Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

IBGUT 200 (Rifaximin Tablets 200 mg)
IBGUT 550 (Rifaximin Tablets 550 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rifaximin Tablets 200 mg
Each film-coated tablet contains:
Rifaximin BP……200 mg
Excipients …… q.s.
Colour: Approved colour used.

Rifaximin Tablets 550 mg
Each film-coated tablet contains:
Rifaximin BP……550 mg
Excipients …… q.s.
Colour: Approved colour used.

Excipients with known effect: None of the excipients have any pharmacological effects

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibugut is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Recommended dose: 200 mg every 8 hours for three days (total 9 doses).

Rifaximin must not be used for more than 3 days even if symptoms continue, and a second course of treatment must not be taken.
Rifaximin can be administered with or without food

Paediatric population
The safety and efficacy of Rifaximin in children (aged less than 18 years) have not been established

Elderly
No dosage adjustment is necessary, as the safety and efficacy data of Rifaximin showed no differences between the elderly and the younger patients.

Hepatic impairment
A dosage adjustment for patients with hepatic insufficiency is not necessary.

Renal impairment
Although a dosing change is not anticipated, caution should be used in patients with impaired renal function.

Method of administration
Orally with a glass of water.
The tablet is to be swallowed with water. It is recommended to take the daily dose in one single intake.

4.3 Contraindications

Hypersensitivity to rifaximin, rifamycin derivatives, or to any of the excipients listed in section 6.1.

Cases of intestinal obstruction.

4.4 Special warnings and precautions for use

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out.
Due to the lack of data and the potential for severe disruption of gut flora with unknown consequences, concomitant administration of rifaximin with other rifamycins is not recommended Patients should be informed that despite the negligible absorption of the drug (less than 1%), like all rifamycin derivatives, rifaximin may cause a reddish discolouration of the urine.
Hepatic Impairment: use with caution in patients with severe (Child-Pugh C)

hepatic impairment and in patients with MELD (Model for End-Stage Liver Disease) score > 25.
Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor such as ciclosporin is needed
Both decreases and increases in international normalized ratio (in some cases with bleeding events) have been reported in patients maintained on warfarin and prescribed rifaximin. If co-administration is necessary, the international normalized ratio should be carefully monitored with the addition or withdrawal of treatment with rifaximin. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

There is no experience regarding administration of rifaximin to subjects who are taking another rifamycin antibacterial agent to treat a systemic bacterial infection.
In vitro data show that rifaximin did not inhibit the major cytochrome P-450 (CYP) drug-metabolizing enzymes (CYPs1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). In *in vitro* induction studies, rifaximin did not induce CYP1A2 and CYP2B6 but was a weak inducer of CYP3A4.
In healthy subjects, clinical drug interaction studies demonstrated that rifaximin did not significantly affect the pharmacokinetics of CYP3A4 substrates, however, in hepatic impaired patients it cannot be excluded that rifaximin may decrease the exposure of concomitant CYP3A4 substrates administered (e.g. warfarin, antiepileptics, antiarrhythmics, oral contraceptives), due to the higher systemic exposure with respect to healthy subjects.
Both decreases and increases in international normalized ratio have been reported in patients maintained on warfarin and prescribed rifaximin. If co-administration is necessary, the international normalized ratio should be carefully monitored with the addition or withdrawal of rifaximin. Adjustments in the dose of oral anticoagulants may be necessary.
An *in vitro* study suggested that rifaximin is a moderate substrate of P-glycoprotein(P-gp) and metabolized by CYP3A4. It is unknown whether concomitant drugs which inhibit P-gp and/or CYP3A4 can increase the systemic exposure of rifaximin.

In healthy subjects, co-administration of a single dose of ciclosporin (600 mg), a potent P-glycoprotein inhibitor, with a single dose of rifaximin (550 mg) resulted in 83-fold and 124-fold increases in rifaximin mean Cmax and AUC∞. The clinical significance of this increase in systemic exposure is unknown.
The potential for drug-drug interactions to occur at the level of transporter systems has been evaluated *in vitro* and these studies suggest that a clinical interaction between rifaximin and other compounds that undergo efflux via P-gp and other transport proteins is unlikely (MRP2, MRP4, BCRP and BSEP).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no or limited data from the use of rifaximin in pregnant women. Animal studies showed transient effects on ossification and skeletal variations in the foetus.
As a precautionary measure, use of rifaximin during pregnancy is not recommended.

Breastfeeding

It is unknown whether rifaximin/metabolites are excreted in human milk.
A risk to the breast-fed child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to male and female fertility

4.7 Effects on ability to drive and use machines

Dizziness has been reported in controlled clinical trials. However, rifaximin has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Clinical Trials:

In clinical studies in subjects who received rifaximin for treatment of travellers' diarrhoea, Adverse Reactions considered as being at least possibly related to rifaximin have been categorised by organ system and frequency.

Post-marketing experience

During post-approval use of rifaximin, further undesirable effects have been reported. The frequency of these reactions is not known (cannot be estimated from the available data).

Frequency categories are defined using the following convention:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), Not known (frequency cannot be estimated from the available data).

MedDRA System Organ Class	Common	Uncommon	Frequency not known
Infections and infestations		Candidiasis, Herpes simplex, Nasopharyngitis, Pharyngitis, Upper respiratory tract infection	Clostridial infections
Blood and lymphatic system disorders		Lymphocytosis, Monocytosis, Neutropenia	Thrombocytopenia
Immune system disorders			Anaphylactic reactions Hypersensitivity
Metabolism and nutrition disorders		Decreased appetite, Dehydration	
Psychiatric disorders		Abnormal dreams, Depressed mood, Insomnia, Nervousness	
Nervous system disorders	Dizziness, Headache	Hypoesthesia, Migraine, Paraesthesia, Sinus headache, Somnolence	Presyncope
Eye disorders		Diplopia	
Ear and labyrinth disorders		Ear pain, Vertigo	
Cardiac disorders		Palpitations	
Vascular disorders		Increased blood pressure Hot flush	
Respiratory, thoracic, and mediastinal disorders		Cough, Dry throat, Dyspnoea, Nasal congestion, Oropharyngeal pain, Rhinorrhea	
Gastrointestinal disorders	Abdominal pain, Constipation, Defecation urgency,	Abdominal pain upper, Dry lips, Dyspepsia, Gastrointestinal motility disorder, Faeces hard, Haematochezia,	

	Diarrhoea, Flatulence, Abdominal distension, Nausea, Vomiting, Rectal tenesmus	Mucous stools, Taste disorders	
Hepatobiliary disorders		Aspartate aminotransferase increased	Liver function test abnormalities
Skin and subcutaneous tissue disorders		Rashes, eruptions and exanthemas, Sunburn	Angioedema Dermatitis Dermatitis exfoliative, Eczema Erythemas Pruritus Purpura Urticarias
Musculoskeletal and connective tissue disorders		Back pain, Muscle spasms, Muscular weakness, Myalgia, Neck pain	
Renal and urinary disorders		Blood in urine, Glycosuria, Pollakiuria, Polyuria, Proteinuria	
Reproductive system and breast disorders		Polymenorrhoea	
General disorders and administration site conditions	Pyrexia	Asthenic conditions, Chills, Cold sweat, Hyperhidrosis, Influenza-like illness, Oedema peripheral, Pain and discomfort	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority pharmacovigilance reporting channels.

4.9 Overdose

No case of overdose has been reported.

In clinical trials with patients suffering from traveller's diarrhoea doses of up to 1800 mg/day have been tolerated without any severe clinical sign. Even in patients/subjects with normal bacterial flora rifaximin in dosages of up to 2400 mg/day for 7 days did not result in any relevant clinical symptoms related to the high dosage.
In case of accidental overdose, symptomatic treatment and supportive care are suggested.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: intestinal, anti-infective - antibiotics

ATC code: A07AA11.

Mechanism of action

Rifaximin is an antibacterial drug of the rifamycin class that irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase and consequently inhibits bacterial RNA synthesis.

Rifaximin has a broad antimicrobial spectrum against most of the Gram-positive and negative, aerobic and anaerobic bacteria, including ammonia producing species. Rifaximin may inhibit the division of urea-deaminating bacteria, thereby reducing the production of ammonia and other compounds that are believed to be important to the pathogenesis of hepatic encephalopathy.

Mechanism of resistance

The development of resistance to rifaximin is primarily a reversible chromosomal one-step alteration in the *rpoB* gene encoding the bacterial RNA polymerase.
Clinical studies that investigated changes in the susceptibility of intestinal flora of patients affected by traveller's diarrhoea failed to detect the emergence of drug resistant Gram-positive (e.g. *enterococci*) and Gram-negative (*E. coli*) organisms during a three-day course of treatment with rifaximin.
Development of resistance in the normal intestinal bacterial flora was investigated with repeated, high doses of rifaximin in healthy volunteers and

Inflammatory Bowel Disease patients.
Strains resistant to rifaximin developed, but were unstable and did not colonise the gastrointestinal tract or replace rifaximin-sensitive strains. When treatment was discontinued, resistant strains disappeared rapidly.
Experimental and clinical data suggest that treatment with rifaximin of patients harbouring strains of *Mycobacterium tuberculosis* or *Neisseria meningitidis* will not select for rifampicin resistance.

Susceptibility

Rifaximin is a non-absorbed antibacterial agent. In vitro susceptibility testing cannot be used to reliably establish susceptibility or resistance of bacteria to rifaximin. There are currently insufficient data available to support the setting of a clinical breakpoint for susceptibility testing.

Rifaximin has been evaluated in vitro on several pathogens including ammonia producing bacteria as Escherichia coli spp, Clostridium spp, Enterobacteriaceae, Bacteroides spp. Due to the very low absorption from the gastro-intestinal tract rifaximin is not clinically effective against invasive pathogens, even though these bacteria are susceptible in vitro.

Clinical efficacy and safety

The efficacy and safety of rifaximin 550 mg twice daily in adult patients in remission from HE was evaluated in a phase 3 pivotal, 6-month, randomised, double-blind, placebo-controlled study RFHE3001.
Two-hundred ninety-nine subjects were randomised to treatment with rifaximin 550 mg twice daily (n=140) or placebo (n= 159) for 6 months. In the pivotal study, 91% of the subjects in both groups received concomitant lactulose. No patients were enrolled with a MELD score > 25.
The primary endpoint was the time to first breakthrough overt HE episode and patients were withdrawn after a breakthrough overt HE episode. A breakthrough overt HE episode was defined as a marked deterioration in neurological function and an increase of Conn score to Grade ≥ 2. In patients with a baseline Conn score of 0, a breakthrough overt HE episode was defined as an increase in Conn score of 1 and asterixis grade of 1.
Thirty-one of 140 subjects (22%) of rifaximin group and 73 of 159 (46%) subjects of placebo group experienced a breakthrough overt HE episode during the 6-month period. Rifaximin reduced the risk of HE breakthrough by 58% ($p < 0.0001$) and the risk of HE-related hospitalizations by 50% ($p < 0.013$), compared with placebo.
The longer-term safety and tolerability of rifaximin 550 mg twice daily

administered for at least 24 months was evaluated in 322 subjects in remission from HE in study RFHE3002. One hundred fifty-two subjects rolled over from RFHE3001 (70 from the rifaximin group and 82 from the placebo), and 170 subjects were new. Eighty-eight percent of patients were administered concomitant lactulose.
Treatment with rifaximin for periods up to 24 months (OLE study RFHE3002) did not result in any loss of effect regarding the protection from breakthrough overt HE episodes and the reduction of the burden of hospitalization. Time to first breakthrough overt HE episode analysis showed long-term maintenance of remission in both groups of patients, new and continuing rifaximin.
Combination therapy with rifaximin and lactulose showed a statistically significant reduction in mortality in HE patients compared with lactulose alone in a systematic review and meta-analysis of four randomized and three observational studies involving 1822 patients (risk difference (RD) -0.11, 95% CI -0.19 to -0.03, P=0.009). Additional sensitivity analyses confirmed these results.

Notably, a pooled analysis of two randomized trials - including 320 patients treated for up to 10 days and followed-up during hospitalisation - demonstrated a statistically significant decrease in mortality (RD -0.22, 95% CI -0.33 to -0.12, P<0.0001).

5.2 Pharmacokinetic properties

Absorption

Pharmacokinetic studies in rats, dogs and humans demonstrated that after oral administration rifaximin in the polymorph α form is poorly absorbed (less than 1%). After repeated administration of therapeutic doses of rifaximin in healthy volunteers and patients with damaged intestinal mucosa (Inflammatory Bowel Disease), plasma levels are negligible (less than 10 ng/mL). In HE patients, administration of rifaximin 550 mg twice a day showed mean rifaximin exposure approximately 12-fold higher than that observed in healthy volunteers following the same dosing regimen. A clinically irrelevant increase of rifaximin systemic absorption was observed when administered within 30 minutes of a high-fat breakfast.

Distribution

Rifaximin is moderately bound to human plasma proteins. In vivo, the mean protein binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment when Rifaximin 550 mg was administered.

Biotransformation

Analysis of faecal extracts demonstrated that rifaximin is found as the intact molecule, implying that it is neither degraded nor metabolised during its passage through the gastrointestinal tract.
In a study using radio-labelled rifaximin, urinary recovery of rifaximin was 0.025% of the administered dose, while <0.01% of the dose was recovered as 25-desacetylrifaximin, the only rifaximin metabolite that has been identified in humans.

Elimination

A study with radio-labelled rifaximin suggested that ^{14}C-rifaximin is almost exclusively and completely excreted in faeces (96.9 % of the administered dose). The urinary recovery of ^{14}C-rifaximin does not exceed 0.4% of the administered dose.

Linearity

The rate and extent of systemic exposure of humans to rifaximin appeared to be characterized by non-linear (dose-dependent) kinetic which is consistent with the possibility of dissolution-rate-limited absorption of rifaximin.

Renal impairment

No clinical data are available on the use of rifaximin in patients with impaired renal function.

Hepatic impairment

Clinical data available for patients with hepatic impairment showed a systemic exposure higher than that observed in healthy subjects. The systemic exposure of rifaximin was about 10-, 13-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy volunteers. The increase in systemic exposure to rifaximin in subjects with hepatic impairment should be interpreted in light of rifaximin gastrointestinal local action and its low systemic bioavailability, as well as the available rifaximin safety data in subjects with cirrhosis.
Therefore, no dosage adjustment is recommended because rifaximin is acting locally.

Paediatric population

The pharmacokinetics of rifaximin has not been studied in paediatric patients of any age. The population studied in both the reduction in recurrence of hepatic encephalopathy (HE) and in the acute treatment of HE included patients aged ≥ 18 years.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional

studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In a rat embryofetal development study, a slight and transient delay in ossification that did not affect the normal development of the offspring, was observed at 300 mg/kg/day (2.7 times the proposed clinical dose for hepatic encephalopathy, adjusted for body surface area). In the rabbit, following oral administration of rifaximin during gestation, an increase in the incidence of skeletal variations was observed (at doses similar to those proposed clinically for hepatic encephalopathy). The clinical relevance of these findings is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rifaximin 200mg:
EDTA (Ethylenediaminetetraacetic acid), Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Purified Talc, Colloidal Anhydrous Silica, Stearic Acid, Opadry II 89F580003, Colour Sunset Yellow Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30° C. Protect from direct sunlight. Keep all medicines out of reach of children

6.5 Nature and contents of container

Alu-Alu Blister Pack of 3x10's, packed in printed unit carton with literature insert.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder:
Dawa Limited,
Plot No. 7879/8, Baba Dogo Road, Ruaraka,
P.O Box 16633-00620,
Nairobi, Kenya

Manufacturer:
Ravenbhel Healthcare Pvt.Ltd.
16-17, EPIP, SIDCO, Kartholi,
Bari Brahmana- 181133, Jammu, India

8. MARKETING AUTHORIZATION NUMBER(S)

IBGUT 200: H2025/CTD11738/24514
IBGUT 550: H2025/CTD11739/24523

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of first authorization:
IBGUT 200: 26/05/2025
IBGUT 550: 26/05/2025

10. DATE OF REVISION OF THE TEXT

June 2023