

## 12 CLINICAL PHARMACOLOGY

### 12.4 Microbiology

#### Mechanism of Action

ENTERAGAM is a serum-derived protein isolate containing immunoglobulins, transferrin, and albumin as well as other proteins and peptides which reflect the composition of plasma. An important function of plasma proteins is their role in endotoxin neutralization and redundant, innate immunity contributions to the gut. Cattle are inherently exposed to a variety of non-pathogenic and pathogenic bacteria and viruses. One recent survey found over 130 different bacterial genera in feedlots and fecal samples. These organisms include *Escherichia coli*, *Prevotella*, *Campylobacter*, *Salmonella*, and *Clostridium*. Different surveys have found that *Prevotella* and *Campylobacter* are the most common genera of bacteria found in feedlots. In addition to the presence of natural antibodies in plasma, mammals, including cattle, develop antibodies to environmental organisms, toxins, and other immunogenic substances, which can be isolated in the immunoglobulin derived from serum.

#### Antibacterial and Antiviral Activity

Innate and adaptive gut immune responses in humans maintain the microbiome and respond to challenges from pathogenic bacteria and viruses. This immunity is maintained in the GI tract primarily by IgA and IgG produced by intestinal B cells. In immunocompromised individuals, the gut immune response and microbiome is altered due to chronic conditions, disease, life-style factors and/or drug treatments which can impact nutritional status. Bovine IgG accounts for approximately 25% of the protein content of plasma and colostrum, depending on postpartum collection, and is in lower concentrations in milk. Anti-*Clostridium difficile* bovine-derived immunoglobulin from colostrums when administered orally to healthy volunteers and collected in the ileum showed reactivity after isolation to *C. difficile*. Isolation of orally-administered bovine anti-*C. difficile* antibodies from colostrums was also shown after collection from feces to react with the bacterium. Bovine-derived immunoglobulins have also been shown in AIDS patients with chronic, severe diarrhea caused by *Cryptosporidium parvum* to reduce the incidence and severity of the enteropathy. When infants suffering from diarrhea induced by enteropathogenic *E. coli* were given oral milk-derived immunoglobulins from lactating cows for 10 days, stool cultures were negative in over 80% of cases. In nonclinical and clinical studies, anti-rotavirus antibodies from milk or plasma protein given orally were effective in maintaining intestinal health and protecting against rotavirus infection. Anti-rotavirus antibodies were found in over 80% of infants administered bovine-derived immunoglobulins. Oral administration of SBI has been shown to improve nutritional status in animals challenged by infection with *E. coli*, *Salmonella*, and *Cryptosporidia*. Therefore, imbalances of the gut microbiome in patients can occur due to therapeutic or chronic medical needs. These patients may have limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients. ENTERAGAM can manage enteropathy in these patients by providing distinct nutrition which can help maintain the gut microbiome and proper immune functions in the intestines.

#### Resistance

Though resistance is possible, there are no reported incidences of resistance to orally-administered bovine-derived immunoglobulin protein isolates.

#### Cross-Reactivity

Serological studies have shown that bovine immunoglobulins, particularly IgG, contain cross-reactive antibodies to lipopolysaccharides from gram-negative bacteria.