# Summary of Product Characteristics

## 1. Name of the medicinal product

RIFAGUT 550mg film-coated tablets

## 2. Qualitative and quantitative composition

Each film-coated tablet contains 550mg RIFAGUT.

Excipients:

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Film-coated tablet.

A Peach Color Oblong Shape Biconvexed Film Coated Tablet, Scored In The Middle On One Side And Plain On Other Side Of The Tablet.

## 4. Clinical particulars

### 4.1 Therapeutic indications

RIFAGUT 550mg is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age (see section 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

### 4.2 Posology and method of administration

**Posology**

Recommended dose: 550mg twice a day as long term treatment for the reduction in recurrence of episodes of overt hepatic encephalopathy (see sections 4.4, 5.1 and 5.2).

In the pivotal study, 91% of the patients were using concomitant lactulose (see also section 5.1).

RIFAGUT 550mg can be administered with or without food.

*Paediatric population*

The safety and efficacy of RIFAGUT 550mg in paediatric patients (aged less than 18 years) have not been established.

*Elderly*

No dosage adjustment is necessary as the safety and efficacy data of RIFAGUT 550mg showed no differences between the elderly and the younger patients.

*Hepatic impairment*

No dosage adjustment is necessary for patients with hepatic insufficiency (see section 4.4).

*Renal impairment*

Although dosing change is not anticipated, caution should be used in patients with impaired renal function (see section 5.2).

**Method of administration**

Orally with a glass of water.

**4.3 Contraindications**

• Hypersensitivity to RIFAGUT, 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**

Severe skin reactions

Severe cutaneous adverse reactions (SCAR) including: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported (frequency unknown) in association with RIFAGUT treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, RIFAGUT should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS or TEN with the use of RIFAGUT, treatment with RIFAGUT must not be restarted in this patient at any time.

*Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including RIFAGUT. The potential association of RIFAGUT 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 RIFAGUT 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, RIFAGUT 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 (see section 5.2).

Caution should be exercised when concomitant use of RIFAGUT and a P-glycoprotein such as ciclosporin is needed (see section 4.5).

Both decreases and increases in international normalized ratio (in some cases with bleeding events) have been reported in patients maintained on warfarin and prescribed RIFAGUT. If co-administration is necessary, the international normalized ratio should be carefully monitored with the addition or withdrawal of treatment with RIFAGUT. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5).

This medicine contains less than 1 mmol sodium (23mg) 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 RIFAGUT to subjects who are taking another rifamycin antibacterial agent to treat a systemic bacterial infection.

*In vitro* data show that RIFAGUT 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, RIFAGUT did not induce CYP1A2 and CYP 2B6 but was a weak inducer of CYP3A4.

In healthy subjects, clinical drug interaction studies demonstrated that RIFAGUT did not significantly affect the pharmacokinetics of CYP3A4 substrates, however, in hepatic impaired patients it cannot be excluded that RIFAGUT 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 RIFAGUT. If co-administration is necessary, the international normalized ratio should be

carefully monitored with the addition or withdrawal of RIFAGUT. Adjustments in the dose of oral anticoagulants may be necessary.

An *in vitro* study suggested that RIFAGUT is a moderate substrate of P-glycoprotein(P-gp) and metabolized by CYP3A4. It is unknown whether concomitant drugs which inhibit CYP3A4 can increase the systemic exposure of RIFAGUT.

In healthy subjects, co-administration of a single dose of ciclosporin (600mg), a potent P-glycoprotein inhibitor, with a single dose of RIFAGUT (550mg) resulted in 83-fold and 124-fold increases in RIFAGUT 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 RIFAGUT 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 RIFAGUT in pregnant women.

Animal studies showed transient effects on ossification and skeletal variations in the foetus (see section 5.3).

As a precautionary measure, use of RIFAGUT during pregnancy is not recommended.

**Breastfeeding**

It is unknown whether RIFAGUT/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 RIFAGUT therapy taking into account the benefit of breast feeding 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 clinical controlled trials. However, RIFAGUT has negligible influence on the ability to drive and use machines.

**4.8 Undesirable effects**

**Summary of safety profile:**

**Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with RIFAGUT treatment (see section 4.4).**

**Clinical Trials**:

The safety of RIFAGUT in patients in remission from hepatic encephalopathy (HE) was evaluated in two studies, a randomised, double-blind, placebo-controlled phase 3 study RFHE3001 and a long-term, open-label study RFHE3002.

Study RFHE3001 compared 140 patients treated with RIFAGUT (dose of 550 mg twice daily for 6 months) to 159 patients treated with placebo, while study RFHE3002 treated 322 patients, of whom 152 from the RFHE3001 study, with RIFAGUT 550 mg twice daily for 12 months (66% of patients) and for 24 months (39% of patients), for a median exposition of 512.5 days.

In addition, in three supportive studies 152 HE patients were treated with varying doses of RIFAGUT from 600 mg to 2400 mg per day for up to 14 days.

All adverse reactions that occurred in patients treated with RIFAGUT at an incidence ≥ 5% and at a higher incidence (≥1%) than placebo patients in RFHE3001 are reported in the following table.

**Table 1:** Adverse reactions occurring in ≥ 5% of patients receiving RIFAGUT and at a higher incidence than placebo in RFHE3001.

| **MedDRA System Organ Class** | **Event** | **Placebo N=159** | | **RIFAGUT N= 140** | |
|---|---|---|---|---|---|
| | | **n** | **%** | **n** | **%** |
| **Blood and lymphatic system disorders** | Anaemia | 6 | 3.8 | 11 | 7.9 |
| **Gastrointestinal disorders** | Ascites | 15 | 9.4 | 16 | 11.4 |
| | Nausea | 21 | 13.2 | 20 | 14.3 |

| | | | | | |
|---|---|---|---|---|---|
| | Abdominal pain upper | 8 | 5.0 | 9 | 6.4 |
| **General disorders and administration site conditions** | Oedema peripheral | 13 | 8.2 | 21 | 15.0 |
| | Pyrexia | 5 | 3.1 | 9 | 6.4 |
| **Musculoskeletal and connective tissue disorders** | Muscle spasms | 11 | 6.9 | 13 | 9.3 |
| | Arthralgia | 4 | 2.5 | 9 | 6.4 |
| **Nervous system disorders** | Dizziness | 13 | 8.2 | 18 | 12.9 |
| **Psychiatric disorders** | Depression | 8 | 5.0 | 10 | 7.1 |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnoea | 7 | 4.4 | 9 | 6.4 |
| **Skin and subcutaneous tissue disorders** | Pruritus | 10 | 6.3 | 13 | 9.3 |
| | Rash | 6 | 3.8 | 7 | 5.0 |

Table 2 includes adverse reactions observed in the placebo-controlled study RFHE3001, long term study RFHE3002 and from post-marketing experience, listed by MedDRA system organ class and frequency category.

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).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 2**: Adverse reactions listed by MedDRA system organ class and frequency category.

| **MedDRA System Organ Class** | **Common** | **Uncommon** | **Rare** | **Not known** |
|---|---|---|---|---|
| **Infections and infestations** | | Clostridial infection, urinary tract infection, candidiasis | Pneumonia, cellulitis, upper respiratory tract infections, rhinitis | |
| **Blood and lymphatic system disorders** | | Anaemia | | Thrombocytopenia |
| **Immune system disorders** | | | | Anaphylactic reactions, angioedemas, hypersensitivity |
| **Metabolism and nutrition disorders** | | Anorexia, hyperkalaemia | Dehydration | |
| **Psychiatric disorders** | Depression | Confusional state, anxiety, hypersomnia, insomnia | | |

| | | | | |
|---|---|---|---|---|
| **Nervous system disorders** | Dizziness, headache | Balance disorders, amnesia, convulsion, attention disorders, hypoesthesia, memory impairment | | |
| **Vascular disorders** | | Hot flush | Hypertension, hypotension | Presyncope, syncope |
| **Respiratory, thoracic, and mediastinal disorders** | Dyspnoea | Pleural effusion | Chronic obstructive pulmonary disease | |
| **Gastrointestinal disorders** | Abdominal pain upper, abdominal distension, diarrhoea, nausea, vomiting, ascites | Abdominal pain, oesophageal varices haemorrhage, dry mouth, stomach discomfort | Constipation | |
| **Hepatobiliary disorders** | | | | Liver function tests abnormalities |
| **Skin and subcutaneous tissue disorders** | Rashes, pruritus | | | Stevens-Johnson syndrome(SJS), Toxic epidermal necrolysis(TEN), Dermatitis, eczema |

| | | | | |
|---|---|---|---|---|
| **Musculoskeletal and connective tissue disorders** | Muscle spasms, arthralgia | Myalgia | Back pain | |
| **Renal and urinary disorders** | | Dysuria, pollakiuria | Proteinuria, | |
| **General disorders and administration site conditions** | Oedema peripheral | Oedema, pyrexia | Asthenia | |
| **Investigations** | | | | International normalised ratio abnormalities |
| **Injury, poisoning and procedural complications** | | Fall | Contusions, procedural pain | |

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the Pharmacy and Poisons Board (PPB) through the Pharmacovigilance Electronic Reporting System (PvERS) at https://pv.pharmacyboardkenya.org/ or by using the approved PPB ADR reporting forms

## 4.9 Overdose

No case of overdose has been reported.

In clinical trials with patients suffering from traveller's diarrhoea doses of up to 1800mg/day have been tolerated without any severe clinical sign. Even in patients/subjects with normal bacterial flora RIFAGUT in dosages of up to 2400mg/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

RIFAGUT 550mg contains RIFAGUT (4-desoxy-4'methyl pyrido (1',2'-1,2) imidazo (5,4-c) rifamycin SV), in the polymorphic form α.

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: intestinal, anti-infective - antibiotics - ATC code: A07AA11.

### Mechanism of action

RIFAGUT 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.

RIFAGUT has a broad antimicrobial spectrum against most of the Gram-positive and negative, aerobic and anaerobic bacteria, including ammonia producing species. RIFAGUT 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 RIFAGUT 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 RIFAGUT.

Development of resistance in the normal intestinal bacterial flora was investigated with repeated, high doses of RIFAGUT in healthy volunteers and Inflammatory Bowel Disease patients. Strains resistant to RIFAGUT developed, but were unstable and did not colonise the gastrointestinal tract or replace RIFAGUT-sensitive strains. When treatment was discontinued resistant strains disappeared rapidly.

Experimental and clinical data suggest that the treatment with RIFAGUT of patients harbouring strains of *Mycobacterium tuberculosis* or *Neisseria meningitidis* will not select for rifampicin resistance.

**Susceptibility**

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

RIFAGUT 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 RIFAGUT is not clinically effective against invasive pathogens, even though these bacteria are susceptible *in vitro*.

**Clinical efficacy**

The efficacy and safety of RIFAGUT 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 RIFAGUT 550mg 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 RIFAGUT group and 73 of 159 (46%) subjects of placebo group experienced a breakthrough overt HE episode during the 6-month period. RIFAGUT 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 RIFAGUT 550mg 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 RIFAGUT group and 82 from the placebo), and 170 subjects were new. Eighty-eight percent of patients were administered concomitant lactulose.

Treatment with RIFAGUT 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 RIFAGUT.

Combination therapy with RIFAGUT 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 RIFAGUT in the polymorph α form is poorly absorbed (less than 1%). After repeated administration of therapeutic doses of RIFAGUT 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 RIFAGUT 550 mg twice a day showed mean RIFAGUT exposure approximately 12-fold higher than that observed in healthy volunteers following the same dosing regimen. A clinically irrelevant increase of RIFAGUT systemic absorption was observed when administered within 30 minutes of a high-fat breakfast.

### Distribution

RIFAGUT 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 RIFAGUT 550mg was administered.

### Biotransformation

Analysis of faecal extracts demonstrated that RIFAGUT 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 RIFAGUT, urinary recovery of RIFAGUT was 0.025% of the administered dose, while <0.01% of the dose was recovered as

25-desacetylRIFAGUT, the only RIFAGUT metabolite that has been identified in humans.

**Elimination**

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

**Linearity/non-linearity**

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

**Special Populations**

*Renal impairment*

No clinical data are available on the use of RIFAGUT 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 RIFAGUT 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 RIFAGUT in subjects with hepatic impairment should be interpreted in light of RIFAGUT gastrointestinal local action and its low systemic bioavailability, as well as the available RIFAGUT safety data in subjects with cirrhosis.

Therefore no dosage adjustment is recommended because RIFAGUT is acting locally.

*Paediatric population*

The pharmacokinetics of RIFAGUT has not been studied in paediatric patients of any age. 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 300mg/kg/day (2.7 times the proposed clinical dose for hepatic encephalopathy, adjusted for body surface area). In the rabbit, following oral administration of RIFAGUT 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

**Tablet core:**

Rifaximin

Microcrystalline Cellulose

Sodium Starch Glycolate

Colloidal Anhydrous Silica

Hypromellose E15

Titanium Dioxide

Iron Oxide of Yellow

Iron Oxide of Red

*Isopropyl Alcohol

*Dichloromethane

*Represents solvents will not be present in finished product.

### 6.2 Incompatibilities

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

Commercial Presentation: 4's, 10's, 20's, 30's & 100's,. 1 x10's (10 tablets are packed in one PVC blister and 1 PVC blister is kept in one carton along with package insert).

**6.6 Special precautions for disposal and other handling**

Store below 30°C.

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

**7. Marketing authorisation holder**

M/s. Innocia Lifesciences Pvt. Ltd.

Block A, No.12, Balaji nagar, Ambattur, Chennai – 53, Tamilnadu, India.

ah@innocialife.com

**8. Marketing authorisation number(s)**

H2021/CTD7898/2064ER

**9. Date of first authorisation/renewal of the authorisation**

2021 September 10

**10. Date of revision of the text**

2021 September 10