP*
- *Neocate Syneo*

Nutricia Ltd
White Horse Business Park
Newmarket Avenue
Trowbridge
Wiltshire BA14 0XQ
T: 01225 751098
E: resourcecentre@nutricia.com
www.nutricia.co.uk

SMA Nutrition
Infant milks produced:
- *SMA Alfamino*
- *SMA Althéra*
- *SMA Wysoy*

Nestlé Nutrition
1 City Place
Gatwick
RH6 OPA
T: 0208 686 3333
www.nestlehealthscience.co.uk
www.smahcp.co.uk

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