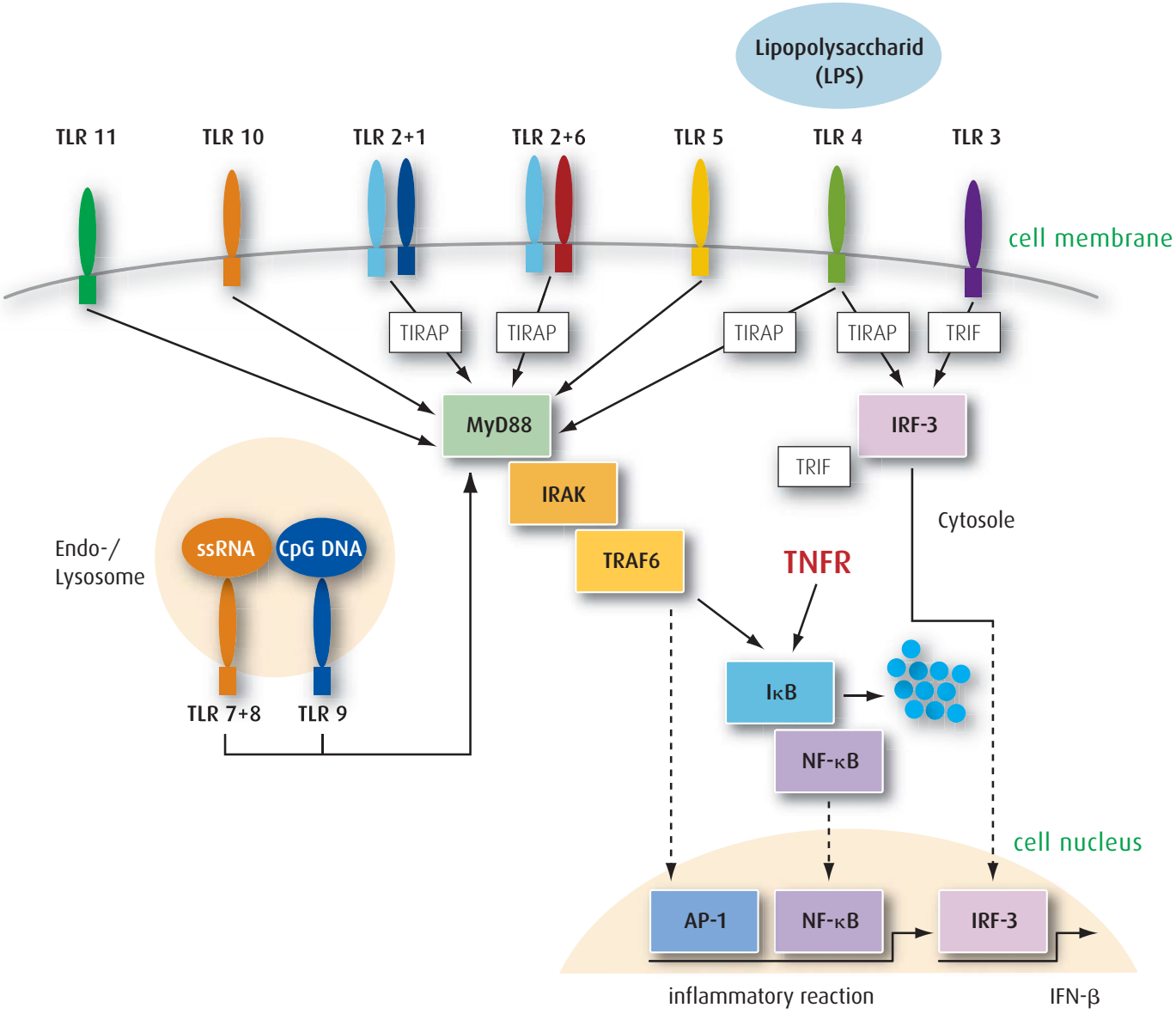

Scheme of TLR signal functions (toll-like receptors) present on phagocytes (preferentially moncytes). TLR's recognise microbiological structures, like LPS as this is exemplarily shown for TLR4 in the scheme above. The signals resulting from the specific interaction with LPS lead to the activation of the innate immune systeme, for instance with a massive production of TNF-α ("inflammatory reaction").

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Lactobin® N

A polyvalent concentrate produced from bovine colostrum – the defence potential of the first milk from mother cows: A food supplement for oral passive immunization of your patients.

Landscape of New Zealand

Table of contents

Lactobin® N, a polyvalent concentrate made of bovine colostrum for clinical use

A new form of oral passive immunisation as an adjunct to therapy with antibiotics, analgesics and anti-inflammatory drugs, respectively.

➜ Bovine colostrum: highly concentrated mixture of immune and growth factors, vitamins, minerals, amino acids, proteins, fats for clinical use

➜ Colostrum contains a concentrate of synergistic factors of congenital and acquired immunity

Principles

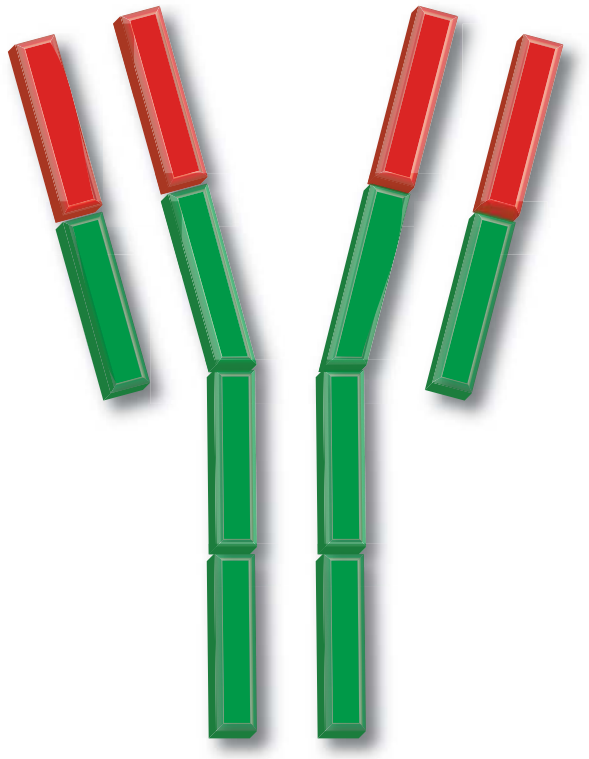
Mammals endow their newborns with "loaned immunity" to exogenous pathogens before, during and after birth by providing them with antibodies, immunocytes and humoral principles. While in humans the majority of immunoglobulins are transferred via the placenta in the weeks before birth, in other mammalian species such as cows it is the pre-milk fluid, the colostrum, which is particularly rich in active substances and provides passive immunisation for the new-born.

Colostrum is a highly complex mixture of immune and growth factors, vitamins, minerals, amino acids, proteins, fats and carbohydrates in which the immunoglobulins play a special role for human medicinal use. The health promoting effects of bovine colostrum have long been known to traditional medicine. In the past, however, its use as a medicinal product was limited by the lack of cooling facilities and the sensitivity of untreated colostrum to atmospheric oxygen. Only from the middle of last century onwards has it been possible to produce stable, standardised BCC-preparations and to test their efficacy in clinical indications. Since the mother cows generally produce an excess of colostrum, the availability of raw material presents no problem and the use of colostrum to manufacture the concentrates does not jeopardize the health of the calves.

Therapeutic effects have already been demonstrated in a wide range of chronic infections. Immunoglobulins present in bovine colostrum for instance show antitoxic effects against enteral bacterial toxins, and anti-inflammatory cytokines offer possibilities for the management of chronic pain.

Colostrum is a mixture of natural substances which in the form of processed concentrates and as a balanced food supplement contributes to the anabolic metabolism and as well to the supply of vitamins and trace elements. By exerting additional pharmacodynamic effects, it can enhance the efficacy of standard treatments without additional risk.[1-7]

[1] Kelly, GS. Bovine colostrums: a review of clinical uses. Altern Med Rev (2003) 8: 378-394.
[2] Reilly, RM et al. Oral delivery of antibodies. Future pharmacokinetic trends. Clin Pharmacokinet (1997) 32: 313-323.
[3] Bitzan, MM et al. Inhibition of Helicobacter pylori and Helicobacter mustelae binding to lipid receptors by bovine colostrum. J Infect Dis (1998) 177: 955-961.
[4] Lissner, R et al. A standard immunoglobulin preparation produced from bovine colostra shows antibody reactivity and neutralization activity against Shiga-like toxins and EHEC-hemolysin of Escherichia coli O157:H7. J Infection (1996) 24: 378-383.
[5] Stephan, W et al. Antibodies from colostrum in oral immunotherapy. J Clin Chem Clin Biochem (1990) 28: 19-23.
[6] Stokes, BC & Bourne, JF. Mucosal immunity – immunoglobulin in cow colostrum. In: Halliwell RE & Gorman NT (eds). Veterinary Clinical Immunology. Philadelphia: WB Saunders (1989) pp. 164-192.
[7] Banks, LK & Mc Guire, TC. Neonatal immunology. In: Halliwell, RE & Gorman, NT (eds). Veterinary Clinical Immunology. Philadelphia: WB Saunders (1989) pp. 193-204.



The product

Lactobin® N is the enhanced successor product of Lactobin® described in the literature (review article in Struff & Sprotte, 2007)[8]. Several controlled studies with the bioequivalent forerunner product Lactobin® demonstrated clinical efficacy in a range of indications.[9-11] These data are also applicable to the successor product Lactobin® N, making Lactobin® N the most thoroughly researched polyvalent standard concentrate among all bovine colostrum concentrates.

In the 1990s, Biotest Pharma GmbH (Dreieich, Germany) developed a special colostrum product, Lactobin®. A bioequivalent successor product made from the colostrum of New Zealand cows, Lactobin® N, is now available.

The essential bioequivalence of the two preparations and hence the applicability of scientific research data of one product to the other was demonstrated by a fingerprint analysis (research report 2005, E.M. Waaga-Gasser, Würzburg University Hospital).

Lactobin® N is a concentrate of proteins (83-86 %), fat (< 2 %) and lactose (7-8 %) and contains not only cytokines, growth factors and enzymes but especially also class IgG1 immunoglobulins with a wide range of specific antibodies against pathogenic bacteria and viruses. It was developed as a medicinal product in accordance with the GMP Guidelines and clinically tested in accordance with GCP. As a mixture of natural substances, it has not only neutralising properties against human pathogens and their toxins, but also has an immunomodulating potential.

In contrast to numerous similar preparations which can be used only for non-clinical indications (lifestyle, sport), Lactobin® N meets all the

The term “polyvalent” refers to the high degree of homogeneity of the production batches manufactured in accordance with the GMP guidelines from several hundred individual colostra. The concentrations of the active agents and their activities are independent of the batch, as has been shown, for example, for antibody specificities by W. Stephan et al.[12] (IgG antibacterial antibodies) and R. Lissner et al.[13] (antibodies against Shiga-like toxins of enterohemorrhagic E. coli). Hyperimmune concentrates, on the other hand, are products manufactured from only a small number of individual colostra of vaccinated mother cows for use in patients with infectious diseases for which a differential diagnosis is available.

➔ The polyclonality principle of acquired immunity cooperates with more than 1012 antibody specificities (idiotypes), which theoretically can also be present in the colostrum concentrates. This is expressed by the term ”polyvalent“.

requirements in terms of analysis, preclinical and clinical documentation for the assurance of safety, tolerability and efficacy of use in patients receiving standard therapies. Not only the scrupulous care taken during production of the individual batches, but also the criteria applied in selecting the raw material result in a final product with a pharmacodynamic potential superior to that of conventional colostrum concentrates, as Lactobin® demonstrated by the much higher concentration of lactoferrin (19 ± 1 mg/1.0 g Lactobin® N), critically important for neutralising LPS (endotoxins from gram-negative bacteria).

Phase I studies in healthy test persons have shown that Lactobin® is outstandingly well tolerated. Repeated high-dose administration also caused no adverse effects.

The only contraindications identified so far are lactose intolerance and hypersensitivity to cow’s milk proteins. In higher dosages (10-20 g) and during prolonged use, an increase in appetite may lead to body weight gain. This might be a desirable effect in certain patient populations, such as geriatric or cancer patients, children showing failure to thrive and for patients after severe (consumptive) surgery.

[8] Struff, WG & Sprotte, G. Bovine colostrum as a biologic in clinical medicine: a review. Part I: Biotechnological standards, pharmacodynamic and pharmacokinetic characteristics and principles of treatment. Int J Clin Pharmacol Ther (2007) 45: in press.
[9] Davidson, GP. Passive protection against diarrheal disease. J Pediatr Gastroenterol Nutr (1996) 25: 207-212.
[10] Korhonen, H et al. Bovine milk antibodies for health. Brit J Nutr (1999) 84: 1-24.
[11] Kelly, GS. Bovine colostrums: a review of clinical uses. Altern Med Rev (2003) 8: 378-394.
[12] Stephan, W et al. Antibodies from colostrum in oral immunotherapy. J Clin Chem Clin Biochem (1990) 28: 19-23.
[13] Lissner, R et al. A standard immunoglobulin preparation produced from bovine colostra shows antibody reactivity and neutralization activity against Shiga-like toxins and EHEC-hemolysin of Escherichia coli O157:H7. J Infection (1996) 24: 378-383.

Pharmacology, pharmacodynamics

Lactobin® N is effective due to its combination of anti-infectious, immunemodulatory, antitoxic and nutritive ingredients. Some of these effector molecules not only interact synergistically but may positively reinforce the efficacy of standard treatment of the patient.

Immunoglobulins rank with the most important defence components of the colostrum concentrates. Although the protein moieties of the colostrum effector molecules are degraded by denaturing and proteolysis during intestinal transit, more than 20 % of the IgG portion reaches the ileocecal valve in active form.[14]

Colostrum concentrates are rich in specific antibodies against bacteria and bacterial toxins (Tab. 1). The mechanisms underlying the high capacity of Lactobin® to neutralise bacterial toxins (e.g. lipopolysaccharides/LPS = endotoxins, shigatoxins etc.) and which prevent LPS invading the blood stream, are not precisely known. However, antibodies against certain portions of the LPS molecule have been found.[15]

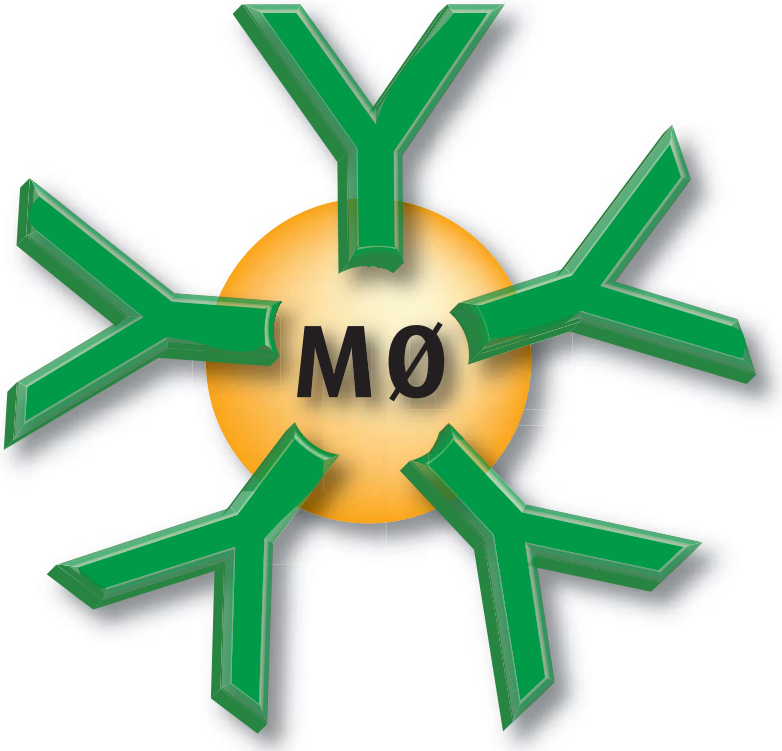
Lactoferrin, as probably the most important LPS inhibitor in Lactobin® N, also binds the lipid A moiety of the LPS molecule and may thereby possibly achieve a synergistic effect with the anti-LPS specificities of the IgG1 type.[17]

Overall, these mechanisms lead to a reduction of the intestinal translocation of endotoxins.

Lactobin® N exerts its effects in the digestive tract which, as an interface with the environment, is exposed to many different influences from the influx of food but also to invading pathogens and their toxins. The integrity of the intestinal wall is critical for its local immune response function and is assured by the continuous regeneration of enterocytes. The protein synthesis required to maintain this situation is highly dependent on the availability of dietary proteins. Food supplementation with high quality proteins from the colostrum preparations therefore makes an important additional contribution to the overall effect.

➜ Enteral LPS translocation is a phylogenetically ancient instrument of immune regulation via Toll-like receptor 4.[16]
An LPS excess however due to an infection with gram-negative infection causes septic shock.

[14] Roos, N et al. 15N-labeled immunoglobulin from bovine colostrum are partially resistant to digestion in human intestine. Nutr (1995) 125: 1238-1244.
[15] Fomsgaard, A. Antibodies to LPS: Some diagnostic and therapeutic aspects. APMIS (1990) 981: 1-38.
[16] Übersicht bei Beutler, B & Rietschel, E. Innate immune sensing and its roots: the story of endotoxin. Nature Rev Immunol (2003) 3: 169-176.
[17] Appelmelk, BJ et al. Lactoferrin is a lipid A-binding protein. Infect Immun (1994) 62: 2628-2632.



The clinical indications

Clinical studies with Lactobin®, the bioequivalent forerunner product of Lactobin® N, have proved its efficacy as an therapeutic adjuvant and supporting standard treatment regimens in a range of indications or have generated working hypotheses for planned clinical use as a balanced dietary product with supportive effects.

1. Intensive care treatment after major surgery

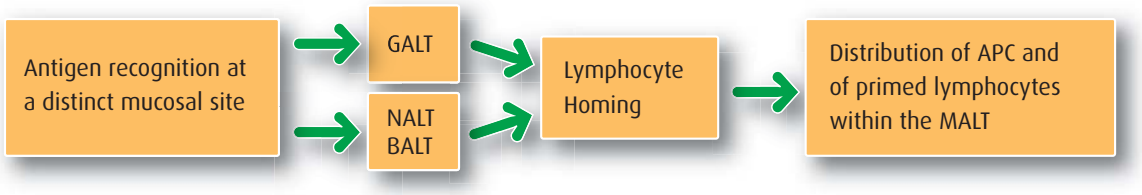
2. Chronic recurrent diarrhea in secondary immunodeficiency

3. Infections with E. coli 0157 (EHEC)

4. Idiopathic pain syndrome

[18] Beutler, B & Rietschel, E. Innate immune sensing and its roots: the story of endotoxin. Nature Rev Immunol (2003) 3: 169-176.
[19] Livingston, DH & Deitch, EA. Multiple organ failure: a common problem in surgical intensive care unit patients. Ann Med (1995) 27: 13-20.
[20] Dofferhoff, ASM et al. Effects of different types and combination of antimicrobial agents on endotoxin release from gram-negative bacteria. Scand J Infect Dis (1991) 23: 745-754.

The defence system of mucosal surfaces – MALT („mucosa associated lymphoid tissue")



(GALT = gut associated lymphoid tissue; NALT = nose associated lymphoid tissue; BALT = bronchus associated lymphoid tissue; APC = antigen presenting cells)

1. Intensive care treatment after major surgery

Lactobin® N neutralises endotoxins and thereby reduces the risk of gram-negative sepsis.

Gram-negative bacteria in the intestinal tract and their toxins are a dominating factor in the development of sepsis after major surgery and in intensive medical care patients. The use of bactericidal antibiotics to prevent the invasion of pathogens from mucosal surfaces releases endotoxins (lipopolysaccharides LPS) from the disintegrating bacteria and results in organ damage.[19-22]

A pathogenically important role, e.g. in hemorrhagic shock, caused by hypoperfusion of the intestinal wall which, depending on its severity and duration, gives rise to a massive LPS influx from the bowel. The administration of Lactobin® N reduces the increase in endotoxins in the intestinal tract and decreases their passage into the blood stream. The ability of bovine colostrum concentrates to neutralise endotoxins has been demonstrated for Lactobin® in clinical use and for Lactobin® N in vitro (fingerprint identity) (Research Report [2005] E.M. Waaga-Gasser, Würzburg University Hospital) and had also been confirmed previously in a rat hemorrhage model.[23]

→ "The poison protection dichotomy of lipopolysaccharides"[18]: LPS anergy is not consistent with survival. A massively increased endotoxin level in the blood, however, is regarded as the main cause of gram-negative septic shock.

[21] Prins, JM et al. Antibiotic-induced endotoxin release in patients with gram-negative urosepsis – a double-blind study comparing imipenem and ceftozidime. J Infect Dis (1995) 172: 886-891.
[22] Jackson, JJ et al. ß-lactam antibiotic-induced release of free endotoxins. J Infect Dis (1992) 165: 1033-1041.
[23] Fitzal, F et al. Immunoglobulin enriched colostral milk reduces gut-derived endotoxemia in a rat hemorrhage model. Eur J Trauma (2001) 27:257-263.

In a clinical study, 40 randomised patients scheduled for gastrointestinal surgery received either Lactobin® N or a placebo preparation. The main objective of the study was to determine the course of the plasma endotoxins (LPS) level and the endotoxin neutralisation capacity (ENC) by daily measurements up to the 10th postoperative day. The endotoxin level increased during the operation in both groups due to translocation from the gastrointestinal tract.

In the Lactobin® N group, however, the endotoxins levels remained significantly ($p < 0.05$) lower than in the placebo group (Fig. 1). At the same time, Lactobin® N delayed the decrease in ENC, which was lower overall and also returned to normal more rapidly postoperatively (Fig. 2).

Overall, the ENC values were significantly higher ($p < 0.005$) in the Lactobin® N group than in the placebo group.[24]

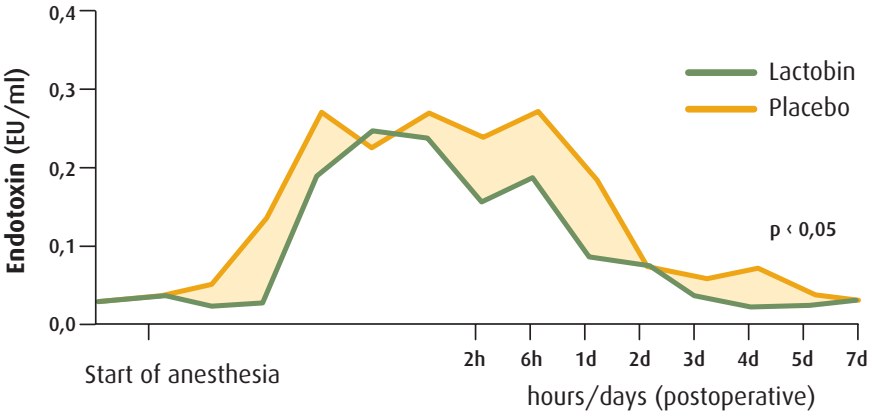


Fig. 1: Intra- and postoperative plasma level curves of LPS in 40 patients undergoing extensive abdominal surgery after preoperative treatment with Lactobin or placebo. The mean LPS concentrations (EU/min) and the significance ranges (p values) for the differences in the area integrals (AUC) of the two patient groups are shown.

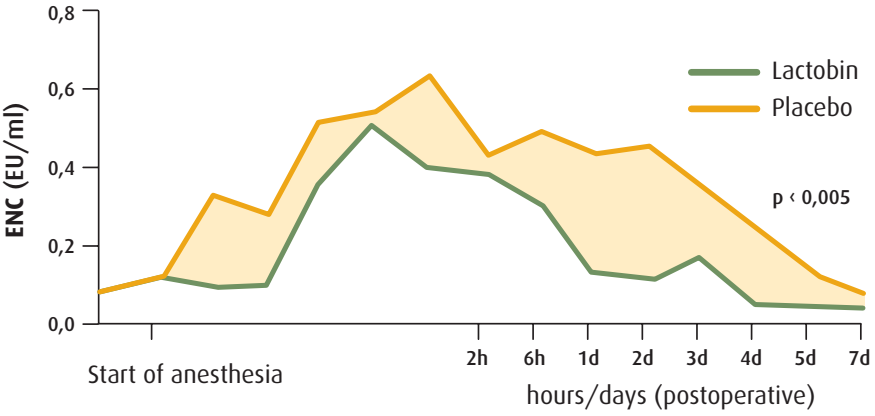


Fig. 2: Comparison of intra- and postoperative endotoxin neutralisation capacity (ENC) of the 40 abdominal surgery patients after randomised preoperative treatment with Lactobin® or placebo. Comparison of the area integrals (AUC) of the two groups.

In a further randomised study, a group of 60 cardiosurgical patients was treated with 42 g Lactobin® daily or placebo for two days before the operation. Although the endotoxin concentrations and the endotoxin neutralisation capacities showed no significant differences in this study, the CRP (-reactive protein) level in the Lactobin® group was significantly lower ($p = 0.034$) than in the placebo group.[26]

CRP levels in patients' plasma generally show a postoperative increase (maximum on 3rd postoperative day). In the event of infectious complications, there is a marked delay in normalisation.[27]

The results of the two studies strongly suggest that the synergistic interplay of the individual active ingredients of the colostrum preparation destroys the microbial pathogens while simultaneously neutralising the toxic products of bacterial decomposition. The integrity of the intestinal wall is protected by the anti-infectious and anti-inflammatory components present in the BCC. The risk of gram-negative sepsis is reduced via suppression of the translocation of bacterial endotoxins into the blood stream.

➜ Tissue trauma and microbial infections are major causal factors in acute phase reactions.[25]

➜ Highly significantly reduced perioperatively CRP levels during Lactobin® therapy, clear evidence of the anti-infectious/anti-inflammatory efficacy of the preparation

[24] Bölke, E et al. Preoperative oral application of immunoglobulin-enriched colostrum milk and mediator response during abdominal surgery. Shock (2002) 17: 9-12.
[25] Übersicht bei Bertsch, T. C-reaktives Protein: Ein „altes" Molekül erhält neue Aufmerksamkeit. Abbott Times 2004; 14: 8-15.
[26] Bölke, E et al. Enteral application of an immunoglobulin-enriched colostrum milk preparation for reducing endotoxin translocation and acute phase responses in patients undergoing coronary bypass surgery – a randomized placebo-controlled pilot trial. Wien Klin Wochenschr (2002) 114: 923-928.
[27] Ehrich, JH et al. Significance of C-reactive protein in pediatric diagnosis. Monatsschr Kinderheilkd (1986) 143: 840-846.

2. Chronic recurrent diarrhea in patients with AIDS and other secondary immunodeficiencies

➔ Lactobin® stops chronic recurrent diarrhea caused by cryptosporidiosis infection in AIDS patients

Lactobin® N reduces stool frequency and improves general well-being.

Patients with AIDS and other secondary immunodeficiencies are often severely debilitated by diarrhea and the resulting weight loss. In many cases the etiologic agents cannot be identified or there is no effective antibiotic therapy.

In a multicentre study with 37 immunodeficient patients with chronic diarrhea, the oral administration of Lactobin® N reduced daily stool frequency from 7.4 to 2.2, thereby achieving a temporary or even permanent normalisation.[28]

These results were however partly confirmed in a placebo-controlled phase III study in 63 AIDS patients (rapid improvement in cryptosporidiosis induced diarrhea). The investigators attribute this result to the modified antiretroviral therapy (HAART) which had partly changed the spectrum of pathogenic organisms detected in the stool.[29,30]

3. Hemorrhagic diarrhea in children caused by infections with enterohemorrhagic E. coli (EHEC)

➔ No antibiotic therapy in severe hemorrhagic diarrhea caused by EHEC infections – risk of HUS development

Lactobin® N reduces daily stool frequency in children with severe hemorrhagic diarrhea caused by food and (usually intrafamilial) smear infections with E. coli 0157.

At present there is no causal therapy for severe hemorrhagic diarrhea caused by shiga-toxin-producing E. coli (EHEC). Antimicrobial therapy of EHEC associated diseases has been contentiously debated for some years. Various antibiotics increase the amount of shigatoxin in vitro and a prospective study of Wong[31] showed that antibiotic therapy in children with EHEC infections increases the risk of developing a hemolytic uremic syndrome (HUS).

In a randomised phase II clinical study, 30 children with acute severe diarrhea caused by enterohemorrhagic E. coli received Lactobin® or a placebo preparation.[32]

On Lactobin® therapy the stool frequency

[28] Rump, JA et al. Treatment of diarrhoea in human immunodeficiency virus infected patients with immuno-globulins from bovine colostrums. Clin Investig (1992) 70: 588-594.
[29] Shield, J et al. Bovine colostrum immunoglobulin concentrate for cryptosporidosis in AIDS. Arch Dis Child (1993) 62: 451-453.
[30] Plettenberg, A et al. A preparation from bovine colostrum in the treatment of HIV-positive patients with chronic diarrhea. Clin Investig (1993) 71: 42-45.
[31] Wong, CS et al. The risk of hemolytic-uremic syndrome after antibiotic treatment of Es-cherichia coli O157:H7 infections. N Engl J Med (2000) 342: 1930-1936.
[32] Huppertz, HJ et al. Bovine colostrum ameliorates diarrhea infection with diarrheagenic Escherichia coli, Shiga toxin producing E. coli and E. coli expressing intimin and hemolysin. J Pediatr Gastroenterol Nutr (1999) 29: 452-456.

decreased from 3 to 1 stools daily ($p < 0.05$) and the time interval required for the normalisation of the stool frequency was at least 50% shorter than in the control group ($p < 0.05$). The excretion rates of E. coli expressing intimin and EHEC-hemolysin were higher in the Lactobin® treatment group compared to the controls. (Tab. 2).

Severe diarrhea caused by EHEC accompanied by the risk of hemolytic uremic syndrome is prevalent among children on all continents. The epidemiology of infections with shigatoxin-producing E. coli has been described for Germany by Karch et al.[34]

The results of the clinical studies, which demonstrate the efficacy of Lactobin® therapy, and the outstanding tolerability of the colostrum preparations in children show Lactobin® N to be the product of choice for effective prophylaxis of hemolytic uremic syndrome.

➜ Lactobin® N contains neutralising antibodies against EHEC pathogenicity factors.[33]

➜ Lactobin® shortens the duration of illness and mitigates the symptoms of EHEC infections in children.

4. Idiopathic pain syndrome*

Polyvalent bovine colostrum concentrates reduce the complaints associated with chronic pain.

There is clear evidence of a relationship between immunopathological processes and chronic pain. The Pain Centre of Würzburg University Hospital headed by Prof. Dr. Sprotte has reported on many years of experience with the treatment of different pain patient populations with bovine colostrum concentrates.[35]

30-40 % of patients with chronic recurrent pain of varying etiology show good to excellent results in response to treatment with colostrum preparations. Patients with idiopathic neuralgic facial pain and patients with chronic unspecific pain such as fibromyalgia (with and without irritable bowel syndrome) respond particularly well. Notably, all pediatric patients who showed a positive response to colostrum therapy had comorbid atopic disorders such as allergic asthma, dermatitis and allergic rhinitis.

The optimal dose for adults with a variety of painful conditions was found to be 10 g Lactobin® each in the morning and in the evening (with a sufficient time interval in relation to main meals). When a stable state is reached after an average of 14 days, in some responder patients, it is even possible to interrupt the therapy for several months.

➜ In Germany alone, 3 million patients suffer from chronic recurrent pain.

[33] Lissner, R et al. A standard immunoglobulin preparation produced from bovine colostra shows antibody reactivity and neutralization activity against Shiga-like toxins and EHEC-hemolysin of Escherichia coli O157:H7. J Infection 1996; 24: 378-383.
[34] Karch, H et al. Shiga toxin producing Escherichia coli infections in Germany. J Food Protect (1997) 30: 1454-1457.
[35] Struff, WG & Sprotte, G. Bovine colostrum as a biologic in clinical medicine: a review. Part I: Biotechnological standards, pharmacodynamic and pharmacokinetic characteristics and principles of treatment. Int J Clin Pharmacol Ther (2007) 45: in press.
* German Patent No. DE59406722

Efficacy, safety, tolerability

A wide range of studies have confirmed the efficacy of Lactobin® for the therapeutic indications mentioned. Further indications are under evaluation.

All studies performed to date have emphasized the outstanding good efficacy of orally administered Lactobin® N, even during repeated use and in high dosages. The absence of adverse drug reactions is due to the fact that bovine colostrum preparations consist exclusively of naturally occurring proteins and small amounts of dietary fats to which man has become adapted over a long period since the beginning of domestic animal husbandry.

So far, adverse reactions have only been observed in persons with lactose intolerance and milk protein allergy. In some patient populations (e.g. with chronic pain), however, the induction of lactose intolerance or sensitisation to milk proteins has been observed after prolonged treatment with bovine colostrum preparations.

Lactobin® N derived from colostrum and manufactured under strict quality controls satisfies all the requirements for its use as a balanced food supplement. Its efficacy as a supplement to standard therapies is based on its antibacterial, nutritional and immunomodulating effects.

Outlook

Promising approaches and working hypotheses for Lactobin® N therapy are also available for several additional indications.

Hepatoprotective effects / Hepatic insufficiencies*

Impairment of the body's immune system in general and a reduction in intestinal wall function (hypoperfusion and malnutrition etc.) in particular can very rapidly lead to undesirable changes in the composition of the enteral bacterial flora, increasing the risk of life-threatening toxin effects of human pathogenic bacteria as described above. Damage to large organs like the lung, cardiovascular system, central nervous system and especially the liver should be countered by therapeutic interventions. Enteral neutralisation of bacterial toxins of endotoxins, shigatoxins or even cholera toxin-associated enterotoxins with bovine colostrum concentrates is an effective co-therapeutic component for integration into the classical anti-infectious interventions in these situations.[36]

Lactobin® is also valuable in the management of hepatic insufficiency of varying etiology. At least 1-2 % of the populations of the industrialised countries suffer from chronic hepatic insufficiency due to liver parenchyma damage. In addition to viral hepatitis, the predominant relevant causalities are alcohol-induced fatty degeneration of the liver and cirrhosis.

The damaged liver is no longer able to adequately neutralise the large amounts of ammonia (breakdown in the urea cycle or by glutamic acid detoxification) produced in the intestine from the bacterial degradation of proteins and the breakdown of amino acids in the liver itself. While the ammonia level in healthy subjects is only about 30-80 µg/100 ml plasma, in liver cirrhosis patients this toxin accumulates to as much as 500 µg/100 ml plasma. Very severe neurological deficits are already observed at such high concentrations of NH3.

In 1994, D. Nitsche (EP 0 652 013B1) reported on 6 cases of patients with severe liver insufficiency (5 with liver cirrhosis, 1 acute hepatitis) who after treatment with Lactobin® exhibited very rapid normalisation of the elevated plasma ammonia levels, in some cases accompanied by a decrease in the previously elevated gamma-GT values. This makes it possible to supply patients with larger amount of proteins and thus with essential amino acids avoiding massive production of toxic degradation products like ammonia.

➜ Endemic disease pathogen Helicobacter pylori: Lactobin® N as a safe remedy which might be capable to support the multifactorial treatment of gastrointestinal infectious diseases caused by this pathogen.

Cachexia in oncological patients

The neutralisation of LPS by Lactobin® demonstrated in clinical studies as reported in the preceeding paragraph also leads to a decrease in the release of tumor necrosis factor alpha (TNF-α/cachectin from monocytes/macrophages). This effect might be favourable in oncological patients with severely reduced body weight due to loss of appetite.[37-39]

Risk-free treatment of this patient population with Lactobin® N has the further advantage that individualised therapeutic regimens can be instituted since this product can also be used practically without dose limits. Home therapy also presents no problems because of the uncomplicated administration, it's safety and the unproblematic storage of Lactobin® N.

Sepsis in burn patents

Patients with extensive burns are at particularly high risk of dying from sepsis. A study by Ulrich et al. showed that burn injuries are associated with a marked increase in plasma LPS concentration, peaking after 47 hours. Of the 7 patients investigated, 2 with a substantially elevated plasma LPS level developed sepsis and died.[39]

Lactobin® N for supportive treatment of infections of the gastroduodenal tract with Heliobacter pylori

The findings of Bitzan et al. (1998) suggest that defined lipids present in the preparation can block the colonisation of mucosal cells of the stomach by Helicobacter pylori.[40]

Important for the pathogenicity mechanisms of an infection with H. pylori are "islands of pathogenicity" (cag PAI, a region comprising about 40 kilodaltons), which are found in 50-60 % of H. pylori positive biopsy samples (in Japan > 90 %).[41]

In 1994, H. pylori was classified as a definite carcinogen by the International Agency for Research on Cancer. Despite the worldwide decrease in incidence, gastric cancer is the second commonest cause of death in men and the third commonest in women. Since an estimated 50 % of the world population are infected with this etiologic agent, a very large number of cancer mortality cases are statistically attributable to H. pylori infection.[42]

[36] Boesmann-Finkelstein, M et al. Bovine lactogenic immunity against Cholera toxin-related enterotoxins and Vibrio cholerae outer membranes. Infection and Immunity (1989) 57: 1227-1234.
[37] Argiles, JM et al. Mediators involved in the cancer anorexia-cachexia syndrome: past, present and future. Nutrition (2005) 21: 977-985.
[38] Beutler, B & Rietschel, E. Innate immune sensing and its roots: the story of endotoxin. Nature Rev Immunol (2003) 3: 169-176.
[39] Watchorn, TM et al. The cachectic mediator proteolysis inducing factor activates NF-kappaB and STAT3 in human Kupffer cells and monocytes. Int J Oncol (2005) 27: 1105-1111.
[40] Ulrich, D et al. Plasma-endotoxin, procalcitonin, C-reactive protein and organ functions in patients with major burns. Handchir Mikrochir Plast Chir (2001) 33: 262-266.
[41] Bitzan, MM et al. Inhibition of Helicobacter pylori and Helicobacter mustelae binding to lipid receptors by bovine colostrum. J Infect Dis (1998) 177: 955-961.
[42] Maeda, S et al. Distinct mechanisms of Helicobacter pylori-mediated NF-kappa B activation between gastric cancer cells and monocytic cells. J Biol Chem (2001) 276: 44856-44864.
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* European patent no. EP0652013B1

Tables

Tab. 1: Antibody activities in Lactobin® and human plasma

Based on fingerprint analysis data (Research Report [2005] E. M. Waaga-Gasser, Würzburg University Hospital), these reciprocal titres with reference to the IgG concentrations are applicable to Lactobin® N.

	Lactobin®	Humanplasma
Escherichia coli	640	640
Escherichia coli 35	640	40
Pseudomonas aeruginosa	640	160
Klebsiella pneumoniae	640	80
Proteus vulgaris	80	n. t.
Serratia marcescens HY	1280	n. t.
Salmonella typhimurium	160	n. t.
Staphylococcus aureus	640	40
Staphylococcus epidermidis	160	n. t.
Streptococcus pyogenes	160	80
Streptococcus faecalis	160	40
Streptococcus viridans	640	80
Streptococcus B	80	n. t.
Candida albicans	320	n. t.

The plasma values are the median of 80 individual plasma values. The Lactobin® values are the median of 3 batches. (n.t. = not tested).

(from: Stephan, W et al. Antibodies from colostrum in oral immunotherapy. J Clin Chem Clin Biochem (1990) 28: 19-23)

Tables

Tab. 2: Efficacy of treatment with Lactobin® or placebo in children with hemorrhagic diarrhea due to infection with enterohemorrhagic E. coli (EHEC).

Based on fingerprint analysis data (Research Report [2005] E. M. Waaga-Gasser, Würzburg University Hospital), these results are applicable to Lactobin® N.

	Lactobin®	Placebo	p-value
Stool frequency at start of study	3 ± 2 (median 3)	3 ± 4 (median 2)	
Stool frequency at end of treatment	1 ± 1 (median 1)	2 ± 3 (median 2)	
Reduction in stool frequency	2 ± 2 (median 2)	1 ± 3 (median 0)	0,027
Elimination of strains with expression of virulence factors:			
Stx1	4/6* (67 %)	3/3 (100 %)	
Stx2	2/2 (100 %)	3/5 (60 %)	
Eae (intimin)	11/13 (85 %)	6/10 (60 %)	
EHEC hemolysin	11/13 (85 %)	5/9 (56 %)	

Stool frequencies as mean ± standard deviation*
Number of patients negative at the end of treatment vs. positive at the start of the study

(from: Huppertz, HJ et al. Bovine colostrum ameliorates diarrhea infection with diarrheagenic Escherichia coli, Shiga toxin producing E. coli and E. coli expressing intimin and hemolysin. J Pediatr Gastroenterol Nutr (1999) 29: 452-456)

Diagram legends

Fig. 1

Time course of intra- and postoperative endotoxin release in patients scheduled for major abdominal surgery after preoperative treatment with Lactobin® or placebo.

Median endotoxin levels in randomised groups of 20 study participants each. Abscissa values 1-6 correspond to defined time points from the start of the operation to wound closure. The other measurements were made at the intervals shown after the end of the operation.

(from: Bölke, E et al. Preoperative oral application of immunoglobulin-enriched colostrum milk and mediator response during abdominal surgery. Shock (2002) 17: 9-12.)

Fig. 2

Time course of the intra- and postoperative endotoxin neutralisation capacity (ENC) in patients scheduled for major abdominal surgery after preoperative treatment with Lactobin® or placebo.

Median ENC values in randomised groups of 20 study participants each.

Abscissa values 1-6 correspond to defined time points from the start of the operation to wound closure. The other measurements were made at the intervals shown after the end of the operation.

(from: Bölke, E et al. Preoperative oral application of immunoglobulin-enriched colostrum milk and mediator response during abdominal surgery. Shock (2002) 17: 9-12.)


Lactobin® N

Product information for Lactobin® N

1. Qualitative and quantitative composition

A natural concentrate of bovine origin, prepared without additives from at least 200 individual colostra and consisting of 80 % proteins, 1.2 % fat, 7.4 % lactose, 5 % water (mean values).

2. Biologically active constituents

Quantitative measurements for IgG (subclass IgG 1) of 21-24 % and lactoferrin (19 mg/g) as the two primary active agents are available for inhibition of intestinal LPS translocation in intensive medical care and cancer patients. Determination of antibody specificities of the IgG1 type in the forerunner product (see Stephan, W et al. Antibodies from colostrum in oral immunotherapy. J Clin Chem Clin Biochem (1990) 28: 19-23 and Lissner, R et al. A standard immunoglobulin preparation produced from bovine colostra shows antibody reactivity and neutralization activity against Shiga-like toxins and EHEC-hemolysin of Escherichia coli 0157:H7. J Infection (1996) 24: 378-383).

3. Administration form

Powder for drinkable solution.

4. Clinical particulars

4.1. Therapeutic indications

4.1.1. Supportive treatment of chronic recurrent diarrhea in patients with primary and secondary immunodeficiency.

4.1.2. Supportive treatment in children with hemorrhagic diarrhea due to EHEC infections for prevention of hemolytic uremic syndrome (HUS).

4.1.3. Supportive treatment of intensive medical care patients with enterogenic gram-negative sepsis.

4.1.4. Supportive treatment of patients with hepatic insufficiency of varying etiology and especially preoperatively before liver transplantations.

4.1.5. Supportive treatment of cancer patients with impaired appetite (prophylaxis of cachexia).

4.1.6. Supportive treatment of patients with chronic recurrent pain.

4.2. Posology and method of administration

Since no undesirable effects are so far known to be associated with the substitution of bovine colostrum concentrate Lactobin® N, apart from lactose intolerance and mild protein sensitisation (diagnosable from the medical history), treatment schedules can be individualised.

The following dosages are recommended (see table on right):

The product is administered in the form of a drinkable solution prepared freshly before use: place about 200 ml of liquid yogurt or milk (lukewarm) in a shaking cup and add the recommended amount of the powdered product. After shaking briefly, the solution is ready to drink.

	Single dose/day	Duration
Diarrhea with immunodeficiency (primary and secondary forms)	10 g	10 days
Children with hemorrhagic diarrhea with proven EHEC excretion	3 x 10 g	14 days
Prophylaxes of gram-negative sepsis in surgical patients	50 - 60 g	3 days preoperatively
Patients with chronic recurrent pain	2 x 10 g	10 days (afterwards 10 g daily if positive therapeutic response)

4.3. Contraindications

Hypersensitivity to heterologous proteins of cow's milk and lactose intolerance (usually known to patients).

4.4. Special warnings and precautions for use

In patients with severe enteritis such as Crohn's disease there is a risk of absorbing intact protein constituents of the preparation and inducing sensitisation processes.

4.5. Overdose

None known

5. Pharmaceutical particulars

5.1. Excipients

None

5.2. Incompatibilities

None known

Lactobin® N should be taken outside the normal mealtimes.

5.3. Shelf life

2 years

5.4. Special instructions for storage

Keep in a cool, dry place

6. Name and address of the marketing authorisation holder

Dr. Wolz Zell GmbH
Marienthaler Str. 3
65366 Geisenheim
Germany
Tel.: +49-67 22-56 100
www.lactobin.com

7. Country of origin of the raw material

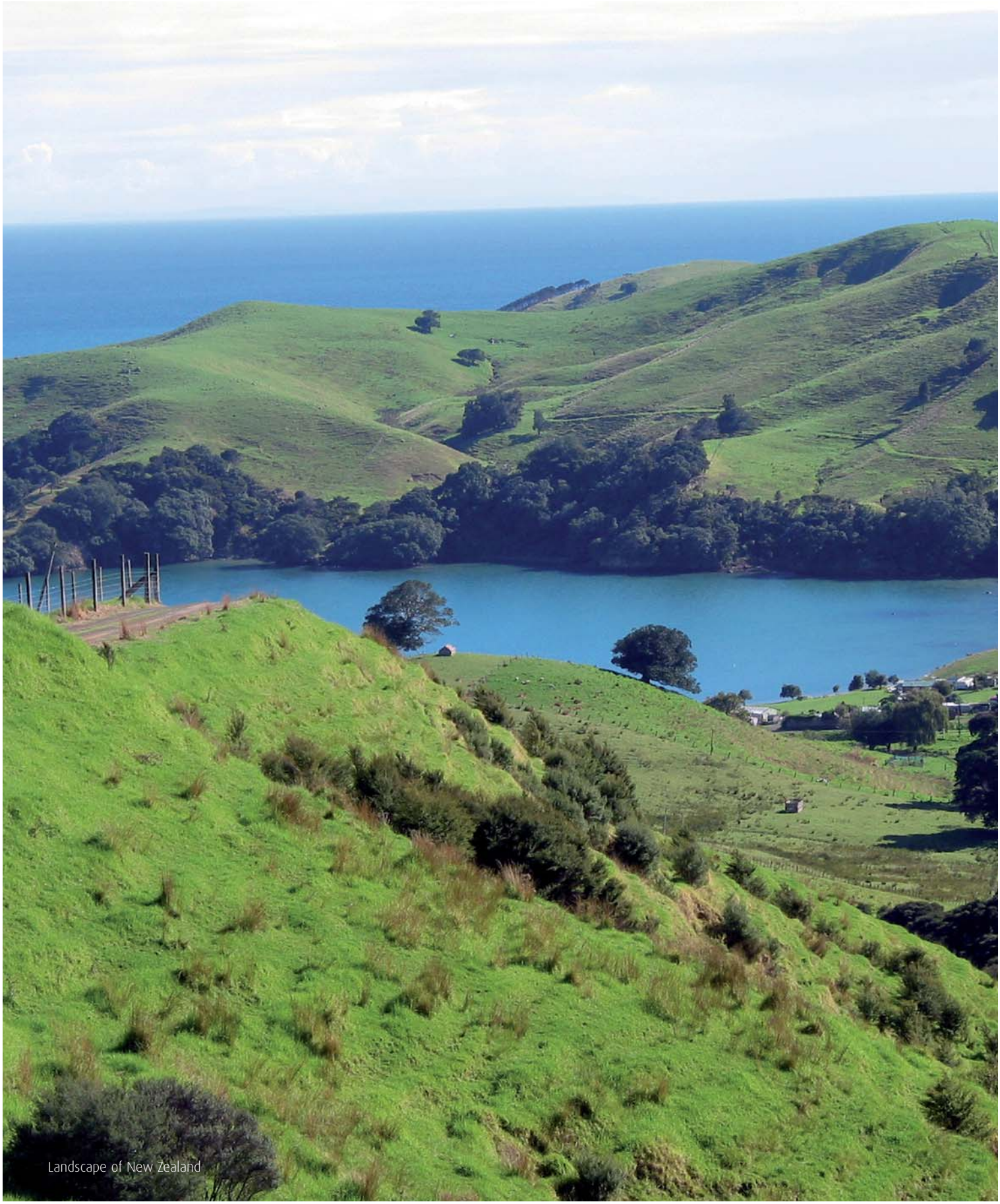
New Zealand

8. Prescription status / pharmacy only

Non-prescription dietary food for special medicinal purposes.
Product licence number (PLN): 3777611

9. Date of revision of the text

May 2007



Landscape of New Zealand