For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

VIZYLAC GG

1. Generic name

Lactobacillus rhamnosus GG (ATCC 53103) Mouth Melt Granules

2. Qualitative and quantitative composition

Each sachet (0.75g) contains:
Lactobacillus rhamnosus GG (ATCC 53103) - 6.0 Billion CFU
Ingredients*: Lactobacillus rhamnosus* GG (ATCC 53103), Bulking agent (1400; 967; 420(i)), Sweetening agent (960).
Nature identical vanilla flavouring substance.
Appropriate overages added to compensate loss on storage.

3. Dosage form and strength

Mouth melt granules and 6.0 billion CFU.

4. Clinical particulars

4.1. Therapeutic indication

Probiotic Food

4.2. Posology and method of administration

Direction for use: The content of this sachet can be consumed directly or can be mixed with 5 ml of lukewarm water and consumed.
Polyols may have laxative effects.
Not for medicinal use
Probiotics are microorganisms with potential health benefits. They may be used to prevent and treat antibiotic-associated diarrhea and acute infectious diarrhea. They may also be effective in relieving symptoms of irritable bowel syndrome, and in treating atopic dermatitis in children. Species commonly used include *Lactobacillus* specie.
Lactobacillus rhamnosus GG is a bacterium that exists naturally in the body, primarily in the intestines. *Lactobacillus rhamnosus* GG has been used as a probiotic, or "friendly bacteria," to prevent the growth of harmful bacteria in the stomach and intestines.
Lactobacillus rhamnosus GG has been used in alternative medicine as a likely effective aid in treating or preventing diarrhea caused by rotavirus in babies and children.
This product has also been used as a possibly effective aid in treating colic in babies, and in preventing diarrhea in children that can occur while taking antibiotics.
In adults, *lactobacillus rhamnosus* GG is possibly effective in preventing diarrhea during a hospital stay, while you are receiving chemotherapy, or during travel to foreign countries ("traveler's diarrhea").
Other conditions for which *lactobacillus rhamnosus* GG is possibly effective include treating irritable bowel syndrome, ulcerative colitis, or vaginal infections caused by bacteria. This product may also lower the risk of lung infections in children who attend daycare centers.
Lactobacillus rhamnosus GG has also been used to treat **Crohn's disease**, lactose intolerance, or vaginal yeast infections. However, research has shown that *lactobacillus rhamnosus* GG may not be effective in treating these conditions.

Other uses not proven with research have included treating **cold sores**, urinary tract infections, **high cholesterol**, **indigestion**, **cold symptoms**, and boosting the immune system.
This product has also been used as a possibly effective aid in treating **colic** in babies, and in preventing diarrhea in children that can occur while taking **antibiotics**.
In adults, *lactobacillus rhamnosus* GG is possibly effective in preventing diarrhea during a hospital stay, while you are receiving **chemotherapy**, or during travel to foreign countries ("**traveler's diarrhea**").
It is not certain whether *lactobacillus rhamnosus* GG is effective in treating any medical condition. Medicinal use of this product has not been approved by the FDA. *Lactobacillus rhamnosus* GG should not be used in place of medication prescribed for you by your doctor.
Lactobacillus rhamnosus GG is often sold as an herbal supplement. There are no regulated manufacturing standards in place for many herbal compounds and some marketed supplements have been found to be contaminated with toxic metals or other drugs. Herbal/health supplements should be purchased from a reliable source to minimize the risk of contamination.
Lactobacillus rhamnosus GG may also be used for other purposes not listed in this product guide.
Dosage: 1 – 2 sachets daily or as directed by healthcare professionals.
To be given only under medical advice by physician/certified dietician/nutritionist for children below 5 years.
Usual Adult Dose for:
For general use as a dietary supplement
Dose:1 sachet per day. Concurrently with antibiotics.
Dose: 1 sachet twice a day throughout antibiotic therapy and for one week after antibiotic therapy.
Traveling
Dose: 1 sachet twice daily throughout the trip
It is best to start 2 to 3 days prior to travel
Usual Paediatric Dose for Dietary Supplement
Dose: One-half to one sachet per day.
Open the sachet and stir the contents into a cool drink or mix into baby food or applesauce.
Uses and Effectiveness
Most of the identified benefits of probiotics relate to GI conditions, including antibiotic-associated diarrhea, acute infectious diarrhea, and irritable bowel syndrome (IBS) (*Table 1*). Some studies indicate a benefit in treating atopic dermatitis in children. Probiotics are also commonly used for conditions including vaginal candidiasis, *Helicobacter pylori* infection of the stomach, inflammatory bowel disease, and upper respiratory infections. These uses are not addressed in this review.
Table 1

Key Points About Probiotics Effectiveness*	Probably effective for antibiotic-associated diarrhea and infectious diarrhea; possibly effective for irritable bowel syndrome symptom reduction and atopic dermatitis for at-risk infants
Adverse effects	Common: flatulence, mild abdominal discomfort
	Severe/rare: septicemia

Interactions	None known
Contraindications	Short-gut syndrome (use with caution); severe immunocompromised condition
Dosage	Dosage should match that used in clinical studies documenting effectiveness: 5 to 10 billion CFUs per day for children; 10 to 20 billion CFUs per day for adults
Bottom line	Safe and effective for preventing and treating antibiotic-associated diarrhea and infectious diarrhea.

CFU = colony-forming unit.

*— *Effectiveness depends on probiotic strain and dosage*.

ANTIBIOTIC-ASSOCIATED DIARRHEA

A meta-analysis of 19 recent studies showed that probiotics reduced the risk of developing antibiotic-associated diarrhea by 52 percent (95% confidence interval [CI], 0.35 to 0.65; $P < .001$).[5] The benefit was greatest when the probiotics were started within 72 hours of the onset of antibiotic treatment. The species that were evaluated included strains of *L. rhamnosus, L. acidophilus*, and *S. boulardii*. The authors found that the magnitude of the effect did not differ significantly among the strains, although a limited number of strains were represented.

In a second meta-analysis of 25 randomized controlled trials (RCTs; n = 2,810), various probiotics were given to prevent or treat antibiotic-associated diarrhea.[6] The relative risk (RR) of developing antibiotic-associated diarrhea with probiotics was 0.43 (95% CI, 0.31 to 0.58; $P < .0001$), which was a significant benefit when compared with placebo. This analysis also found that *L. rhamnosus, S. boulardii*, and mixtures of two or more probiotic species were equally effective in preventing antibiotic-associated diarrhea. The mean daily dosage of the bacterial species in these studies was 3 billion colony-forming units (CFUs), but studies using more than 10 billion CFUs per day showed that these dosages were significantly more effective. The dosages of *S. boulardii* were 250 mg or 500 mg per day.

The same meta-analysis examined the prevention and treatment of *Clostridium difficile* disease. Six RCTs were analyzed and revealed a prevention benefit for participants taking probiotics. The RR of developing *C. difficile* disease was 0.59 (95% CI, 0.41 to 0.85; $P = .005$). Only *S. boulardii*showed a reduction in recurrence with treatment.

A meta-analysis of six RCTs (n = 766) that focused on preventing antibiotic-associated diarrhea in children found a reduction in risk from 28.5 to 11.9 percent (RR = 0.44; 95% CI, 0.25 to 0.77) in those using probiotics. This analysis showed no difference among *L. rhamnosus* GG, *S. boulardii*, and a combination of *Bifidobacterium lactis* and *Streptococcus thermophilus*. However, a recent Cochrane review found that although a per-protocol analysis of 10 trials showed a benefit in prevention of antibiotic-associated diarrhea in children, a more sensitive intention-to-treat analysis failed to show a benefit.[8] The authors did find greater effectiveness in the studies that used dosages of more than 5 billion CFUs per day than those that used lower dosages, regardless of the type of probiotic.

Preliminary evidence suggests that probiotics delivered via fermented milk containing *L. casei* DN-114 001 and the yogurt starter cultures *L. bulgaricus* and *S. thermophilus* may be useful dietary components that can reduce the risk of antibiotic-associated diarrhea and *C. difficile* toxin formation in hospitalized patients.

ACUTE INFECTIOUS DIARRHEA

A Cochrane review examined 23 studies (n = 1,917) that used different types of pro-biotics to treat acute infectious diarrhea. Definitions of diarrhea and specific outcomes varied. The reviewers concluded that probiotics significantly reduced the risk of diarrhea at three days (RR = 0.66; 95% CI, 0.55 to 0.77; $P = .02$). The mean duration of diarrhea was also reduced by 30.48 hours (95% CI, 18.51 to 42.46 hours; $P < .00001$). This analysis included all causes of infectious diarrhea (e.g., viral diarrhea, traveler's diarrhea). The authors concluded that probiotics appear to be a useful adjunct to rehydration therapy in treating acute infectious diarrhea in adults and children.

A meta-analysis examining *S. boulardii* for treatment of acute diarrhea in children combined data from four RCTs (n = 619). The authors found that *S. boulardii* significantly reduced the duration of diarrhea when compared with the control group, for a mean difference of −1.1 days (95% CI, −1.3 to −0.8). However, a large trial (n = 571) comparing several probiotic preparations to oral rehydration solution concluded that *L. rhamnosus* GG or a combination of *Lactobacillus delbrueckii* subsp. *bulgaricus, S. thermophilus, L. acidophilus,* and *Bifidobacterium bifidum* was more effective than *S. boulardii* or oral rehydration therapy alone in reducing the duration and severity of acute diarrhea in children.

Another trial examined the prophylactic benefits of probiotics in preventing GI infections in children. In a double-blind, placebo-controlled RCT at 14 child care centers, infants four to 10 months of age (n = 201) were fed formula supplemented with *L. reuteri* SD2112, *B. lactis* Bb-12, or no probiotic for 12 weeks. Both probiotic groups had fewer and shorter episodes of diarrheal illness, with no change in respiratory illness. Effects were more prominent in the *L. reuteri* group, which had fewer absences, clinic visits, and antibiotic prescriptions during the study.

Therapeutic yogurts have also been studied in the prevention and treatment of community-acquired diarrhea in children. Although a benefit is suggested, more confirmatory studies are indicated.

A meta-analysis of 12 studies (n = 4,709) found a modest decrease in the risk of traveler's diarrhea, with an RR of 0.85 (95% CI, 0.79 to 0.91; $P < .0001$) in patients taking probiotics. No difference was found among organisms, including *S. boulardii* or mixtures of *Lactobacillus* sp. and *Bifidobacterium* sp.

IRRITABLE BOWEL SYNDROME

Although definitive evidence is still lacking, several studies have found probiotics to be effective in relieving symptoms of IBS, particularly abdominal pain and bloating. One study found a 20 percent reduction in symptoms of IBS with *Bifidobacterium infantis* 35624 at a dose of 1×10^8 CFUs compared with placebo in 362 patients. In another study, 50 children fulfilling the Rome II criteria for IBS were given *L. rhamnosus* GG or placebo for six weeks. *L. rhamnosus* GG was not superior to placebo in relieving abdominal pain, but there was a lower incidence of perceived abdominal distention ($P = .02$).

IBS symptoms may also be managed by adding components to patients' diets. One yogurt (Activia), which contains *Bifidobacterium animalis* DN-173 010, improved health-related quality of life scores and decreased bloating symptoms in patients with IBS.

ATOPIC DERMATITIS

There may be a role for probiotics as prophylaxis in the development of atopic dermatitis in high-risk infants. One double-blind, placebo-controlled RCT (n = 132) of children with

a strong family history of atopic disease administered *L. rhamnosus* GG (1×10^{10} CFUs) months. The incidence of diagnosis of eczema by two years of age was reduced by one half (23 percent in the probiotic group versus 46 percent in the placebo group [RR = 0.51; 95% CI, 0.32 to 0.84]). Follow-up visits at four and seven years of age showed no reduction in asthma, food allergy, or allergic rhinitis, suggesting that this intervention will not prevent other manifestations of atopy.

A larger study (n = 925) using *L. rhamnosus* GG combined with *L. rhamnosus* LC705, *Bifidobacterium breve* Bb99, *Propionibacterium freudenreichii* subsp. *shermanii* JS, and 0.8 g of galacto-oligosaccharides (newborns only) showed similar effectiveness for atopic dermatitis at two years of age.[23] A placebo-controlled study using *L. acidophilus* LAVRI-A1 administered to 231 newborns at high risk of atopic dermatitis failed to replicate this finding, possibly because of a different strain or dosage.[24]

Several small RCTs have shown some benefit in children with established atopic dermatitis treated with probiotics. In another study, 56 children six to 18 months of age with moderate or severe atopic dermatitis were recruited into a randomized, double-blind, placebo-controlled trial. The children were given a probiotic (1×10^9 *Lactobacillus fermentum* VRI-033) or an equivalent volume of placebo twice daily for eight weeks. A final assessment at 16 weeks showed a significant reduction in the Severity Scoring of Atopic Dermatitis (SCORAD) index over time in the probiotic group ($P = .03$) but not in the placebo group. Significantly more children receiving probiotics (92 percent) had a SCORAD index that was better than baseline at week 16, compared with the placebo group (63 percent; $P = .01$). However, other interventions to improve allergic symptoms have not been successful.

or placebo to mothers for two to four weeks prenatally and then to infants postnatal for six.

4.3 Contraindications

There are no absolute contraindications to probiotics comprised of *Lactobacillus* sp. But some may have an Allergies to *Lactobacillus rhamnosus*.

There are typically few or no adverse effects; flatulence or mild abdominal discomfort, usually self-limited, are reported occasionally. There have been reports of pathologic infection, including bacteremia with probiotic species following oral administration. These are rare, occurring in severely ill or immunocompromised hosts, or in children with short-gut syndrome. It is prudent to avoid probiotics in these patients, or to be aware of the risk of sepsis. A recent systematic review examined the safety of *L. rhamnosus* GG and *Bifidobacterium*sp. and concluded that the risk of sepsis is low, with no cases reported in any prospective clinical trial. There are no reports of sepsis or other pathologic colonization in healthy patients. There are also no known interactions with medications or other supplements.

4.4 Special warnings and precautions for use

Before using this product, tell the doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to pharmacist for more details.

If you have any of the following health problems, consult the doctor or pharmacist before using this product: diarrhea lasting more than 2 days (especially if you also have a high fever), weakened immune system (such as due to chemotherapy, HIV infection), recurring vaginal infections, recurring urinary tract infections.

Liquid products, foods, powders, or chewable tablets may contain sugar and/or aspartame. Caution is advised if you have diabetes, phenylketonuria (PKU), or any other condition

that requires you to limit/avoid these substances in your diet. Ask your doctor or pharmacist about using this product safely.

4.5 Drugs interactions

Antibiotic drugs interact with *LACTOBACILLUS*

Antibiotics are used to reduce harmful bacteria in the body. Antibiotics can also reduce friendly bacteria in the body. Lactobacillus is a type of friendly bacteria. Taking antibiotics along with lactobacillus can reduce the effectiveness of lactobacillus. To avoid this interaction, take lactobacillus products at least 2 hours before or after antibiotics.

Medications that decrease the immune system (Immunosuppressants) interacts with *LACTOBACILLUS*

Lactobacillus contains live bacteria and yeast. The immune system usually controls bacteria and yeast in the body to prevent infections. Medications that decrease the immune system can increase your chances of getting sick from bacteria and yeast. Taking lactobacillus along with medications that decrease the immune system might increase the chances of getting sick.

Some medications that decrease the immune system include azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD3, mycophenolate, tacrolimus, sirolimus, prednisone, corticosteroids (glucocorticoids), and others.

4.6 Use in special populations

Fertility, pregnancy and lactation

Pregnancy

We found no evidence that taking probiotics or prebiotics during pregnancy either increases or decreases the risk of preterm birth or other infant and maternal adverse pregnancy outcomes.

Breast-feeding

Because probiotics are rarely systemically absorbed, they are not expected to transfer into breast milk. One randomized control trial examined *Lactobacillus reuteri* levels in 174 colostrum samples after maternal and infant oral supplementation of this probiotic. Although higher in the active than in the placebo group, the prevalence of *L reuteri* in colostrum was low and not clinically important. Abrahamsson et al suggested that the most likely origin of *L reuteri* in colostrum was external contamination from the gastrointestinal tract. There are no published data regarding adverse effects in breastfed infants. In several of the studies previously mentioned, infants received probiotic therapy after delivery without an increase in adverse effects.

Fertility

Results indicated that *Lactobacillus* intermitted colonization of pathogenic strains that resulted in reinforcement of natural microflora and resurge fertility.

4.7 Effects on ability to drive and use machines

Although there is no evidence of lactobacillus on ability to drive and use machine probiotics have ability to decrease metabolic endotoxemia by restoring the disrupted intestinal mucosal barrier. Patient should be warned accordingly. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Probiotics are generally regarded as safe, and side effects in ambulatory care have rarely been reported. Bacterial translocation, sepsis, and the risk of carrying antibiotic resistance plasmids that may spread resistance to antibiotics have been reported. The latter has been reported for some probiotics, such as L. reuteri ATCC 55730 and Enterococcus faecium but not for LGG.

4.9 Overdose

If patient may has overdosed may suffer from serious symptoms such as passing out or trouble breathing.

5 PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

The underlying mechanisms of probiotic action are unclear but may include strengthening of the non-immunological gut barrier, pathogen growth inhibition and interference with adhesion, and enhancement of mucosal immune systems, as well as the systemic immune response. Probiotics appear effective in preventing and reducing the severity of a number of conditions, but there is insufficient evidence with respect to any suggested benefits from probiotics in prevention or therapy of ischaemic heart diseases, autoimmune disease or cancer.

5.2 Pharmacodynamic properties

There are various proposed mechanisms by which probiotic may protect the host from intestinal disorders. Probiotics have an antimicrobial effect through modifying micro flora, secreting antibacterial substances, competing with pathogens to prevent their adhesion, competing with nutrients necessary for pathogen survival, producing an antitoxin effect and reversing some of the consequences of infection on the gut epithelium – such as secretory changes and neutrophil migration. Inhibitory substances such as organic acids, hydrogen peroxide and bacteriocins inhibits bacterial metabolism or toxin produced by bacteria. They also block the receptor sites by competitive inhibition for bacterial adhesion sites on intestinal epithelial surfaces. In addition to that Probiotics also competes with pathogenic microorganisms for the nutrition. In C. difficile intestinal disease, S. boulardii protects through degradation of the toxin receptor on the intestinal mucosa. Other proposed mechanisms include strengthening tight junctions between enterocytes, increasing IG-A.
Production and stimulation of specific and nonspecific immunity. In sum, Probiotics are generally thought to affect the gastrointestinal tract and the associated CD (local) immune system. Several studies have been performed to investigate the effects of different probiotic bacteria. From these studies it has become clear that different strains of lactobacilli induce very different effects. In addition, effects seen in a certain human population with one strain of bacteria can often not be reproduced. This makes a final overall conclusion very difficult. Probiotic treatment is not known. The quality control of the commercialised probiotic food supplements, the exactness of the label and the indications need to be improved. More research on pharmacodynamic and pharmacokinetic aspects is also needed. Safety should be better assessed in pre-term, immunodeficient and immunocompetent individuals for any risk of overstimulation (or modification) of the immune system in susceptible subjects. The establishment of standards of identity for probiotic-containing food products will serve to accelerate their development and availability

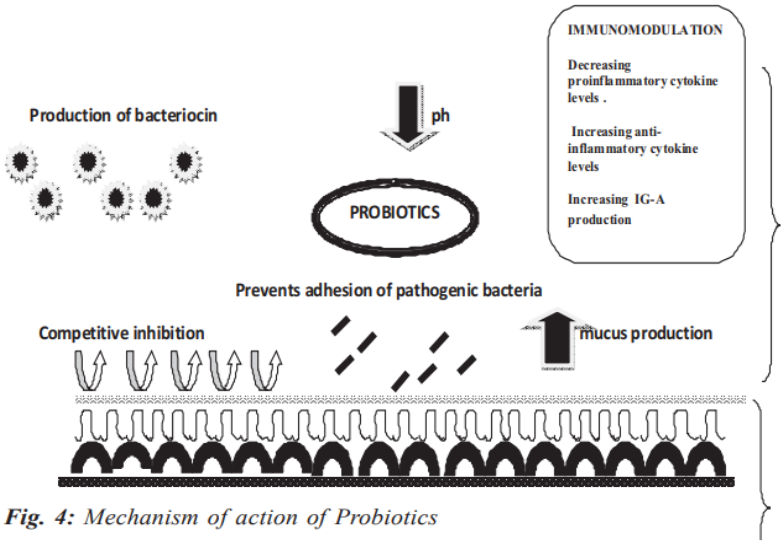

Fig. 4: Mechanism of action of Probiotics

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6–7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.

One weeks treatment with esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of H. pylori in approximately 90% of patients.

After eradication treatment for one week, there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

In a reported randomised, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10% respectively) were randomised to receive Nexium solution for infusion (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72-hour period, all patients received open label 40 mg oral Nexium for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the Nexium treated group compared to 10.3% for the placebo group. At 30 days' post-treatment, the occurrence of rebleeding in the Nexium treated versus the placebo treated group was 7.7% vs 13.6%.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine

tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.
An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long-term treatment with esomeprazole. The findings are considered to be of no clinical significance.
During long-term treatment with antisecretory drugs, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.
Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalised patients, possibly also *Clostridium difficile*.
Clinical efficacy
In two studies with ranitidine as an active comparator, Nexium showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.
In two studies with placebo as comparator, Nexium showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged >60 and/or with previous ulcer), including COX-2 selective NSAIDs.
Paediatric population
In a study in paediatric GERD patients (<1 to 17 years of age) receiving long-term PPI treatment, 61% of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or carcinoid tumours.

5.3 Pharmacokinetic properties

It been shown that some probiotic strains can adhere to cell lines such as CaCo2 or HT29. These epithelial cell lines are of colonic or intestinal origin. The cells are polarized like in an intestinal epithelium, and many characteristics and functions of a normal epithelium are expressed on the cells. They are therefore thought to be fair models to predict in vivo adhesion. Using other cell lines or colon tissues have also been proposed. The epithelial adhesion property differs between strains, and this property might be correlated with competitive exclusion properties and immunomodulatory activities in vivo. Until now, competitive exclusion properties of adhering strains have only been shown in vitro. Validation of the in vitro models with in vivo data is therefore warranted, and the possibility for a probiotic to adhere to the intestinal epithelium during its intestinal transit has to be studied. Survival of ingested probiotics to different sites of the gastrointestinal tract. The survival of ingested microorganisms differs among genus and strains. Some microorganisms are destroyed in the stomach while others have a high survival till feces. Lactobacillus bulgaricus and Streptococcus thermophilus have a poor intrinsic resistance to acid, and are destroyed within few minutes at pH 1 and in about 1 hr at pH 3. Pochart et al. observed that the concentrations of viable yogurt bacteria reaching the duodenum after ingestion of 430 g yogurt in healthy humans were around 105 cfu/ml. This survival represented approximately 1% of the ingested bacteria. Using a dynamic in vitro model, we observed that 26% of "ingested" L. bulgaricus survived passage through the stomach when the model simulated the pH and gastric emptying of yogurt. Pettersson et al. reported that viable yogurt bacteria reached the ileum in 1/4 of the subjects after ingestion of 500 ml

yogurt, and Lindwall & Fonden reported that after consumption of a yogurt containing 109 L. bulgaricus/g, the concentration of lactobacilli in the ileostomy bag was 105 to 106 cfu/ml. Using an intestinal intubation technique, we showed that one fifth of the lactase contained in yogurt bacteria survives till the end of the small bowel and participates to the digestion of lactose in the human gut. It is to note that this effect does not need the bacteria to be of human origin, and does not require that they survive in the GIT (but even rather that they lyse there, releasing then the lactase that they contain). As the survival of yogurt bacteria is low in the upper gastrointestinal tract, their survival and probiotic effects downstream (in the colon) are probably not relevant. The capacities of survival of L. acidophilus, L. reuteri, L. rhamnosus strain GG in acid conditions are higher than that of L. bulgaricus. About 1-10% of L. acidophilus ingested in fermented products were found to survive until the ileum in several human studies using intestinal intubation techniques. In one of our studies, the concentrations of lactobacilli flowing through the ileum after ingestion of a cup of milk product containing 108 cfu/ml of Yoplait-Al strain were 100 times higher than the concentrations after ingestion of a control meal; the passage lasted for more than 5 hr, and no permanent colonization of the small bowel was observed. Studies in healthy volunteers ingesting different probiotic preparations showed that concentrations of L. acidophilus, L. reuteri, L. rhamnosus strain GG reached around 106 cfu/g . Some Bifidobacterium sp. from fermented dairy products exhibited a high survival in the GIT i.e. 30% of the ingested bacteria could be recovered in the ileum and in feces (. Concentrations above 106 cfu/g in the small bowel and around 108 cfu/g in the colon were reached. After cessation of the oral administration of these probiotic strains, the kinetics of their elimination paralleled that of an inert marker indicating the absence of colonization. Several human studies were performed to describe the pharmacokinetics of Saccharomyces boulardii in man, a yeast which has proven efficient in decreasing the risk of antibiotic associated diarrhea and the risk of recurrence of Clostridium difficile colitis. About 60% of the ingested yeasts were recovered as dead cells in feces; the survival in feces was about 0.1%-which is about the same as what was measured with S. cerevisiae -; concentrations of living yeasts were above 105 cfu/g in the colon. Colonization of the gastrointestinal tract by probiotics? Some authors observed the persistence of some probiotic strains in the feces of a few subjects for longer periods than what can be expected from a "normal persistence" of a "normal person" with a "normal intestinal transit" (17, 25). This might indicate colonization, but this remains unproved. Probiotics are usually excreted within a few days after their ingestion in feces at the same rate or even quicker than a transit marker. However, Johansson et al. provided interesting results which suggest a colonization of the jejunal and rectal mucosa with alimentary lactobacilli (18). These authors administered a soup containing 19 different lactobacilli to healthy volunteers, and searched for colonization in the jejunum and rectum using probes on biopsies which were taken on days one and eleven after ingestion of the lactobacillus soup. Two strains of Lactobacillus plantarum were detected 11 days after their ingestion. One (Lp299) was of human origin; the other (Lp299v) had been initially isolated from a sour dough. Confirmation of this result and testing of other strains with the same methodology seems an important issue both for fundamental research in intestinal ecology and for safety aspects of probiotics.

6. Nonclinical properties

Safety assessment

These include pathogenicity, infectivity and virulence factors comprising toxicity, metabolic activity and intrinsic properties of the microbes. The classic risk assessment approach like that used for pathogens could be misleading for probiotic microbes. Factors such as adhesion which may lead to colonization are regarded as virulent factors in studies

of pathogens. In contrast, most probiotic Lactobacilli strains are initially selected on the basis of their ability to adhere to the various mucosa models. However, some lactobacilli may produce biogenic amines such as tyramine and histamine, but no such potentially harmful compounds have been found in fermented milk prepared with probiotic lactobacilli. Some strains of probiotic lactobacilli are known to produce bacteriocins that are toxic to other pathogenic bacteria, but such molecules are nontoxic to humans and truly meet the requirements for food preservatives. Few cases of lactobacillemia have been reported in at-risk populations, but lactobacilli present an essentially negligible biological risk. Recent review by Bernardeau *et al*. analyzed the current European guidelines for safety assessment in food/feed and concluded that they are not relevant for the *Lactobacillus genus*. They proposed new specific guidelines, beginning by granting a 'long-standing presumption of safety' status to *Lactobacillus genus* based on its long history of safe use. Then, based on the available body of knowledge and intended use, only such tests as are useful will be necessary before attributing 'qualified presumption of safety status.

While most of the species and genera are apparently safe, certain micro-organisms may be problematic, particularly the enterococci, which may harbour transmissible antibiotic resistance determinants and bacilli, especially those belonging to the *Bacillus cereus* group that are known to produce enterotoxins and an emetic toxin. The history and the current legislation in the European Union on probiotics feed additives including the requirements for the safety assessment for the target animal species, consumers, workers and environment have been documented. In an opinion article, Reid made recommendations based on current understanding of scientific, clinical and regulatory issues with a special focus on safety. This is based on the fact that each year, >20 billion doses of probiotics are used by healthy people and by those diagnosed with a range of medical conditions. Compared to many pharmaceutical agents, probiotics are well tolerated and extremely safe and serious adverse effects rarely occur.

Toxicity-Related Assessment

Conventional toxicology and safety evaluation that is usually employed for pharmaceutical products may be of limited value in assessing the safety of probiotics. Toxicity testing has grown to maturity and presently a systematic approach is used to establish whether adverse effects occur and if so to investigate at level of exposure such adverse effects remain absent and whether a dose-response relationship can be established. On the basis of these findings, a safety evaluation may be performed to assess at what levels of exposure humans may not experience any risk. The safe levels of exposure for humans has been identified for individual chemicals in the risk assessment of compounds with known toxicological profiles. Attempt to develop safe level of exposure' to probiotic microbes may be complicated in that the microbial cell and human cell ratio is already 9:1. The Threshold of Toxicological Concern (TTC) will refers to the establishment of a level of exposure for existing probiotic microbes, whether or not there are probiotic-specific toxicity data, below which there would be no appreciable risk to human health.

Applying 'probiotic-threshold' as it is done in classical pharmacology to define a level above which a desired effect is seen may be difficult to establish as probiotic microorganisms are part of the human microbiota. If probiotic toxicology is to be developed, then a 'threshold' defined as a dose at or below which a response is not seen in an experimental setting will have to be evaluated.

Establishing proof of absence of an effect at such a dose in absolute terms is scientifically and practically demanding. This approach though, may seem promising with the cell signaling experimental cascades that are now available. Recent data indicate that enteric

bacteria use several quorum-sensing mechanisms including the LuxR-I quorum-sensing system, the LuxS/AI-2 system and the AI-3/epinephrine/norepinephrine system to assess their environment and to recognize the host environment. These systems allow bacteria to communicate across species boundaries and the AI-3/epinephrine/norepinephrine system is involved in inter-kingdom signaling. Given the enormous number and diversity of bacteria inhabiting the gastrointestinal environment, it should not be surprising that the members of this community especially beneficial probiotics microbes communicate amongst themselves and with the host itself to coordinate a variety of adaptive processes with potential pathogens such as *Escherichia coli* and *Salmonella* (Walters and Sperandio, 2006).

Some studies have attempted to mimic or devise means of testing the toxicity profile of probiotic lactobacilli and Bifidobacterium with mixed results. *Lactobacillus* and *Bifidobacterium* species have not been reported to produce very harmful compounds such as ammonia, indol, phenols and amines by metabolic activities. Araya-Kojima *et al*. (1996) measured the enzyme activities related to the consumption and generation of ammonia in *Bifidobacterium* sp. of human origin. Compared with other bacteria of the intestinal microbiota, *Bifidobacterium* sp. have a lower deaminase activity involved in the production of ammonium from amino acids but a higher ammonia assimilation activity. Zhou *et al*. (2000), studied acute oral toxicity, bacterial translocation and intestinal mucosal pathology in BALB/c mice inoculated with three probiotics strains (*Lactobacillus rhamnosus* HN001-DR20^{TM}, *Lactobacillus acidophilus* HN017 and *Bifidobacterium lactis* HN019-DR10$^{®}$).

The three probiotic strains had no adverse effect on the general health status, feed intake, body weight gain and intestinal mucosal morphology. The study recovered no viable bacteria from blood and tissue samples. Lethal dose (LD_{50}) of the strains was more than 50 g^{-1} kg^{-1} day^{-1} for the tested mice. Pavan *et al*. (2003) evaluated the persistence of strains of Lactic Acid Bacteria (LAB) in the digestive tracts of mice, their immunomodulation capacity and their safety in healthy animals and in a colitis model. Following daily administration of 10^9 cfu of viable LAB orally, intragastrically, or intrarectally, the animals' feces were examined for bacterial excretion and cytokines were quantified in intestinal samples by quantitative reverse transcription-PCR. The level of bacterial translocation was assessed in healthy mice and in mice suffering from colitis induced by 2, 4, 6-trinitrobenzene sulfonic acid (TNBS). Irrespective of the route of administration, the potential probiotic strain *Lactobacillus plantarum* NCIMB8826 was found to persist for up to 10 days in the digestive tracts of mice. This strain did not induce detrimental effects in healthy or in TNBS-treated animals, as was reflected by the absence of weight loss, intestinal inflammation, modification of cytokine levels in the ileum and colon (healthy mice) and bacterial dissemination (healthy and colitic animals).

In another animal model toxicity study, Daniel *et al*. fed high doses (10^{10}cfu) of **lactic acid** bacteria strains to healthy and to mice treated with 2, 4, 6-trinitrobenzene sulfonic acid (TNBS) to induce acute colitis. There was no bacterial translocation to extra-intestinal organs in both the healthy and TNBS-treated mice; instead oral administration of *Lactobacillus salivarius* had a significant preventive effect on colitis in mice. In contrast, *L. paracasei* exacerbated colitis under severe inflammatory conditions and translocated to extra-intestinal organs. This recent finding indicated that toxicity and or translocation to visceral organs may be dependent on the health condition and species specificity.

Some concerns have equally been raised in terms of transfer of antibiotics resistant genes to the probiotic microbes in the gastrointestinal tract. Saarela *et al*. investigated the effects of oral therapy with doxycycline, a tetracycline group antibiotic, on the gastrointestinal (GI)

survival and tetracycline susceptibility of probiotic strains *Lactobacillus acidophilus* LaCH-5 and *Bifidobacterium animalis* subsp. lactis Bb-12. Although doxycycline consumption did not have a large impact on GI survival of the probiotics, it had a detrimental effect on the bifidobacteria and on the diversity of the dominant faecal microbiota. A higher proportion of tetracycline-resistant anaerobically growing bacteria and bifidobacteria was detected in the antibiotic group than in the control group. The study reported that concomitant ingestion of probiotic *L. acidophilus* LaCH-5 and *B. animalis* subsp. lactis Bb-12 with the antibiotic did not generate a safety risk regarding the possible GI transfer of tetracycline resistance genes to the ingested strains.

7. Description

Cream colour granules with characteristic odour.
The excipients used are *Lactobacillus rhamnosus* GG (ATCC 53103), Bulking agent (1400; 967; 420(i)), Sweetening agent (960).
Nature identical vanilla flavouring substance.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not available

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

VIZYLAC GG is available in 0.75g sachet

8.4. Storage and handing instructions

Store below 25°C, protected from moisture and direct sunlight

9. Patient Counselling Information

You have been prescribed a probiotic capsule to reduce your risk of developing a bowel infection called Clostridium difficile (otherwise known as C. diff). C. diff is an infection which can occur after you have received antibiotics for another infection which then disrupt the normal ("good") bacteria in your gut. This then allows the problem C. diff bacteria to grow in your gut, where it can lead to diarrhoea which in some cases can be very severe. The probiotic capsule contains a mixture of several "good" bacteria which are intended to stop the C. diff from causing a problem whilst you are taking the antibiotics. Probiotics are already used in many NHS trusts across the country to reduce the C. diff risk. Who should be taking the probiotic? We know that certain people are at more risk from C. diff infection and therefore these are the people who will be given the probiotic at the same time that they are prescribed antibiotics. This includes people who are:

- over 65 years
- OR over 18 years AND with one of the following risk factors:
- Past C. diff infection
- On a prolonged antibiotic course for more than 7 days
- People prescribed proton pump inhibitors (stomach acid suppressing tablets e.g. omeprazole, lansoprazole)
- History of multiple antibiotic courses during or prior to admission

If you fall into one of these groups and are prescribed an antibiotic course, probiotics can be prescribed by your medical team to take during the antibiotic course and for 5 days afterwards. If you go home before the end of the antibiotic course and the 5 days afterwards, the probiotics will be discontinued at discharge because it is while you are in hospital that the greatest risk of picking up the C. diff bacteria occurs.

Who should not be taking the probiotic? Some people will not be prescribed the probiotic even if they fall into one of the above groups because of other medical conditions they have. For example:

- People who have problems with their immune system or who are taking drugs that could stop their immune system from functioning effectively, should not usually take the probiotic.
- People with bowel perforation (hole in the gut) or conditions with a high risk of bowel perforation should also not take the probiotic.

With these conditions, there may be a higher risk of the probiotic bacteria themselves causing an infection, although this is very rare.

If the medical team looking after you think you are at very high risk of C. diff infection they may still prescribe you the probiotic even if you have problems with your immune system as the potential benefit in reducing your C. diff infection risk may outweigh the very small risk of the probiotic causing a problem.

To be given only under medical advice by physician/certified dietician/nutritionist for children below 5 years.

Potential side effects:

Possible side effects include: abdominal cramping, nausea, fever, soft stools, flatulence and taste disturbance. However, these are also common effects of antibiotics and there is evidence that these symptoms are actually less likely in people taking a probiotic with their antibiotics compared to those on antibiotics without taking a probiotic.

How to take the probiotic:

The probiotic capsule is taken just once a day, with or before a meal. The capsule contents can be mixed with other food/fluid if you are unable to swallow tablets or have a feeding tube in place.

10. Details of manufacturer

Manufactured in India by:
Allianz Biosciences Private Limited
55/1, 2 & 3, Whirlpool road, Thiruvandarkoil, Puducherry-605 102

11. Details of permission or licence number with date

Licence No.: 10017045000128 issued on date 08.10.2018

12. Date of revision

Oct-20

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