Introduction	**Brand Name :** Sporlac **Qik** **Therapeutic Category – GI Care** The term “probiotic” has been firstly defined by Fuller as “a live microbial feed supplement which beneficially affects the host by improving its intestinal microbial balance”. His definition has been extended to health and probiotics and were redefined as “live micro-organisms that, when administered in adequate amounts, confer a health benefit to the host”. The intestine contains a complex and dynamic microflora, including more than 2,000 micro-organism species coexisting in a complex equilibrium with the host. This microflora has various effects, including metabolic activities, trophic effects on the intestinal epithelium, interactions with the host immune system and acts as a barrier to prevent colonization by opportunistic and pathogenic micro-organisms. The immune system and particularly the gut-associated lymphoid tissues provides the host with protective mechanisms against pathogen invasion across the intestinal mucosal surface. However, disequilibrium in the gut microflora ecology and in the immune response could induce gastrointestinal diseases. Saccharomyces boulardii, isolated from lychee fruit by Henri Boulard in the 1920s, belongs to the Saccharomyces genus, which is commonly used in several food processes including beverages and bread fermentation. This yeast is frequently prescribed in a lyophilized form as a biotherapeutic agent. Controlled clinical trials have shown that oral administration of S. boulardii could treat or prevent gastrointestinal diseases such as antibiotic-associated diarrhea , recurrent Clostridium difficile-associated diseases, traveler's diarrhea, children acute diarrhea , enteral tube acute diarrhea in children, enteral tube feeding-associated diarrhea , AIDS-associated diarrhea, intestinal bowel disease such as Crohn’s disease and ulcerative colitis and irritable bowel syndrome.
Bacillus coagulans Characteristics	Bacillus coagulans is a rod-shaped, gram-positive, non-pathogenic spore-forming bacteria. A facultative anaerobe that grows at 37°C, has the ability to survive at temperatures of up to 90°C due to its spore forming ability [endospore]. As the organism is administered in a spore form, the organism is resistant to changes in the pH both in the stomach and the intestines. Both in-vitro and in-vivo studies have shown that the organism is tolerant to bile acids. The spores germinate and proliferate within the GI tract within a few hours after ingestion, Bacillus coagulans, is metabolically active and is involved in the production of L (+) Lactic acid, preventing the growth of pathogens and allows the growth of Bacillus coagulans alone. In addition to lactic acid, B. coagulans also produces bacteriocins [proteins that exhibit antimicrobial properties], against both gram positive and negative organisms. B. coagulans, does not colonize the gastro-intestinal tract. On discontinuation of therapy, Bacillus coagulans is slowly excreted from the system, usually within 7 days. Questions regarding the safety of the product have been raised by many Physicians, but safety and efficacy studies conducted on rodent models for a generation have demonstrated no adverse effects. Centuries of consumption of fermented products, such as curds and kefir have had no toxic effects on humans, thus making the use of probiotics a viable therapeutic option for treating both acute and chronic disorders.
Saccharomyces boulardii Characteristics	Saccharomyces boulardii is a non-pathogenic yeast which was isolated from lychees in Indochina, and which grows at the unusually high temperature of 37^{o} .It is commercially available as a freeze-dried viable preparation and is the only yeast with which double-blind studies have been carried out. Saccharomyces boulardii survives gastric acid and bile and can be detected alive throughout the entire digestive system if it is given daily in its freeze-dried form. Two to five days after administration, the yeast becomes undetectable in the faces. Saccharomyces boulardii is intrinsically resistant to antibacterial antibiotics. Concomitant administration of Ampicillin, Nystatin and Clindamycin in human volunteers, increase the fecal concentration of yeast cells recovered. The pharmacodynamics of Sacrharomyces boulardii involve three different aspects: a direct antagonistic effect, an anti-secretory effect, by acting specifically on the binding of toxins to intestinal receptors, and a trophic effect, by stimulating enzymatic activities and intestinal defense mechanisms. Oral Saccharomyces boulardii induces several cellular and humeral immunologic changes in the peripheral blood of healthy volunteers. Saccharomyces boulardii is a non-bacterial biotherapeutic agent, and is the only biotherapeutic agent with systematic convincing data from double-blind studies. Results show significant efficacy in the prevention and treatment of acute diarrhea. The WHO considers Saccharomyces boulardii to be a possible treatment for recurrent Clostridium difficile colitis.

Clinical Overview & Mechanism of Action	**Effects of Saccharomyces boulardii on Gastro-Intestinal Diseases** The efficacy of S. boulardii in the prevention and the treatment of gastrointestinal diseases which induce diarrhea have been assessed by clinical trials. Diarrhea is defined as frequent watery stools resulting from impaired fluid and electrolyte absorption in the intestinal lumen and is usually caused by pathogenic micro-organisms. Studies revealed the anti-diarrheal effects of the yeast which reduce the duration and the frequency of diarrhea after oral administration. 1. **Antibiotic-Associated Diarrhea** - Antibiotic-associated diarrhea (AAD) is an acute inflammation of the intestinal mucosa caused by the administration of antibiotics and resulting in the disruption of the intestinal microflora. Clostridium difficile infection caused 10-20% of AAD and 95% of pseudomembranous colitis. Other infectious organisms causing AAD include Clostridium perfringens and Staphylococcus aureus. The risk factors to develop AAD are multiple: Host factors, anti-biotherapy and exposure to nosocomial pathogens. Several meta-analyses were performed to evaluate the efficacy of probiotics for the prevention of AAD. These studies concluded that S. boulardii is effective in preventing AAD in adults and children 2. **Recurrent Clostridium Difficile-Associated Diseases -** Treatment of Clostridium difficile-associated diseases with metronidazole or vancomycin is effective, but in few patients, the disease recurs after the anti-biotherapy. Several clinical trials have shown the efficacy of S. boulardii in combination with antibiotics for treating relapses of diarrhea and colitis. S. boulardii, Lactobacillus rhamnosus GG and probiotics mixtures) in the prevention of AAD and the treatment of Clostridium difficile-diseases. The authors concluded that the three types of probiotics significantly reduced the development of AAD but only S. boulardii was shown to be effective for Clostridium difficile-associated diseases 3. **Traveler's Diarrhea** - Traveler's diarrhea is the most frequent disorder encountered by persons travelling from one region to another, especially from low risk zones to areas , where contamination of food and water is high. Enterotoxigenic E. coli, Shigella and Salmonella account for about 80% of acute traveler's diarrhea as an identified pathogen. The treatment should begin at least 5 days prior to travel and continue for the entire duration of the journey. A study was performed to assess the efficacy of probiotics in the prevention of traveler's diarrhea and the authors concluded that S. boulardii and a mixture of Lactobacillus acidophilus have shown clinical efficacy in prevention of traveler's diarrhea. 4. **Acute Diarrhea in Children** - Diarrheal diseases are a leading cause of childhood morbidity and mortality in developing countries The etiology of acute diarrhea in children includes infections of the gastrointestinal tract due to bacteria, viruses or protozoa, systemic infections, malabsorption disorders, nutritional deficiency, allergy and intolerance to food or drugs. There are several randomized placebo-controlled studies showing the efficacy of S. boulardii in the management and prevention of acute childhood diarrhea. Data generated during the course of studies has shown that S. boulardii reduces the episodes of diarrhea significantly and the duration and the risk of prolonged diarrhea, normalizing the stool consistency. 5. **Diarrhea in Patients with Total Enteral Feeding** - Diarrhea is the most frequent complication in enteral tube feeding. Alterations in the colonic microflora have been identified in patients receiving enteral tube feeding and these changes may be associated with the diarrhea incidence. S. boulardii can be used to prevent these negative alterations and to reduce the diarrhea incidence and reduce the length of diarrhea 6. **AIDS-Associated Diarrhea** - Acquired immune deficiency syndrome (AIDS) is a viral infection characterized by immune cell dysfunction and subsequent immunodeficiency, as well as intestinal disorder. Administering have shown that administering 3g/day, for 7 days alone reduces incidence of diarrhea. Combinations with other probiotics have been studied and L. sporogenes with S, boulardii have shown excellent clinical benefits in reduction in the number of episodes of diarrhea. 7. **Inflammatory Bowel Diseases - Ulcerative colitis (UC) and Crohn's disease (CD)** - The primary constituents of inflammatory bowel disease (IBD) are precipitated by a complex interaction of environmental, genetic, and immunoregulatory factors. Regardless of the underlying genetic predisposition, a growing body of data implicates a dysfunctional mucosal immune response to commensal bacteria in the pathogenesis of IBD, especially CD. Possible triggers include a chronic inflammatory response precipitated by infection with a particular pathogen or virus or a defective mucosal barrier. Intestinal inflammation in ulcerative colitis is primarily limited to the colon, whereas the whole gastrointestinal tract can be involved in Crohn's disease. In pilot studies conducted in patients, administration of S. boulardii in addition of conventional therapy was found superior to placebo in promoting reduction of bowel movements In other clinical trials conducted, in patients, the preventive effect of S. boulardii was evaluated in relapses of Crohn's disease (Guslandi et al.,2000). After six months, patients treated with mesalamine alone (3 g/d) presented more clinical relapses compared to patients receiving S. boulardii (1 g/d) plus mesalamine (2 g/d). The same author evaluated the effectiveness of S. boulardii in the treatment of ulcerative colitis in 25 patients. Administration of S. boulardii (750 mg/d) plus mesalamine for 4 weeks resulted in clinical remission for 68% of patients. In IBD, NO production exerts inflammatory effects on the GI tract due to conversion of L-Arginine to NO due to a series of bio-chemical reactions. NO is released through conversion of L-arginine to NO and L-citrulline. This reaction is catalyzed by three isoforms of the nitric oxide synthase (NOS): Neuronal NOS, endothelial NOS and inducible NOS. The iNOS activity is up-regulated during immune activation and can result in the synthesis of high levels of NO. S. boulardii inhibitory effect in iNOS activity was displayed in the rat castor oil-induced diarrhea model. The citrulline level (a marker of NO production) was increased in the colon of rats whereas S. boulardii administration was shown to block this production. The same effect is reported with the iNOS inhibitor. These results suggest that iNOS inhibition by S. boulardii may be beneficial in the treatment of diarrhea and/or IBD associated with overproduction of NO. 8. **Irritable bowel syndrome (IBS)** - A chronic disorder involving a combination of abdominal pain and change in bowel habit and bloating. Recent evidence suggests a role of the microflora in IBS pathogenesis. In a double-blind, placebo-controlled study conducted in 34 patients with predominant episodes of diarrhea, treatment with S. boulardii decreased the daily number of stools and improved their consistency. 9. **Other Benefits of Saccharomyces boulardii** - These effects have been assessed in several studies and showed that S. boulardii exerts beneficial mechanisms in animal models displaying IBD as well as in pathogenic or opportunistic micro-organism infection models such as Clostridium difficile, Vibrio cholerae, Escherichia coli, Salmonella enterica subspecies enterica serovar, Typhimurium, Shigella flexneri, Citrobacter rodentium and Candida albicans. These mechanisms include the modification of host cell signaling pathways implicated in proinflammatory response and in hydroelectrolytic secretion, the stimulation of host immune defenses, the neutralization of bacterial toxins and the decrease of bacterial adherence to intestinal epithelial cells, the maintenance of membrane permeability and the inhibition of

	pathogen translocation. 10. **In Diarrhea of Varied Etiology –** The efficacy of S. boulardii, is well established in a number of clinical studies, both in adults and children. The mechanisms that play a vital role in controlling have been identified, are: **Neutralization of Bacterial Toxins** - It has been shown that S. boulardii has the capacity to release factors which neutralize bacterial toxins and decrease the deleterious effects of infectious pathogens.S. boulardii produces a protease exerting a proteolytic activity on toxins produced by the pathogenic bacteria. This proteolysis results in the inhibition of toxins binding on their intestinal receptors. Thus S. boulardii treatment enhances transepithelial resistance, epithelial barrier integrity and decreases hydroelectrolytic secretions in both rat ileum and colonic mucosa. 11. **Maintenance of Epithelial Barrier Integrity** - Several pathogenic microorgansims such as Shigella, Enterohemorrhagic and entero-pathogenic E. coli have mechanisms of infection characterized by bacterial adhesion to the intestinal mucosa resulting in alteration of tight-junctions, disruption of membrane permeability and enterocyte secretion of pro-inflammatory cytokines. S. boulardii acts on the epithelial barrier in improving tight junctions structure and in restoring membrane permeability disrupted by infectious pathogens. Results demonstrate that S. boulardii enhances the cell ability to restore tight-junctions structure and barrier permeability. **12. Additional Effects** **Decrease of Bacterial Adhesion To Intestinal Epithelial Cells –** S. boulardii, may have a role in decreasing, bacterial adhesion of pathogenic bacteria. **Cytokine inhibition and Anti-inflammatory Effects -** Several experimental studies showed that S. boulardii interferes with the host cell signaling pathways and decreases the expression of inflammation-associated cytokines such as interleukin 8 (IL-8), IL-6, IL-1β, tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ). These studies showed that the yeast can reduce inflammation in blocking nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) activation, in decreasing nitric oxide (NO) production, in enhancing peroxisome proliferators-activated receptor-gamma (PPAR-γ) expression and in moduling T cell migratory behavior. **Maintenance of Epithelial Barrier Integrity -** Several pathogenic microorgansims such as Shigella flexneri, enterohemorrhagic and enteropathogenic E. coli have mechanisms of infection characterized by bacterial adhesion to the intestinal mucosa resulting in alteration of tight-junctions, disruption of membrane permeability and enterocyte secretion of pro-inflammatory cytokines. S. boulardii acts on the epithelial barrier in improving tight junctions structure and in restoring membrane permeability disrupted by infectious pathogens. S. boulardii enhances the cell ability to restore tight-junctions structure and barrier permeability. 13. **Trophic Effects on Intestinal Mucosa -** Acute and chronic gastrointestinal diseases often induce diarrhea. The microflora and the intestinal mucosa are disrupted, resulting in a deficit of intestinal enzymatic activity and transporter expression, and an increase of inflammation and water loss. Several studies have shown that S. boulardii exerts trophic effects restoring the intestinal homeostasis. Studies conducted in humans and rodents administered S. boulardii for 8 days, showed that oral administration of S. boulardii for 8 days increased the activity of sucrase-isomaltase (+82%), lactase (+77%) and maltase-glucoamylase (+75%). These results showed that S. boulardii enhances the release of brush-border membrane enzymes implicated in the nutrient degradation and absorption. These intestinal enzymes are often altered during acute or chronic enteropathies suggesting that the increased expression of intestinal enzymes could be in part due to an endoluminal release of polyamines by S. boulardii, mainly spermine and spermidin. Another effect of the yeast is based on the modification of luminal short-chain fatty acids (SCFAs) concentration. SCFAs which are among the most important metabolites produced by anaerobic bacteria in the colon are involved in water and electrolyte absorption by the colonic mucosa. Patients on long-term total enteral nutrition have a decrease in the number of fecal anaerobic bacteria and in fecal. Patients treated with S. boulardii had an increase in total fecal SCFAs levels and total SCFAs remained high 9 days after discontinuation of the treatment.
Safety of Administration	**Safety of Administration** - S. boulardii is administrated to patients in a lyophilized form and the treatment is well tolerated in healthy patients. However, in severely immunocompromised individuals or long in-dwelling catheters, as these people are at risk of developing fungemias, the use of S.boulardii, should be avoided in them. Gastrointestinal diseases are characterized by an alteration of the microbial balance and the intestinal homeostasis. Several clinical trials and experimental studies demonstrated the role of S. boulardii as a good biotherapeutic agent allowing to prevent and/or treat several gastro-intestinal diseases. The probiotic bacteria, the use of probiotic yeast is beneficial when the treatment is combined to antibiotherapy. Oral treatment with S. boulardii induces modulation of the host cell signaling pathways implicated in pro-inflammatory response and in hydroelectrolytic secretion, neutralization of bacterial toxins, inhibition of pathogen translocation, stimulation of the host immune response, restoration of intestinal permeability, and stimulation of brush-border membrane enzymes and transporters. Thus, S. boulardii is involved in the restoration of intestinal homeostasis. The yeast does not colonize the human intestine and is not a permanent resident of the GIT. It is completely excreted from the system in 3-5 days after stopping the treatment.
Dosage	The suggested dosage: 1. **Diarrhea of varied Etiology -** In adults and children, 1 sachet BID for at least 5 days and may be continued as per the advice of the treating physician 2. In IBS, IBD – The duration of treatment is prolonged, and QIK is administered as 1 Sachet BID for at least a minimum duration of 8 - 12weeks or until resolution of symptoms. The treatment must be continued under the supervision of the Physician 3. Traveler's Diarrhea – The treatment must be initiated at least 3-5 days prior to travel to endemic areas and must be continued until at least 4-5 days after completion of travel.
Composition	Each 1gm Sachet contains: 1. Bacillus coagulans – 200 Million CFU 2. Saccharomyces boulardii – 250 mg

Storage	The box containing the sachets must be stored in a cool-dry place away from heat and direct sunlight and must be kept away from the reach of children.
Presentation	Each Carton of Sporlac Qik Contains, 10 Sachets per box