ENTOBAN CAPSULE
BRIEF CHARACTERISTIC OF MEDICAL PREPARATION

1. NAME OF PREPARATION
Entoban Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Capsule contains:

Active Ingredients:

Thick extract of	
Cholarchena antidisenterica	400 mg
Myrtus communis L.	400 mg
Aegle marmelos L.	100 mg
Quercus infectoria Olivier.	100 mg
Berberis aristata DC.	100 mg
Butea frondosa Koen. & Roxb	100 mg

For excipients, see 6.1.

3. MEDICINAL FORM & DESCRIPTION
Capsule

Green capsules No. 0 containing hygroscopic brown powder or hygroscopic brown powder or hygroscopic brown powder with the presence of white blotches. "ENTOBAN" is printed on the body and cap.

4. CLINICAL CHARACTERISTICS
4.1. Therapeutic indications
Adjuvant agent in the treatment of food poisoning, nonspecific diarrhea, gastroenteritis.

4.2. Dosage and administration
Adults: primary dose: 2 capsules,
then: 1 capsule every 4 hours.
Or as prescribed by doctor

4.3. Contraindications:
- Allergic conditions
- Individual intolerability to components of the preparation
- Pregnancy and lactation, age below 18 years

4.4. Special instructions and special safety measures

Pregnancy and lactation.

Clinical data for use of drug during pregnancy and lactation are not available.

Impact of the preparation on the ability to drive or operate potentially dangerous mechanisms:

Does not affect

4.5. Side effects:

Possible allergic reactions to the drug components.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic and Pharmacokinetic Properties:

Pharmacokinetics

The effect of the drug Entoban is the combined action of its components, therefore pharmacokinetic studies are not possible: all together, the components cannot be traced using markers or bioassays. For the same reason, it is impossible to detect the metabolites of the drug.

Pharmacodynamics

Entoban - Complex herbal preparation having antidiarrheal, antibacterial, and antiprotozoal effects. Due to the high content of tannins, the drug has antidiarrheal, astringent and antiseptic properties. Effects on smooth muscles, reduces intestinal motility, alleviates the condition with colic. The complex of biologically active substances that make up the drug has a bactericidal effect on the strain of E. histolytic STA (Amoeba dysenteries) associated with inhibition of synthesis and violation of the structure of DNA. Entoban has a pronounced antibacterial (bactericidal and bacteriostatic). The tannins that make up the components of the drug act as antibacterial agents, coagulating the protoplasm of pathogenic microorganisms. Does not violate the natural intestinal micro flora. Increases the secretion of digestive glands, improves digestion.

Cholarchena antidisenterica contains alkaloids of the steroid type of the conessin series. It has antimicrobial and anti-amoebic activity.

Myrtle (Myrtus communis) contains myrtle oil, tannins, and bitterness. It has a bactericidal (especially against staphylococci and streptococci), antiviral, fungicidal and anti-inflammatory effects. Stimulates regeneration processes. Bitterness - increase the secretion of digestive glands, improve digestion.

Berberis aristata contains alkaloids (berberine, berbamine), sugars, tannins, pectin, vitamins C, K, organic acids (malic, tartaric, citric, etc.), microelements (P, K, B, Ca, Mg, Fe). It has anti-inflammatory, antidiarrheal, astringent and antiseptic effects. Berberine alkaloid has a pronounced antibacterial activity.

Aegle marmelose contains glycoside marmelosin, azulene, tannin and pectin, coumarins, essential oil, gums, mucus, vitamin B2. It has a hypoglycemic effect, promotes digestion of food.

Quercus Infectoria contains gallotanin, tannins. It has astringent, anti-inflammatory and antimicrobial and antimicrobial effects.

The *Butea frondosa* contains glycosides, butin. It has astringent and anthelmintic properties.

5.2. Pharmacotherapeutic group

Other antidiarrheal remedies.

ATC Code: Absent

5.3. Preclinical safety data

The study was conducted in Moscow in the year 2005 at the Russian academy of agricultural sciences where the safety of Entoban cap/syrup was determined in animals which included rabbits and rats.

Objectives

The study overall composed of the following objectives:

1. Acute toxicity of Entoban
2. Sub-acute toxicity of Entoban capsule on rabbits during 4 weeks
3. Macro-and microscopic investigation of internal organs in rabbits receiving Entoban capsules during 4 weeks.
4. Sub-acute toxicity of Entoban syrup on rats during 4 weeks.
5. Macro-and microscopic investigation of internal organs in rats receiving Entoban syrup during 4 weeks.
6. Allergenic Reactions
   - Anaphylactogenic activity
   - Active skin anaphylaxis
   - delayed type hypersensitivity
7. Immunotoxic properties of Entoban
   - Effects on Humoral immunity
   - Effects on cellular immunity
8. Mutagen activity of Entoban
   - Chromosomal aberrations induced by Entoban in bone marrow cells of mice.
9. Ability of Entoban to induce genetic mutations on indicated bacteria by Ames-test in Salmonella/Microsomes

ACUTE TOXICITY OF ENTOBAN

The acute toxicity of Entoban was carried out on rats and were known to be called from animal house at Moscow area. All the animals were kept under normal healthy living conditions with good clinical monitoring.

The mice were given doses of 5000 up to 12000 mg / kg unitary intra-gastric administration and were observed for 10-15 minutes where with slight anxiety, excitation within 10minutes of administration which prevailed for another 30-40 minutes. All the impellent actions were disappeared within 2-3 hours with tidy appearance.

In rats a dose of 14000mg/kg unitary intra-gastric administration was observed where there were no deaths observed.

SUB-ACUTE TOXICITY OF ENTOBAN CAPSULES ON RABBITS DURING 4 WEEKS

For measurement of sub-acute toxicity of Entoban on rabbits for duration of 4 weeks of study, hematological group of rabbits were administered with 143mg/kg and 286mg/kg of the Entoban capsule doses. Whereas, the biochemical parameters were assessed by administering the rabbits with a placebo (control group), group II (143mg/kg) and group III (286mg/kg) of Entoban capsules.

Sub-acute toxicity parameters were assessed through hematological limits where hemoglobin (width, volume and content), leukocytes, thrombocytes and hematocrit values were calculated, other than these biochemical parameters such as cholesterol, bilirubin, glucose, urea, alkaline phosphatase, alanine-and aspartate transaminase and cardiovascular values were measured. Electrocardiograms were also observed after rabbits being administered with doses 143 and 286mg/kg

All values came out to be normal and with no death rates marked. Hence during 4 weeks of measuring sub-acute toxicities, Entoban capsule were concluded to be safe in animals showing no toxicities.

MACRO-AND MICROSCOPIC RESEARCH ON RABBITS

Rabbits group of animals were divided into three groups; control (placebo), Group I (143mg/kg) and group II (286 mg/kg) and internal organs including, Liver, kidney, heart, adrenal glands, spleen, lungs, thymus gland, pancreas, sperm, ventricles, thin and thickness of intestines, color and sizes of the organs were also investigated.

Patho-morphological results have shown group I (143mg / kg) revealed moderate general-toxic action and stimulated effect on mucous gastro-enteric path of rabbits. Whereas group II (286 mg / kg) showed amplified general-toxic actions which is expressed in increase in volume dystrophic and necrotic changes in liver, and also irritating effect on gastro-enteric tract rabbits.

SUB-ACUTE TOXICITY OF ENTOBAN SYRUPS ON RATS DURING 4 WEEKS

Sub-acute experiments of Entoban Syrup were assessed through intra-gastric administration at doses 178.5 mg/kg and 892.5mg/kg compared with standard control group for duration of 4 weeks.

Sub-acute toxicity parameters were assessed through hematological limits where hemoglobin (width, volume and content), leukocytes, thrombocytes and hematocrit values were calculated, other than these biochemical parameters such as cholesterol, bilirubin, glucose, urea, alkaline phosphatase, alanin-and aspartate transaminase and cardiovascular values were measured. Kidney experiments were also observed where diuretic actions were observed. The neuronal activity was assessed by observing animal physical and motor activity in an open field and mink reflex. Electrocardiograms and weight changes were also observed.

All values came out to be normal and with no death rates marked. There was an authentic weight gain in group II animals during 2nd and 4th weeks. Also all other testing was significantly normal and there were no apparent damages or toxicity production in all parameters. Hence during 4 weeks of measuring sub-acute toxicities, Entoban capsule were concluded to be safe in animals showing no toxicities.

MACRO-AND MICROSCOPIC RESEARCH ON RATS

Rats were divided into three groups; control (placebo), Group I (178.5mg/kg) and group II (892.5 mg/kg) and internal organs including, Liver, kidney, heart, adrenal glands, spleen, lungs, thymus gland, pancreas, sperm, ventricles, thin and thickness of intestines, color and sizes of the organs were also investigated

Patho-histologic researches show that Entoban syrup in dose of 178.5 mg / kg (5- multiple daily therapeutic) did not cause local irritated and common toxic effect. Increase in dose of preparation up to 892.5 mg / kg (25-fold daily therapeutic) was accompanied by local irritation on gastro-enteric path and massive reversible dystrophy of hepatocyte cells.

ALLERGENIC REACTIONS

- Anaphylactogenic activity

For estimation of anaphylactogenic activity in mice, 30 albino male rats (380-400 weight) were divided into three groups; Group I, control (0.85% NaCl), Group II 36mg/kg and Group III 360mg/kg of thick Entoban extract was administered accordingly. Each group of animal were sensitized equally allowed as Entoban sensitized dose and control (0.85% NaCl) for 14 days.

In group I, the anaphylaxis results were negative. Whereas, group II (36mg/kg) animals showed anxiety, grumping and twitching. Group III animals besides showing above mentioned effects developed bronchospasm and caused death of seven animals. Thus, Entoban possesses sensitized action when a 10 times daily therapeutic dose was administered.

- Active skin anaphylaxis

30 albino rats were selected and grouped into 10 animals to be served as Group I, control 0.85% NaCl, Group II (36mg/kg) and Group III (360mg/kg). All the groups of animals were administered 1% Evans solution (0.5ml) to initiate sensitization and that each group was treated with 50ml of each NaCl, 36mg/kg and 360mg/kg of the doses and checked for diameters of the blue spots on internal region. All the spots were within the negative range of diameters (2-3mm). Thus, Entoban extract actively control skin anaphylactic reaction.

- Delayed type hypersensitivity

The estimation of delayed type sensitivity was determined by administering a chemical substance Full Adjuvant Friend (FAF0 which helps detect even weak allergen reaction. Hypostasis of the paw was measured by administering FAF and solution henx in controlled group of animals (n=10) and 40mcl of 10mm solution of Entoban at the pillow of hinder leg. The index of the reaction was calculated using a formula which estimated that Entoban does not induce Delayed type hypersensitivity reactions in mice.

IMMUNOTOXIC PROPERTIES OF ENTOBAN

The immune-toxic properties were assessed as per WHO guidelines of Principles and methods for assessing direct immunotoxicity associated with exposure to chemicals (Environmental Health Criteria, 1996).

- Humoral immunity

Humoral immunity of Entoban was determined on number of antibody forming cells (AOK) in

spleens of mice. The animals were intravenously administered with Erythrocyte ram (ER) to a dose of 5 x108 to the mouse.
The animals were divided into three groups; Control group I (0.85% NaCl), Group II 36mg/kg and Group III 360mg/kg; and were administered within 10 days intra-gastric doses of Entoban in group II and III and 0.85% NaCl to group I.
After 5 days of immunization, the quantity of number of AOK of spleen was determined in whey of blood - credit of antibodies to ER (in micro-test hem agglutination)., where it was concluded that Entoban did not cause changed in research parameter when compared to control when tested by definition of quantifiable number of Antibody forming cells.

- Cellular immunity

The cellular immunity was determined on 49 animals divided into 7 group each with different study methods. To study the slowdown type hypersensitivity reaction, blade to blade part erythrocyte ram in a dose of 2x 108 was used.
(a) Group I and II: Entoban thick extract in dose 30 and 360mg/kg was introduced intra-peritoneal one day before immunization
(b) Group III and IV: Entoban thick extract in dose 36 and 360mg/kg was introduced intra-peritoneal one hour after immunization
(c) Group V and VI: Entoban thick extract in dose 36 and 360mg/kg was introduced intra-peritoneal 24 hour after immunization.
After 5 days of receiving immunization in left hinder leg ER in a dose 5x108 (50mcl) in skilled paw and 0.85% NaCl solution (50mcl) as control paw, the index of reaction was calculated by determining the difference in weight of "test" and "control" paws characterized size of hypostasis and intensity of reaction STH was determined using a formula

$$U= (m0-mk)/ mk \times 100\%,$$

Where
mo - weight of test paw;
mk - weight of control paw.
The study testifies that Entoban thick extract in the tested dose of 36 and 360 mg / kg does not influence formation of reaction ГЗТ at mice and accordingly on cellular immunity.

POTENTIAL MUTAGEN ACTIVITY ENTOBAN

The study was conducted by analyzing cells of bone brain of mice at 6, 24 and 48 hours after introduction of Entoban thick extract in doses of 3600mg/kg (~0.5ml); 10 times the therapeutic dose, and control group received same volume of water to be served as placebo.
Before entering in to the metaphase phase of the bone brain, the mice were administered with 0.025% working solution of colchicine (0.01ml/u of animal weight). A bone brain from femurs of the mice was quickly washed away in hypotonic solution (0.555% KCl) solution right after hammering and centrifuged then fixed to obtain an appropriate suspension to be studied. It was determined that there were no chromosomal aberrations found and Entoban thick extract did not produce any mutagenic activity in test of aberrations of chromosomes in cells of bone brain of mice.

ABILITY OF ENTOBAN TO INDUCE GENIC MUTATIONS ON DISPLAY BACTERIA IN AMES TEST IN SALMONELLA/MICROSOMES

The test was conducted to estimate the potential of Entoban thick extract to cause induction of mutagenicity in Ames test in Salmonella/Microsomes. Under influence of enzymes microsomal oxidations, contained in fractions S-9, preparation was exposed to process of biotransformation with formation of lines metabolite. As initial substance, and it {he} metabolite if they possess mutagen activity, is induced with mutations at microorganisms.

The experiments were carried out on Salmonella typhimurium TA97, TA98 and TA100, offered Ames and employees. Induction of enzymes microsomal oxidations carried out with the help of preliminary intro-duction to rats of mix polychlorinated biphenyl Domestic production. Necessary equipment for the experiments were gathered, reception of fraction S-9, corresponding bacterial cultures and applicable methodology was collected.

A series of dilution of standard concentration was prepared (1.0; 10.0; 100.0; 1000.0; 10000.0 mcg / ml). Selective half-enriched an agar (0.7 %) in test tubes were fused in a water bath at 100C temperature and controlled temperatures. After treatments agar was transferred to a petri dish and compared with the formation of pre mutagen metabolite results received at analysis of data tests of substances in variants PMAM and CMAM. As a control variant suspension of bacteria with semiliquid agar was used, as positive control used substances, induced mutations at corresponding stamm-TA at presence or absence of conditions of activation. For variants CMAM have been used 2-Nitrofuranum (2-NF) for stamm TA 98, acid Na - for stamm THAT 100 and 9-aminocridin (9-AC) for stamm THAT 97. Activity of fraction S-9 supervised, using in parallel in variants with CMAM and PMAM 2-aminoanthracene (2-AA). In each control and skilled variants used on 3 petri dishes.

Carried out experiments testify that Entoban does not induce genetic infringements in somatic cells mammal in investigated dose. Preparation does not show also mutagen activity on stamm salmonella, recording various types' point mutations.

Conclusion:

Thus, it is clearly evident form the above conducted studies that Entoban capsules do produce dose dependent liver toxicity and irritant action. However, Entoban syrup at doses five times the daily therapeutic dose did not cause any toxic effect but at doses 25 times the normal (892.5mg/kg) showed an irritant effect on gastrointestinal linings.

Entoban possesses sensitizing action but does not show immunotoxicity and mutagenic activity in animals.

Thus it is important to carefully administer in patients with diseases of liver and gastrointestinal tract when given at high doses whereas studies proved 5 times normal exceeded doses to be harmless and nontoxic in animals.

6. PHARMACEUTICAL CHARACTERISTICS

6.1. List of excipients:

Dibasic calcium phosphate, maize starch, microcrystalline cellulose.

6.2. Shelf life:

3 years

Do not use after the expiry date mentioned on the pack

6.3. Special safety measures at storage

Store at temperature below 25 ^{o}C.

Keep out of reach of children.

6.4. Type and volume of primary packing

20 and 60 in the bottle

6.5 Conditions of release

To be sold without prescription

7. TRADE LICENSE HOLDER

Herbion Pakistan (Pvt.) Ltd. »,
30/28, Korangi Industrial Area, Karachi, Pakistan

8. MANUFACTURER

Herbion Pakistan (Pvt.) Ltd. »,
30/28, Korangi Industrial Area, Karachi, Pakistan

9. DATE OF LAST REVISION

20.12.2021