

Safety of a new, ultrafiltrated whey hydrolysate formula in children with cow milk allergy: a clinical investigation

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The purpose of this study was to determine whether a new ultrafiltrated whey hydrolysate infant formula, Profylac®, could be administered safely to children with cow milk protein allergy/intolerance. Profylac has a stated molecular weight of <8 kD and at least 30,000 times reduced antigenicity which is controlled by a combination of ELISA-techniques and immunochemical methods. The study comprised 66 children with cow milk protein allergy/intolerance diagnosed by controlled elimination/challenge procedures. The children were aged 1 month–14.5 years, median 1½ years and 15 were below 1 year. Thirty-five of these children had proven IgE-mediated reactions (cow milk protein allergy). Sixty-one of the children had at least two different symptoms and 31 had concomitant allergies to other foods and/or inhalants. All 66 children underwent and tolerated open, controlled challenges with Profylac. A total of 64 children continued having Profylac daily for at least 3 months and 58 for at least 6 months after challenge. Nine of the children older than 1 year did not like the taste and only had Profylac in minor amounts. No side effects were registered. Fifteen of the infants were below 1 year of age, and this group was compared with an age matched group of 16 infants challenged with and fed an extensively hydrolysed casein hydrolysate, Nutramigen®. All the infants in these two groups accepted and tolerated Profylac and Nutramigen, respectively, and no side effects were registered. Among the 35 patients with IgE-mediated reactions 6% (2/35) had positive skin prick tests and 11% (3/28) had specific IgE class 2 against Profylac, 2 of the latter before intake of Profylac. None of the patients with non-IgE-mediated reactions had a positive skin prick test or specific IgE against Profylac. The study provides 95% confidence that this product is tolerated by at least 95% of children with cow milk protein allergy/intolerance and by 90% with IgE-mediated reactions. We conclude, that this ultrafiltrated whey hydrolysate is generally safe to feed to children with verified adverse reactions to cow milk protein, including children with IgE-mediated reactions. The taste of the product was widely accepted, also by older children.

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Cow milk protein allergy/cow milk protein intolerance (CMPA/CMPI) is mainly a problem in infancy and early childhood, and has its onset mostly during infancy. Recent prospective studies (1–3) have reported incidences between 1.9% and 5.2% based on well-defined elimination/challenge procedures. The treatment is total avoidance of

cow milk protein, and in infants and young children substitute “hypoallergenic” formulae are recommended. Soy formulae have been used, but allergy to soy protein has been recognized in up to 36% of the children with CMPA/CMPI (4,5). For many years the extensively hydrolysed casein-based formulae Nutramigen® and Pregestemil®

Table 1. Patients. Description in relation to age groups

	Profylac group		Nutramigen group 0-1 yr
	0-1 yr	1-15 yr	
Number	15	51	16
Median age	5 mo	2½ yr	4 mo
Sex, boys/girls	12/3	36/14	6/10
Symptoms:			
Anaphylaxis	0	1	0
Asthma	2	29	2
Rhino-conjunctivitis	3	14	1
Atopic dermatitis	10	34	10
Urticaria	3	7	4
Vomiting/diarrhoea	9	30	13
Colic	8	14	7
Other symptoms	3	11	3
≥ 2 symptoms	13	48	16
Other allergies	3	28	1
SPT ≥ 3 mm and/or specific IgE ≥ class 2	7	28	6

have been used in children with CMPA/CMPI. Although no formal clinical challenges in humans with CMPA/CMPI have been performed, these formulae are generally regarded as "hypoallergenic" and safe for the great majority of children with CMPA/CMPI. Only very few allergic reactions to those products have been reported (6, 7).

Because of extensive hydrolysis, the casein hydrolysates Nutramigen® and Pregestimil® have an unpleasant, bitter taste, and previously some infants had problems with diarrhoea due to hyperosmolarity of the products. To reduce these problems, by reducing the degree of hydrolysis, an ultrafiltrated whey hydrolysate (Profylac®) was developed.

The aim of the present study was to examine, whether this less extensively hydrolysed, but ultrafiltrated whey hydrolysate (Profylac®) was safe in, and tolerated by children with CMPA/CMPI.

Subjects and methods

The study included 66 children (19 girls and 47 boys) with verified CMPA/CMPI diagnosed by controlled elimination/challenge procedures by one of the authors at the departments of pediatrics at the hospitals in Odense (n = 30) and Viborg (n = 36). The latest positive milk challenge was performed less than 3 months prior to the start of the study. At the time of inclusion the children were from 1 month to 14½ years of age (median 1½ years). Fifteen infants were below 1 year, and this group was compared with an age-matched group of 16 infants challenged with and fed an extensively hydrolysed casein hydrolysate (Nutra-

migen, Mead Johnson, Evansville, Indiana, US). Table 1 shows further data on the children related to age.

Diagnostic criteria

The diagnosis CMPA/CMPI was established by generally accepted criteria: a) definite disappearance of symptoms after each of two dietary eliminations of cow milk and cow milk products, b) recurrence of identical symptoms after one challenge, and c) exclusion of lactose intolerance and coincidental infection. All challenges were open, but with equivocal results the challenge was repeated and eventually blind. In none of the patients included in this study the result of the milk challenge was equivocal, and therefore no blind challenges was performed.

Milk challenges

The children were on a milk free diet for at least 4 weeks before milk challenge. All challenges were performed in a controlled hospital setting observed by professionals. The challenges were performed with cow milk or an ordinary cow-milk based formula (Allomin®) starting with a dose of 5 ml followed by 10, 20, 40 and 80 ml at intervals of 2 h. If no symptoms occurred after 8 h (a total cumulated dose of 155 ml) the child was sent home with increasing amounts to be taken at home until customary daily intake of milk was tolerated. In the case of late reactions the patients were reexamined in the hospital as soon as possible, and at a suspected reaction the last dose was repeated once. Before and after challenge and at any adverse reaction the patients were examined and symptoms and signs were noted.

Children responding to cow milk within 1 h after up to a maximum of 155 ml Allomin (equivalent to 66 ml whole cow milk and to 2.3 g of cow milk protein) were classified as "immediate reactors" and those reacting later were defined as "late reactors".

Immunological classification of the patients

In 64 children, skin prick tests (SPT) were performed. The extracts used were 1/20 w/v raw cow milk in 50% glycerol diluent (Soluprick, ALK, Hørsholm, Denmark). As positive reference was used histamine dihydrochloride 10 mg/ml in 50% glycerol diluent (Soluprick), and as negative reference 0.5% NaCl + 0.25% NaHCO₃ in 50% glycerol diluent (Soluprick). All SPT tests were performed by the same two experienced nurses. The results were given as mean wheal diameters (d1 + d2/2), from which the mean diameters of the

Table 2. Immunological classification of the patients according to the results of SPT and specific IgE to cow milk protein.

	Number
Patients	66
SPT	64
Specific IgE	63
Specific IgE and SPT	61
Specific IgE and/or SPT	66
SPT ≥ 3 mm	30
Specific IgE $\geq$ class 1	31
Specific IgE $\geq$ class 2	23
SPT ≥ 3 mm and/or specific IgE $\geq$ class 1	44
SPT ≥ 3 mm and/or specific IgE $\geq$ class 2	35

negative reference were deducted. A SPT ≥ 3 mm was regarded as positive.

In 63 children specific IgE (Diagnose Laboratory, ALK, Hørsholm, Denmark) was analysed, and the scoring scale used was as advised by the manufacturers and graded 0–4.

In 66 children, SPT and/or specific IgE against cow milk were performed. A total of 35 children had evidence of milk-specific IgE antibodies as indicated by a positive SPT reaction ≥ 3 mm (mean wheal diameter) and/or specific IgE of class 2 or more. The reactions in these 35 children were identified as CMPA, while those without detectable milk-specific antibodies were identified as CMPI. Further details are shown in table 2.

Symptomatology of the patients

Of the 66 included children 44 had atopic dermatitis, 31 had asthma, 17 had rhinoconjunctivitis, 10 had urticaria, 39 had vomiting/diarrhoea, 22 had infantile colic, 1 had an anaphylactic reaction and 14 had other symptoms (failure to thrive, angioedema, exanthema). 61 of the children had at least two different symptoms and 31 had concomitant allergies to other foods ($n=23$) and/or inhalants ($n=15$). Table 1 shows the symptoms related to age. At milk challenge 40 children were classified as "immediate reactors" with symptoms within 1 h after a maximum of 155 ml Allomin or 65 ml whole milk (equivalent to 2.3 g milk protein) and 26 as "late reactors", of whom 14 developed symptoms very late, more than 24 h after the beginning of milk challenge (after intake of more than 8 g milk protein). Table 3 shows symptoms and number of immediate and late reactors in the CMPA and CMPI groups.

Hypoallergenic infant formula, Profylac

Profylac (ALK, Hørsholm, Denmark) is a hypoallergenic milk powder based on bovine whey. No

native proteins are present in the product as proteins are hydrolysed and ultrafiltrated through a filter with a pore size of maximum 6000 Dalton. The remaining peptides and amino acids have an allergenic activity, which is reduced at least 30,000 times relative to cow's milk. No high-molecular weight precipitates are present. Profylac is tested by means of RIE (rocket immuno electrophoresis) in order to control any residual antigenic activity. Antibodies against bovine whey are used in the gel to precipitate remaining antigens. No precipitation must be present. An ELISA test is performed using anti-bovine-whey antibodies and enzyme-linked antibodies. A standard solution of bovine whey is run parallel ensuring a 30,000 times reduced antigenicity of Profylac (8, 9).

Profylac represents a full diet for infants during the first 6 months of life, contains all necessary nutrients and meets the nutritional demands of infants during the first 6 months of life. The content of protein in the mixture is 15 g/l (1.5%). Bovine fats are replaced with unsaturated vegetable fats. Saccharides like lactose and galactose are removed. All essential vitamins and minerals are present and the amount of single components is within the recommendations from WHO (10).

Study design

The patients were examined objectively at inclusion and after 3 and 6 months by one of the authors. At inclusion and after 6 months they were tested for specific IgE (Diagnose Laboratory, ALK, Hørsholm, Denmark) against cow milk and Profylac, and skin prick tests (SPT) with cow milk

Table 3. Milk challenges. Symptomatology and time of onset of reactions in relation to immunological type of reaction (CMPA/CMPI).

	Profylac group		Nutramigen group	
	CMPA +IgE	CMPI -IgE	CMPA +IgE	CMPI -IgE
Total number	35	27	6	10
<1 year	7	8	6	10
Anaphylaxis	1	0	0	0
Asthma	17	14	1	1
Rhino-conjunctivitis	9	8	0	1
Atopic dermatitis	25	19	3	7
Urticaria	8	2	3	1
Vomiting/diarrhoea	15	24	4	9
Colic	9	13	1	6
Other symptoms	8	6	1	2
≥ 2 symptoms	33	28	6	10
Immediate reactors <1 h*	26	14	5	6
Late reactors >1 h	9	17	1	4

* Immediate reactors: At milk challenge reaction within 1 hour after a maximum of 2.3 g milk protein. For further explanation see text.

Table 4. Number of children with performed SPT and specific IgE against Profylac in relation to challenge.

	Before	After	Before and/or after
SPT	63	47	65
SPT = 3 mm	2	0	2
SPT > 3 mm	0	1	1
Specific IgE	46	32	56
Specific IgE class 1	1	2	3
Specific IgE class 2	2	2	3
Specific IgE > class 2	0	0	0

(Soluprick, ALK, Hørsholm, Denmark) and Profylac (in the recommended "ready to eat" concentration) were performed. At inclusion the children were challenged with Profylac using the same procedure as for milk challenge. If a suspected reaction or coincidental infection was registered the challenge was repeated later. All possible reactions were evaluated by one of the authors. After challenge the children had a normal daily dose (250–750 ml) of Profylac for 6 months if they accepted and tolerated the product. Also during this period any possible adverse reaction was noted.

Results

Skin prick tests

As shown in Table 4, SPT with Profylac was performed in 65 patients in total (35 with CMPA and 30 with CMPI). Prior to challenge, SPT with Profylac was performed in 63 patients and in 2 cases SPT reactions were positive (= 3 mm). These two cases were children with severe CMPA with very high levels of specific IgE (RAST class ≥ 4) and positive SPT to cow milk of 9 and 8 mm. One of these children had symptoms after challenge and will be described in detail later on. The other child tolerated Profylac without problems. After 6 months SPT with Profylac was performed in 47 children. One had a positive SPT reaction at 6 mm but no clinical reaction, and as this child was not tested with SPT before challenge it is uncertain whether he had an IgE-mediated or a non-IgE-mediated reaction against cow milk protein. None of the tested children with non-IgE mediated reactions ($n = 30$) showed positive SPT against Profylac.

Specific IgE

In 25 cases specific IgE to cow milk was analysed both before Profylac challenge and after 6 months. During this period-specific IgE was unchanged in 21 cases, a slight decrease (from class 1 to 0) in 2 cases and a slight increase (from class 2 to 3 and 0 to 2) in 2 cases was seen.

Sera from 56 children were analysed for specific IgE to Profylac, 46 before challenge, 32 six months after challenge and 25 before, as well as after, challenge with Profylac. Three children had positive reactions of class 2, 2 before and 1 six months after Profylac challenge, the latter was not tested before challenge. One of the positive reactions before challenge was unchanged after and the other was not controlled (refusal by parents). None had reactions above class 2 and none of the 25 children who were tested both before and after challenge showed increasing values. Further details are shown in Table 4.

Profylac challenges

At inclusion all 66 children were challenged with Profylac. At initial challenge with Profylac, 62 of the children showed no reactions. Apart from one early drop-out these children had Profylac in increasing amounts until normal daily intake without problems. A total of 4 children had doubtful reactions:

- 1) An 11½-year-old girl with recurrent urticaria had an episode of urticaria 2 days after challenge. Rechallenge was negative. SPT and specific IgE to Profylac were negative.
- 2) A 13½-year-old boy had a transitory episode of supposed rhinoconjunctivitis at home 4 h after challenge. The symptoms disappeared before he was seen at hospital and rechallenge was negative. SPT and specific IgE to Profylac were negative.
- 3) A 5½-year-old boy had a small hive in his face 2 h after ingestion of 40 ml Profylac but no other symptoms and rechallenge was negative. SPT with Profylac were negative. Specific IgE to Profylac was slightly positive, class 2 both before and after challenge.
- 4) A 6-year-old-boy with severe CMPA (high RAST class and a large SPT against cow milk) with the symptoms asthma, atopic dermatitis and urticaria, had abdominal colic 2 days after challenge. At rechallenge 1 week later he developed asthma and urticaria. However, the symptoms at the challenges were not identical and the reaction could not be confirmed at a third challenge. He then tolerated Profylac in normal amounts during the following weeks, but did not want to go on participating in the study. SPT with Profylac was 3 mm and 5 mm, before and 1 month after challenge, respectively. The corresponding values with cow milk were 11 mm and 7 mm, and the histamin reactions were 3 and 5 mm. SPT with Nutramigen was 3 mm after challenge.

Thus, none of these 4 children had significant symptoms due to the challenge with Profylac, and after rechallenges they all tolerated Profylac in a normal daily dose without any problems.

Using confidence intervals generated for a binominal outcome, this study provides 95% confidence that at least 95% of children with CMPA/CMPI, and at least 90% of children with CMPA, will have no reactions when ingesting Profylac.

Follow up

A total of 64 children continued having Profylac as milk substitute for at least 3 months and 58 for at least 6 months after challenge. Eight children dropped out during the study. At the day of inclusion one boy developed an infectious disease with fever, catharralia and diarrhoea, and his parents did not want him to continue the challenge. One boy left the country after one month but until then he had 500 ml Profylac per day without problems. After the first 3 months the parents of 2 infants did not want to participate any longer – both of the infants tolerated 500–1000 ml Profylac pr day without problems. Three children aged 22 months, 4½ years and 10 years also tolerated Profylac, but disliked the taste and stopped using Profylac after the first 3 months. One 6-year-old boy with initially suspicious reaction at challenge (number 4 mentioned above) did not want to participate after the first 3 months. Of the 58 children, who had Profylac for at least 6 months, one child (age 2½ years) only had Profylac in varying amounts due to family problems, and 6 children (aged 1½–9 years at inclusion) only had small amounts (about 100 ml per day) due to the taste. The rest of the children aged <1 year at inclusion (n = 13) had a daily intake of Profylac at 500–1000 ml, whereas the children aged >1 year at inclusion (n = 46) had 250–750 ml per day.

Taste and possible side effects

All 15 infants less than 1 year of age at inclusion drank Profylac without problems. Nine of the 51 (17.6%) children older than one year at inclusion disliked the taste. Three of them refused to have Profylac at all after 3 months and another six only had small amounts in mixture with cocoa and used in daily cooking. None of the children had diarrhoea or other gastrointestinal problems due to Profylac.

Comparison with Nutramigen

The 15 infants aged less than 1 year at inclusion were compared to a corresponding group consist-

ing of 16 infants with CMPA/CMPI defined exactly in the same way. These 31 infants were initially randomized to Nutramigen or Profylac and the 16 infants in the Nutramigen group were followed in the same way as the infants in the Profylac group. The groups were comparable as regards age, symptoms and results of SPT and specific IgE (Table 1). As described earlier, 2 of the infants in the Profylac group did not want to participate after 3 months. None of the infants in the Nutramigen-group dropped out. All the infants in both groups tolerated Nutramigen or Profylac in a normal daily intake.

All infants in both groups had a normal weight gain and normal increase of length and head circumference during the study period. None of the infants had problems with diarrhoea or other gastrointestinal problems due to Nutramigen or Profylac.

Discussion

The basic and only effective treatment of CMPA/CMPI is complete avoidance of cow milk protein. During infancy and early childhood an alternative hypoallergenic milk substitute is necessary.

Children with reproducible clinical reactions against cow milk protein can usually be classified as having IgE mediated reaction (CMPA), if a positive SPT (mean wheal diameter ≥ 3 mm) and/or a positive RAST ($\geq$ class 2) to cow milk protein is demonstrated (1, 11). Children with IgE mediated reactions to cow milk protein often show immediate reactions after intake of even small amounts of cow milk protein, and severe anaphylactic reactions may occur (12). In children with immediate reactions, only documented hypoallergenic formulae can be used as milk substitutes.

Alternate milk substitutes such as soy bean formula and goat milk have been applied, but these unaltered proteins are potentially allergenic and allergic reactions to them have been documented. Soy protein is reported to be at least as allergenic as cow milk protein, and in children with cow milk allergy, soy protein allergy has been recorded with frequencies between 17 and 36% (4, 5). Soy formula is not generally recommended to children with cow milk allergy (13). Most of the proteins of goat milk share identity with those of cow milk resulting in cross reactivity (14, 15). Thus, individuals with cow milk allergy may react at the first exposure to goat milk, and goat milk should not be recommended to children with cow milk allergy.

Extensively hydrolysed infant formulae provide an alternative source of nutrition that is unlikely to provoke immune responses. The extensively

hydrolysed casein formulae, Nutramigen and Pregestimil, have been widely used in cow milk allergic children for 50 years, and are generally regarded as "hypoallergenic" (13,16). These formulae are enzymatically extensively hydrolysed, and effectiveness of this preparation is documented in clinical reports on cow milk allergy (1,2,16–19). In one of these studies (16), 23 children with CMPA underwent double-blind, placebo-controlled challenges with a new casein hydrolysate, Alimentum. No significant symptoms occurred, but after challenge only 7 patients continued ingesting Alimentum for 2 days to 14 months (median 1 week). However, some intolerances to casein hydrolysates have been noted (20) and a few casuistic reports on allergic reactions to casein hydrolysates have been published (6,7,21–23). In another recent study 20 children with CMPA underwent and tolerated double-blind placebo-controlled challenges and subsequent open challenges with an aminoacid-derived infant formula (Neocate, Scientific Hospital Supplies, Gaithersburg, MD) (23).

The use of extensively hydrolysed cow milk based formulae is hampered by a poor, bitter taste. Moreover, the high concentration of aminoacids may result in hyperosmotic abilities and cause problems with diarrhoea in some infants. These problems would be reduced by a less complete hydrolysis, which may on the contrary result in increased remaining antigenicity and a higher risk of allergic reactions. Partially hydrolysed whey hydrolysates have been used for a few years. Several cases of allergic reactions to these products have been reported in children with cow milk allergy (19,24,25), and generally, these preparations are not recommended to children with cow milk allergy.

Recently, the American Academy of Pediatrics Subcommittee on Nutrition and Allergic Disease recommended that a formula could be designated hypoallergenic when the base protein has been modified to reduce antigenicity, so that 90% of subjects allergic to the base protein can tolerate the formula without symptoms (16,26,27). In addition several physicochemical and immunochemical tests were recommended to evaluate hydrolysate formulae. These criteria are consistent with the perception that a "hypoallergenic formula" ought to be safe for ingestion by most children with adverse reactions to cow milk protein. The purpose of this study was to assess whether a new less hydrolysed but ultrafiltrated whey formula, Profylac, was safe in children with cow milk protein allergy/intolerance. Moreover, the study design allowed to compare Profylac with Nutramigen in infants with cow milk allergy. Profylac has a stated molecular weight < 8 kD and at least 30,000

times reduced antigenicity. The product is controlled by a combination of ELISA-techniques and immunochemical methods. In a recent Swedish study (22) antigenicity and allergenicity of Profylac and 3 other hydrolysates were investigated. It was found (SDS-PAGE electrophoresis) that Profylac contained low molecular weight proteins (1–10 kD), whereas another whey hydrolysate Beba HA (Good Start HA) contained a number of unresolved proteins, non- or partially degraded whey proteins in the range of 5–20 kD and a weak band corresponding to bovine serum albumin (MW 67 kD). No protein bands could be identified in the casein based hydrolysates Nutramigen and Alimentum. The content of betalactoglobulin was found to be <0.06 µg/g dry weight in Profylac, Nutramigen and Alimentum, whereas it was 200 µg/g dry weight in Beba HA. Cow milk contained approximately 117 mg betalactoglobulin/g dry weight, and thus, the content of betalactoglobulin in Profylac was 100,000 times less than in cow milk.

These preclinical data indicated that the product was unlikely to provoke hypersensitivity reactions in cow milk allergic patients. Our study comprised 66 children with verified CMPA/CMPI diagnosed according to generally accepted criteria by controlled elimination and challenge procedures and 35 had proven IgE mediated severe reactions. Most of the infants had recurrent symptoms from more than one organ system and 31 also had other concomitant allergies. As all the children showed a positive milk challenge less than 3 months prior to inclusion it is unlikely that tolerance to Profylac was due to tolerance to cow milk proteins. None of the children had significant symptoms during initial challenge with profylac. A few (n=4) developed symptoms during the first days after challenge. However, none of these could be confirmed at rechallenges and all the children tolerated daily consumption of Profylac during follow-up. Thus, Profylac was tolerated by all 35 children with IgE-mediated CMPA as well as all 31 with CMPI without IgE-mediated reactions.

As measured by SPT and specific IgE only few and not clinical significant reactions against Profylac were found, and no increase in the reactions to cow milk during the follow up period was registered. In a previous study (16) positive SPT with Nutramigen and Alimentum was positive in 5 and 6 of 10 patients tested, but none of them had clinical reactions. Another recent study (22) showed positive SPT against Beba HA (good start HA) in 24% (10/41), against Profylac in 15% (5/34) and against Alimentum (1/42) and Nutramigen (1/42) in 2.5% each. In the latter study positive RAST against Beba HA was detected in 11/45 sera

(24%) compared to 7–13% against the other 3 hydrolysates. Only one patient had a positive challenge to Alimentum and he also had a positive RAST and a borderline SPT against Alimentum. Differences in frequencies of positive tests in these studies and the present study might be explained by different study populations, test methods and evaluations. These results indicate that minimal residual peptide fractions of cow milk proteins are sufficient to provoke cutaneous mast cell activation and that a positive SPT or specific IgE against cow milk hydrolysates do not necessarily predict symptomatic reactivity. However, these tests might be useful to evaluate the allergenicity prior to challenge in highly allergic individuals. All the infants younger than 1 year at inclusion accepted to drink Profylac as well as Nutramigen. In contrast to a previous study (16) with extensively hydrolysed casein formulae most of the older children also accepted the taste of profylac during at least 3 to 6 months. No side effects were reported.

We conclude that Profylac is safe and tolerated by children with verified adverse reactions to cow milk, including children with IgE-mediated reactions. However, even high degree hydrolysates of casein or whey may contain residual quantities of cow milk proteins against which highly sensitive children may react. Therefore, whatever hypoallergenic formula is chosen, it is recommended to perform an open challenge under the supervision of a qualified physician in children with immediate reactions before starting treatment with the product. Before challenge with the hypoallergenic formula an evaluation of the possible allergenicity of the product can be performed by a skin prick test with a fresh sample of the product.

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