

tients hypersensitive to iodine. Clearance of indocyanine green may be altered by drugs that interfere with liver function.

References

1. Jackson TL. Indocyanine green accused. *Br J Ophthalmol* 2005; **89**: 395–6.
2. Cheng SN, *et al*. Ocular toxicity of intravitreal indocyanine green. *J Ocul Pharmacol Ther* 2005; **21**: 85–93.

Hypersensitivity. A report of anaphylactoid reactions to indocyanine green in 3 patients.¹ The authors commented that of 20 reactions that had been reported 9 involved anaphylactoid shock (with 2 subsequent deaths) and 11 involved hypotension or bronchospasm; they suggested that such reactions were dose-dependent and had a non-immune mechanism.

1. Speich R, *et al*. Anaphylactoid reactions after indocyanine-green administration. *Ann Intern Med* 1988; **109**: 345–6.

Pharmacokinetics

After intravenous injection indocyanine green is rapidly bound to plasma protein. It is taken up by the liver and is rapidly excreted unchanged into the bile.

Uses and Administration

Indocyanine green is an indicator dye used for assessing cardiac output and liver function, and for examining the choroidal vasculature in ophthalmic angiography. It is also used to assess blood flow and haemodynamics in various organs including the liver.

The usual dose for cardiac assessment is 5 mg injected rapidly via a cardiac catheter. A suggested dose for children is 2.5 mg, and for infants 1.25 mg. Several doses need to be given to obtain a number of dilution curves. However, the total dose should not exceed 2 mg/kg.

The usual dose of indocyanine green for testing liver function is 500 micrograms/kg given intravenously.

Diagnostic use. Indocyanine green has been used to assess blood flow to various organs and in other haemodynamic studies. However, some methods of determination of indocyanine green clearance as a measure of liver blood flow have been questioned on the grounds that extraction of the dye by the liver is not complete as is often assumed.¹ Interindividual variability in indocyanine clearance may introduce further error.²

There have been reports of the use of indocyanine green to assess cerebral blood flow in children during cardiopulmonary bypass³ and to measure plasma volume in neonates.⁴ In ophthalmology, indocyanine green angiography is used to visualise the choroidal circulation,^{5,6} and as a stain during surgical repair of macular holes.^{7,8}

1. Skak C, Keiding S. Methodological problems in the use of indocyanine green to estimate hepatic blood flow and ICG clearance in man. *Liver* 1987; **7**: 155–62.
2. Bauer LA, *et al*. Variability of indocyanine green pharmacokinetics in healthy adults. *Clin Pharm* 1989; **8**: 54–5.
3. Roberts I, *et al*. Estimation of cerebral blood flow with near infrared spectroscopy and indocyanine green. *Lancet* 1993; **342**: 1425.
4. Anthony MY, *et al*. Measurement of plasma volume in neonates. *Arch Dis Child* 1992; **67**: 36–40.
5. Owens SL. Indocyanine green angiography. *Br J Ophthalmol* 1996; **80**: 263–6.
6. Dzurinko VL, *et al*. Intravenous and indocyanine green angiography. *Optometry* 2004; **75**: 743–55.
7. Rodrigues EB, *et al*. Intravitreal staining of the internal limiting membrane using indocyanine green in the treatment of macular holes. *Ophthalmologica* 2005; **219**: 251–62.
8. Lee KL, *et al*. A comparison of outcomes after indocyanine green and trypan blue assisted internal limiting membrane peeling during macular hole surgery. *Br J Ophthalmol* 2005; **89**: 420–4.

Preparations

USP 31: Indocyanine Green for Injection.

Proprietary Preparations (details are given in Part 3)

Fr.: Infracyanine; **Ger.:** ICG-Pulsion; **Gr.:** ICG-Pulsion; **Israel:** IC Green; ICG-Pulsion; **Neth.:** ICG-Pulsion; **USA:** Cardio-Green†; IC Green.

Inhibin

Inhibina.

ИНГИБИН

CAS — 57285-09-3.

NOTE. The name inhibin has also been used as a proprietary name for hydroquinine hydrobromide (p.2322).

Profile

Inhibin is a dimeric glycoprotein secreted by the testes and ovaries that suppresses secretion of follicle-stimulating hormone by the pituitary. As a member of the transforming growth factor-β family, it is also involved in mediation and regulation of many other physiological processes. Its two isoforms inhibin A and inhibin B have been widely investigated for their potential as markers of male infertility, ovarian cancer, and placental function. It has also been studied as a prognostic indicator of ovarian function in women undergoing assisted reproduction.

References

1. Kumanov P, *et al*. Significance of inhibin in reproductive pathophysiology and current clinical applications. *Reprod Biomed Online* 2005; **10**: 786–812.

Inosine (riNIN)

Hypoxanthine Riboside; Inosina; Inosinum. 6,9-Dihydro-9-β-D-ribofuranosyl-1H-purin-6-one.

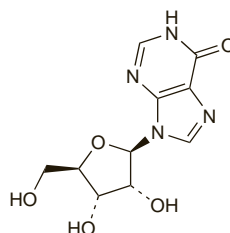
ИНОЗИН

C₁₀H₁₂N₄O₅ = 268.2.

CAS — 58-63-9.

ATC — D06BB05; G01AX02; S01XA10.

ATC Vet — QD06BB05; QG01AX02; QS01XA10.



Pharmacopoeias. In Chin.

Profile

Inosine has been used in the treatment of anaemias and cardiovascular, liver, and skin disorders and has been used as a tonic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: **Cz.:** Laevadosin†; **Ital.:** Neo-Eparibol†; **Spain:** Nutracel; Rubrocortin†.

Inositol

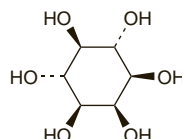
i-Inositol; meso-Inositol; Inositol; Inositolum; myo-Inositolum; mio-Inozitol; myo-Inositol; myo-Inositol; myo-Inositolum. myo-Inositol.

C₆H₁₂O₆ = 180.2.

CAS — 87-89-8.

ATC — A11HA07.

ATC Vet — QAI1HA07.



Pharmacopoeias. In Eur. (see p.vii). Also in USNF.

Ph. Eur. 6.2 (*myo*-Inositol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in alcohol. **USNF 26** (inositol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dehydrated alcohol and in ether.

Profile

Inositol, an isomer of glucose, has traditionally been considered to be a vitamin B substance although it has an uncertain status as a vitamin and a deficiency syndrome has not been identified in man. Sources of inositol include whole-grain cereals, fruits, and plants, in which it occurs as the hexaphosphate, fytic acid. It also occurs in both vegetables and meats in other forms. The usual daily intake of inositol from the diet is about 1 g. It is an ingredient of numerous vitamin preparations and dietary supplements, and of preparations promoted for a wide variety of disorders.

Inositol appears to be involved physiologically in lipid metabolism and has been tried, with little evidence of efficacy, in disorders associated with fat transport and metabolism. It has been investigated in the treatment of depression and anxiety, in diabetic neuropathy, and in neonatal respiratory distress syndrome and retinopathy of prematurity.

Neonatal respiratory distress syndrome. Inositol supplementation has been tried in premature infants with respiratory distress syndrome (p.1508). A meta-analysis¹ found that infants given inositol had improved survival and lower rates of bronchopulmonary dysplasia and retinopathy of prematurity than those given placebo.

1. Howlett A, Ohlsson A. Inositol for respiratory distress syndrome in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 19/04/06).

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Inositech.

Multi-ingredient: **Arg.:** Bifena; **Austral.:** Hair and Skin Formula†; Liv-Detox†; **Austria:** Aslavit†; Lemazol; **Braz.:** Hecrosine B12†; Hepatogenol†; Hormo Hepaticol†; Metiocolin B12; Xantonin Complex; **Canad.:** Amino-Cerv; **Chile:** Hepabil; **Cz.:** Lipovitan†; **Fr.:** Hepagrum; **Ger.:** Lipovitan†; **Hong Kong:** Bilsan; Lipocho; **India:** Alcrin-M†; Delphicol; **Indon.:** Naturica DFM; **Ital.:** Digelax†; Hepatos B12; Porfirin 12; Stimolift; **SAfr.:** Hepavite; Prohep; **Spain:** Complidermol†; Dertrase; Policolinosil; Tri Hachemina; **Thai.:** Lipocho; Liporon; **UK:** Lipotropic Factors; **USA:** Amino-Cerv.

Interleukins

Интерлейкины

Profile

Interleukins are cytokines (p.2292) that are thought to target leukocytes. As with other cytokines, interleukins are involved in the regulation of normal immune and inflammatory responses and have both proinflammatory and anti-inflammatory actions. Interleukins used clinically include interleukin-1 (p.2325), interleukin-2 (p.735), and aldesleukin (recombinant interleukin-2) (p.735). Interleukins under investigation include interleukin-3 (p.1073), ilodecakin (recombinant interleukin-10) (p.2326), and edodekin alfa (recombinant interleukin-12) (p.2326).

Interleukins have also been implicated in the pathogenesis of some diseases, and inhibitors of interleukins or their receptors may therefore be of therapeutic value.

Antagonists acting against interleukin receptors used clinically include anakinra (recombinant interleukin-1 receptor antagonist) (p.19), basiliximab (p.1821), and daclizumab (p.1833), which are all interleukin-2 receptor antibodies, and tocilizumab (recombinant interleukin-6 receptor antibody) (p.2326). Inolimomab (p.1835) is an interleukin-2 receptor antibody under investigation.

Antibodies targeting interleukins have been developed and those under investigation include mepolizumab (recombinant interleukin-5 antibody) (p.743) and elisilimomab (recombinant interleukin-6 antibody) (p.2326).

Interleukin fusion toxins are produced by combining interleukin protein sequences with a bacterial toxin (e.g. diphtheria or pseudomonas) with the aim of inhibiting specific interleukin activity. Those under investigation include interleukin-2 fusion toxins (p.2326), interleukin-4 fusion toxins, and cintredekin besudotox, an interleukin-13 fusion toxin.

Soluble interleukin receptors may have therapeutic value and are also being tried therapeutically: riloncept (p.2379) is an interleukin-1 blocker used in the treatment of a group of rare inherited auto-inflammatory disorders; interleukin-4 receptor is also being investigated.

Inhibitors of cysteine protease IL-1β converting enzyme (ICE) have been investigated as a means of reducing secretion of interleukin-1β (p.2325).

Interleukin-1

Catabolin; Endogenous Pyrogen; Haematopoietin-I; IL-1; Interleucina 1; Leucocyte Endogenous Mediator; Lymphocyte Activating Factor.

Интерлейкин-1

Profile

Interleukin-1 is one of a number of polypeptides known collectively as interleukins (p.2325). It is produced in blood and a variety of tissues by mononuclear phagocytes involved in the complex regulation of immune responses. It enhances the immune response and has proinflammatory and pyrogenic properties. There are two distinct forms, interleukin-1α and interleukin-1β.

Interleukin-1 may also be produced by recombinant DNA technology, and human recombinant interleukin-1β has been used as an adjunct to cancer chemotherapy or radiotherapy for its haematopoietic activity. It has also been investigated for its immunotropic effects in purulent infections of the lung and ear, although it has no intrinsic antibacterial activity. Adverse effects of interleukin-1 include fever, chills, flu-like symptoms, hypotension, and pain, swelling, and erythema at the site of subcutaneous injection.

Interleukin-1 is also implicated in the pathogenesis of some diseases, particularly auto-immune and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

Preparations

Proprietary Preparations (details are given in Part 3)

Rus.: Betaleukin.

Interleukin-1 Receptor Antagonists

Antagonista del Receptor de la Interleucina 1; IL-1ra; IL-1i; Interleukin-1 Inhibitors.

Profile

Endogenous antagonists to interleukin-1 receptor block the actions of interleukin-1 (p.2325) and recombinant forms have been investigated in inflammatory and immune-modulated disorders. Anakinra (p.19) is a human recombinant interleukin-1 receptor antagonist used in the treatment of rheumatoid arthritis.

Interleukin-2 Fusion Toxins

Toxinas de fusión de interleucina 2.

Profile

Interleukin-2 fusion toxin is produced by replacing the receptor binding domain of diphtheria toxin with sequences from interleukin-2, thus producing specific cytotoxicity in cells expressing the interleukin-2 receptor. The interleukin-2 fusion toxin denileukin difitox (p.710) is used in the treatment of cutaneous T-cell lymphoma. The related compound DAB₄₈₆ interleukin-2 has also been investigated in a variety of disorders.

Interleukin-6

B-cell Stimulatory Factor-2; BSF-2; Hepatocyte-Stimulating Factor; Hybridoma Growth Factor; IFN-β₂; IL-6; Interferon-β₂.

Интерлейкин-6

Profile

Interleukin-6 is one of a number of polypeptides known collectively as interleukins (p.2325). It is produced by many cell types and induces differentiation of B-lymphocytes and activation of T-cells. It has proinflammatory and pyrogenic properties and is involved in the regulation of immune responses and inflammation. Interleukin-6 has also been implicated in haematopoiesis. Atekin alfa is human recombinant interleukin-6 under investigation.

Since overproduction of interleukin-6 plays a crucial role in the pathogenesis of chronic inflammatory diseases, interleukin-6 antibodies (p.2326) and interleukin-6 receptor antagonists (p.2326) are being investigated or used as therapeutic agents.

Interleukin-6 Antibodies

IL-6 Antibody.

Elisilimomab (rINN)

Elisilimomabum. Immunoglobulin G1, anti-(human interleukin 6) (mouse monoclonal B-E8 heavy chain), disulfide with mouse monoclonal B-E8 κ-chain, dimer.

Эльсалимомаб

CAS — 468715-71-1.

Profile

Monoclonal antibodies to interleukin-6 (p.2326) are under investigation for the treatment of disorders including post-transplant lymphoproliferative disorders and renal cell carcinoma.

Elisilimomab is an interleukin-6 monoclonal antibody under investigation.

Interleukin-6 Receptor Antagonists

Tocilizumab (USAN, rINN)

Atlizumab; MRA; R-1569; Tocilizumabum. Immunoglobulin G1, anti-(human interleukin 6 receptor) (human-mouse monoclonal MRA heavy chain), disulfide with human-mouse monoclonal MRA κ-chain, dimer.

Тоцилизумаб

CAS — 375823-41-9.

Profile

Antagonists to the interleukin-6 receptor block the actions of interleukin-6 (p.2326) and are under investigation for rheumatoid arthritis, systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, Crohn's disease, and haemolytic anaemia.

Tocilizumab is a recombinant monoclonal antibody that targets the interleukin-6 receptor and is used for the treatment of Castleman's disease, a rare lymphoproliferative disorder. It is also used for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis.

References.

1. Nishimoto N, *et al.* Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood* 2000; **95**: 56–61.
2. Ito H, *et al.* A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 2004; **126**: 989–96.

3. Nishimoto N. Clinical studies in patients with Castleman's disease, Crohn's disease, and rheumatoid arthritis in Japan. *Clin Rev Allergy Immunol* 2005; **28**: 221–30.
4. Yokota S, *et al.* Clinical study of tocilizumab in children with systemic-onset juvenile idiopathic arthritis. *Clin Rev Allergy Immunol* 2005; **28**: 231–8.
5. Lipsky PE. Interleukin-6 and rheumatic diseases. *Arthritis Res Ther* 2006; **8** (suppl 2): S4. Available at: <http://arthritis-research.com/content/8/S2/S4> (accessed 11/02/08)
6. Maini RN, *et al.* Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006; **54**: 2817–29.
7. Paul-Pletzer K. Tocilizumab: blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. *Drugs Today* 2006; **42**: 559–76.
8. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. *Nat Clin Pract Rheumatol* 2006; **2**: 619–26. Correction. *ibid.*: 691.
9. Kanda J, *et al.* Reversible cardiomyopathy associated with multicentric Castleman disease: successful treatment with tocilizumab, an anti-interleukin 6 receptor antibody. *Int J Hematol* 2007; **85**: 207–11.
10. Matsuyama M, *et al.* Anti-interleukin-6 receptor antibody (tocilizumab) treatment of multicentric Castleman's disease. *Intern Med* 2007; **46**: 771–4.
11. Smolen JS, *et al.* OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008; **371**: 987–97.
12. Yokota S, *et al.* Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008; **371**: 998–1006.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Actemra.

Interleukin-10

CSIF; Cytokine synthesis inhibitory factor; IL-10.

Интерлейкин-10

CAS — 130068-27-8.

Ilodecakin (USAN, rINN)

Ilodecakin; Ilodécakine; Ilodecakinum; Interleukin-10 (human clone pH15C); rIL-10; Sch-52000.

Илодекакин

CAS — 149824-15-7.

Profile

Interleukin-10 is one of a number of polypeptides known collectively as interleukins (p.2325). It regulates the differentiation and proliferation of several immune cells including T-cells and B-cells. It is postulated that it has immunostimulant as well as immunosuppressive properties; it also has anti-inflammatory actions. Interleukin-10 is under investigation for inflammatory bowel disease, malignant neoplasms, skin disorders including psoriasis and reduction of scarring, rheumatoid arthritis, hepatitis C, and organ transplantation.

Ilodecakin is a recombinant form of interleukin-10 under investigation.

References.

1. Asadullah K, *et al.* Interleukin-10 therapy—review of a new approach. *Pharmacol Rev* 2003; **55**: 241–69.
2. Braat H, *et al.* Interleukin-10-based therapy for inflammatory bowel disease. *Expert Opin Biol Ther* 2003; **3**: 725–31.
3. Weiss E, *et al.* The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases. *J Am Acad Dermatol* 2004; **50**: 657–75.
4. Asadullah K, *et al.* Interleukin-10: an important immunoregulatory cytokine with major impact on psoriasis. *Curr Drug Targets Inflamm Allergy* 2004; **3**: 185–92.
5. Vicari AP, Trinchieri G. Interleukin-10 in viral diseases and cancer: exiting the labyrinth? *Immunol Rev* 2004; **202**: 223–36.
6. Mocellin S, *et al.* Interleukin-10 and the immune response against cancer: a counterpoint. *J Leukoc Biol* 2005; **78**: 1043–51.
7. Mege JL, *et al.* The two faces of interleukin 10 in human infectious diseases. *Lancet Infect Dis* 2006; **6**: 557–69.

Interleukin-12

IL-12.

Интерлейкин-12

Edodekin Alfa (USAN, rINN)

Edodekina alfa; Édodékin Alfa; Edodekinum Alfa; Ro-24-7472/000.

Эдодекин Альфа

CAS — 187348-17-0.

Description. A recombinant human interleukin-12.

Profile

Interleukin-12 is one of a number of polypeptides known collectively as interleukins (p.2325). It is produced by macrophages and dendritic cells and enhances cellular immunity through induction of the activity of interferon-γ and cytotoxic T-lymphocytes. It has been investigated for the treatment of severe infections such as mycobacterial infections; it is worthy of note

that children with a rare inherited susceptibility to fatal mycobacterial infections exhibit mutations in the interleukin-12 gene. Interleukin-12 is also under study for the treatment of various cancers, including as adenovirus-mediated gene therapy.

Edodekin alfa is human recombinant interleukin-12 under investigation for the treatment of renal cell carcinoma.

References.

1. Mazzolini G, *et al.* Gene therapy of cancer with interleukin-12. *Curr Pharm Des* 2003; **9**: 1981–91.
2. Kikuchi T, *et al.* Vaccination of glioma patients with fusions of dendritic and glioma cells and recombinant human interleukin 12. *J Immunother* 2004; **27**: 452–9.
3. Trudeau C, *et al.* A single administration of recombinant human interleukin-12 is associated with increased expression levels of interferon-gamma and signal transducer and activator of transcription in healthy subjects. *J Clin Pharmacol* 2005; **45**: 649–58.
4. Sangro B, *et al.* Gene therapy of cancer based on interleukin 12. *Curr Gene Ther* 2005; **5**: 573–81.
5. Little RF, *et al.* Activity of subcutaneous interleukin-12 in AIDS-related Kaposi sarcoma. *Blood* 2006; **107**: 4650–7.

Intrinsic Factor

Antianemic Factor; Castle's Intrinsic Factor; Gastric Intrinsic Factor.

Внутренне Присуший Фактор

CAS — 9008-12-2.

Profile

Intrinsic factor, a glycoprotein secreted by the parietal glands in the stomach, is required for absorption of vitamin B₁₂ in the small intestine. Deficiency in intrinsic factor leads to vitamin B₁₂ deficiency disorders and pernicious anaemia.

Intrinsic factor is given orally with cyanocobalamin in the Schilling test in the differential diagnosis of pernicious anaemia (see p.1981). It is also included in some oral preparations containing cyanocobalamin, presumably as an aid to absorption.

Difficulty in obtaining intrinsic factor and/or radio-labelled cyanocobalamin for the original Schilling test prompted studies using a recombinant human intrinsic factor in a new vitamin B₁₂ absorption test. Initial results with this recombinant form were promising.¹

1. Hvas A-M, *et al.* The effect of recombinant human intrinsic factor on the uptake of vitamin B12 in patients with evident vitamin B12 deficiency. *Haematologica* 2006; **91**: 805–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: **Braz.**: Hemofert; **Indon.**: Biosanbe; **Philipp.**: Tri-HEMIC; **USA**: Anemagen; Chromagen; Contrin; Ferotinsic; Fetrin; Livit-rinsic-f; Pronemia Hematinic; Tri-HEMIC; Trinsicon.

Inulin (BAN)

Alant Starch; Inulina.

CAS — 9005-80-5.

Pharmacopoeias. In *Br.* and *US*.

BP 2008 (Inulin). A polysaccharide obtained from the tubers of *Dahlia variabilis*, *Helianthus tuberosus*, and other genera of the family Compositae. It is a white, odourless or almost odourless, hygroscopic, amorphous, granular powder. Slightly soluble in cold water, but freely soluble in hot water; slightly soluble in organic solvents.

USP 31 (Inulin). A polysaccharide which, on hydrolysis, yields mainly fructose. A white, friable, chalk-like, amorphous, odourless powder. Soluble in hot water; slightly soluble in cold water and in organic solvents. A 10% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Pharmacokinetics

Inulin is rapidly removed from the circulation after intravenous doses but is not metabolised. A trace may be found in the bile and may cross the placenta, but it is mainly eliminated in the urine by glomerular filtration without secretion or reabsorption in the renal tubule.

Uses and Administration

Inulin is used intravenously as a diagnostic agent to measure the glomerular filtration rate. Although an accurate test, it is complex to perform and is generally reserved for research purposes. Crystals of inulin may be deposited on storage of the injection; they should be dissolved by heating for not more than 15 minutes before use and the injection cooled to a suitable temperature before use.

Polyfructosan, an inulin analogue of lower average molecular weight, has been used similarly.

Preparations

BP 2008: Inulin Injection;

USP 31: Inulin in Sodium Chloride Injection.

Proprietary Preparations (details are given in Part 3)

Austria: Inutest; **Cz.**: Inutestf.

Multi-ingredient: **Chile**: Reduc-Te; Reducform-F; **Fr.**: Actilyul; Effadiane relipdantes; **Ital.**: Enterolactis; Lactolas; Naturalass; Snellf.