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ABIMIX 200 MG FILM-COATED TABLETS
NORMICRON 200 MG FILM-COATED TABLETS
PL 19364/0030 and 0033

LAY SUMMARY

On 2\textsuperscript{nd} December 2010, the MHRA granted licences for the medicinal products Abimix 200 mg film-coated tablets and Normicron 200 mg film-coated tablets (PL 19364/0030 & 033, respectively). These are Prescription-Only Medicines (POM) to treat traveller’s diarrhoea in adults where diarrhoea is not accompanied by fever or blood in stools, or eight or more unformed (soft or liquid) stools in the last 24 hours.

Abimix 200 mg film-coated tablets are an intestinal antibiotic, containing the active substance rifaximin.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Abimix 200 mg film-coated tablets and Normicron 200 mg film-coated tablets outweigh the risks, hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Abimix 200 mg film-coated tablets and Normicron 200 mg film-coated tablets (PL 19364/0030 & 033, respectively) to UKR Regulatory Affairs Limited on 2nd December 2010. These products are Prescription-Only Medicines (POM) for the treatment of traveller’s diarrhoea that is not associated with fever, bloody diarrhoea, eight or more unformed stools in the previous 24 hours, or occult blood or leucocytes in the stool.

These applications for Abimix 200 mg film-coated tablets and Normicron 200 mg film-coated tablets were submitted as full-dossier applications, according to Article 8.3 of Directive 2001/83/EC. These products contain the active substance rifaximin.

Rifaximin is a semi-synthetic, rifamycin-based, non-systemic antibiotic, meaning that very little drug is passed into the circulation from the gastrointestinal tract, as is typical for other orally administered antibiotics. Its biological activity relies on the inhibition of DNA-dependant RNA synthesis. This is due to the high affinity of rifamycin to prokaryotic RNA polymerase. Evidence suggests that rifamycin blocks synthesis by causing strong steric clashes with the growing oligonucleotide, leading to a physical blocking of chain elongation.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture and assembly of this product.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Rifaximin

INN: Rifaximin

Structure:

Molecular formula: C_{45}H_{51}N_{3}O_{11}
Molecular weight: 785.89
Appearance: A red-orange crystalline powder Soluble in methanol, chloroform, acetone, ethyl acetate, practically insoluble in water

Rifaximin is the subject of a European Pharmacopoeia monograph, which states that Rifaximin shows polymorphism. The polymorphic form of the intended commercial product is the form α.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance rifaximin. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period, when stored in the proposed containers.

**DRUG PRODUCT**

**Other ingredients**
Other ingredients consist of pharmaceutical excipients, namely sodium starch glycinate type A, glycerol distearate, colloidal anhydrous silica, talc, microcrystalline cellulose, hypromellose, titanium dioxide, disodium edetate, propylene glycol and red iron oxide. All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of red iron oxide (which complies with the US Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients use materials sourced from animal or human origins. None of the excipients are sourced from genetically modified organisms.

**Product development**
The objective of the pharmaceutical development programme was to produce a safe, efficacious film-coated tablet that could be used for the treatment of the proposed indications. The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid.

**Manufacture**
A description and flow-chart of the manufacturing method have been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of finished product and the results appear satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The finished product is packaged in polyvinylchloride/aluminium blisters in pack sizes of nine tablets.
Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with current EU regulations regarding the contact of materials with foodstuff.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, with no specific storage instructions.

Bioequivalence
No bioequivalence studies were submitted, which is appropriate as these products were submitted under Article 8.3, as full-dossier applications.

Administrative

Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SmPC)
These are pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
These are pharmaceutically satisfactory.

The results of the PIL user testing have been submitted. These indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
This is pharmaceutically satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

1 PHARMACOLOGY
Rifaximin is an antibiotic belonging to the rifamycin group. As other rifamycin analogues, rifaximin acts by inhibiting the bacterial ribonucleic acid (RNA) synthesis. Therefore, it is assumed that the mechanism of action of rifaximin is likely to be the same, i.e. irreversibly binding to bacterial deoxyribonucleic acid (DNA)-dependent RNA polymerase.

In pharmacodynamic studies, rifaximin has shown antibacterial activity \textit{in vitro} against Gram-positive and Gram-negative, aerobic and anaerobic bacteria, isolated from various clinical materials and from stock culture collections. The antibacterial activity of rifaximin was comparable to that of rifampicin, its structural analogue, both in terms of breadth of spectrum and potency of action, but in particular rifaximin was less active against Gram-negative organisms. The activity of rifaximin on enteropathogens producing traveller’s diarrhoea, i.e. the proposed indication, was evaluated in some experiments where the drug was tested on bacteria isolated from patients. Due to its very low absorption \textit{in vivo}, oral rifaximin exerts its pharmacological activity locally in the gastrointestinal tract.

Altogether, there is sufficient evidence of the antimicrobial activity of rifaximin to support the claimed indication. Five distinct crystalline polymorphous forms of rifaximin have been recently identified. These polymorphous forms of rifaximin showed a marked difference in terms of intrinsic dissolution and \textit{in vivo} absorption. According to the Applicant, the consistency in the method of production and the lack of significant absorption \textit{in vivo} support the claim that most of the studies analyzed in this non clinical overview were performed with one of the negligibly absorbed polymorphous forms, the most likely being form $\alpha$. Hence, although the content of polymorphs of the batches tested in the non-clinical studies could not be identified, the evidence supports that it is likely to have been form $\alpha$. The polymorphic form of the Italian market product and the current intended commercial formulation is the form $\alpha$. The source and characterisation of the non-clinical batches used have been provided.

Also, it is difficult to predict the clinical relevance of the MICs observed \textit{in vitro}, since rifaximin is expected to act locally in the gut at much higher faecal concentrations than the tested ranges. Due to the poor systemic availability of oral rifaximin, unlike rifampin, conclusions reached using the rifampicin systemic breakpoints are not relevant. Moreover, the \textit{in vivo} dose-response of rifaximin has not been investigated.

In general, rifaximin showed an intermediate \textit{in vitro} activity in comparison with the other antimicrobial agents, with MICs values moderately high. MIC$_{50}$ and MIC$_{90}$ values of rifaximin, determined against many different enteropathogens isolated in different countries were between 8-64 $\mu$g/ml and 64-256 $\mu$g/ml respectively. It is expected that the concentration of rifamixin attained in stool, up to 8000 $\mu$g/g the day after oral administration, is high enough to overcome the concerns of a modest antibacterial activity and the potential of acquired resistance showed in several \textit{in vitro} experiments.
Rifaximin appeared more active against Enterobacteriaceae, *Staphylococcus* spp. and *Enterococcus* spp. than its derivative 25-desacetyl rifaximin, the only metabolite found at very low concentration in human faeces, as rifaximin is not degraded during the passage in the gastrointestinal tract.

The bactericidal activity of rifaximin was determined against *E.coli* and *S. aureus*. Rifaximin and rifampicin had similar bactericidal activity.

Across the studies, the MICs were variable both between and within strains, with ranges of several orders of magnitude, indicating the potential for exposure to rifaximin to select resistant mutants. To further discuss the clinical relevance of *E.coli* resistance to rifaximin and the consequences for the treatment of traveller’s diarrhoea, results were analysed in patients with ulcerative colitis. In patients with ulcerative colitis, the results showed no resistant strains after three courses of rifaximin 1,800 mg/day for 10 days, each followed by a 25-day washout period. Additionally, in a comparative study carried out between rifaximin and rifampicin where 27 coliforms were identified biochemically as *Escherichia coli*, the results showed no significant difference between rifaximin and rifampicin resistant coliforms after 3 days of treatment followed by a 2-day washout period. Therefore, the potential of rifaximin to select *E. coli*-resistant mutants obtained *in vitro* is likely to have little or no clinical relevance.

In the light of the submitted experimental data, the minimal systemic exposure to rifaximin does not appear to be a threat to the utility of rifamycins particularly in the treatment of tuberculosis. However, patients bearing *M. tuberculosis* should not be treated with rifaximin.

Studies of safety pharmacology after oral administration of rifaximin were performed without revealing any concern on potential undesirable effects of rifaximin on physiological functions. However, due to its limited bioavailability in the gastrointestinal tract, the exposure levels attained after oral administration of rifaximin were only in-line with the therapeutic plasmatic range. Since rifaximin is negligibly absorbed in animals and humans, and the clinical treatment for traveller’s diarrhoea is limited to only 3 days, the investigation of the QT interval is unnecessary, particularly when the chronic administration of rifaximin for 26 weeks to rats and 39 weeks to dogs did not show any sign of cardiac adverse effect. In addition, one cannot ignore the comprehensive clinical data collected over the last 21 years, where no cardiac adverse event has been reported.

Pharmacodynamic interactions have not been investigated and they would not be expected to occur systemically, due to the low systemic bioavailability of rifaximin. However, pharmacodynamic interaction in the gastrointestinal system cannot be excluded.
2 PHARMACOKINETICS

The old pharmacokinetic investigations demonstrated a low systemic absorption of oral rifaximin that is suitable for its localized action in the gastrointestinal tract.

The results of an absorption study performed in dogs with the five identified forms of rifaximin (α, β, γ, δ, ε) exhibited marked differences in their oral bioavailability, being α and β the less absorbed. According to the Applicant, the pharmacokinetic studies carried out before the polymorphism identification were most likely performed with a rifaximin of form α.

Several different methods have been used to measure the plasma concentrations of rifaximin: a microbiological assay in old studies, 14C-rifaximin liquid scintillation spectrometry and liquid chromatographic tandem mass spectrometric (LC-MS/MS).

In rats, dogs and rabbits, the systemic exposure showed non-linear (dose-dependent) kinetics, with increasing exposure after repeated dose oral rifaximin up to a maximum value of C_\text{max} nearly 20 ng.h/ml, comparable in all the tested species systemic exposure and in humans. Above this value, the systemic exposure did not increase by increasing the dose consistent with a limited capacity for the absorption of rifaximin. This poor absorption was not affected by food, according to the results in normally fed or fasting rats. There were no significant evidence of accumulation.

The studies with the radiolabelled compound showed that the greatest concentration of radioactivity was associated with the gastrointestinal tract, which is the therapeutic target organ. Concentrations of radioactivity in organs other than the gastrointestinal tract were generally small, and only liver and kidney contained > 0.01% dose, with the highest concentration present in the liver at 0.5 hours.

In pigmented rats, radioactivity was detected in all tissues analyzed only 2 hours after dosing and there was no persistence of radioactivity in melanin-containing tissues. Transplacental transfer and excretion in milk have not been investigated.

The metabolic profile of rifaximin has not been characterised in laboratory animals and a possible metabolic pathway has not been elucidated. 25-desacetyl rifaximin has been identified as the main human metabolite, but it accounted for less than 1% of dose.

The potential in vivo interconversion of stereoisomers in the gastrointestinal tract has not been investigated.

The major route of excretion of 14C-rifaximin was in faeces, with all rats excreting >89% dose; the excretion in urine was < 1%, with means of 1.72% dose (male) and 0.5% dose (female) excreted in bile. Summation of the proportions of the dose in bile, urine and the carcass suggested that the total absorbed was less than about 5% dose. The difference in bile excretion between male and female animals emphasized the possibility of a sex-dependent difference in excretion. The biliary excretion data suggest that of the small proportion of the oral dose absorbed, there is a significant first-pass removal of rifaximin by the liver.
In dogs, after oral and intravenous administration, most of the recovered radioactivity was excreted in faeces (>88% and >83%dose, respectively), while the urine was only a minor pathway of excretion (6% dose intravenously, <0.6% dose orally).

**Pharmacokinetic drug interactions**
Specific studies in animals have not been performed, but considering the scanty absorption of oral rifaximin pharmacokinetic drug interaction would not be expected. Rifaximin did not show any modification of the anticonvulsant effect of diazepam, contrary to rifampicin.

The potential of rifaximin for the inhibition or the induction of cytochrome P450 (CYP450) isozymes was evaluated *in vitro* with human hepatocytes and liver tissue. The results indicated that rifaximin, unlike rifampicin, at anticipated clinical plasma concentrations has no potential to inhibit or to induce human hepatic cytochrome P450.

**Other pharmacokinetic studies**
The administration of rifaximin to rats with mild and severe induced enterocolitis showed an increase in the systemic absorption when ulceration was induced, only in fasting rats. In the presence of inflammation only, the absorption did not change. Caution should be exercised to avoid the administration of rifaximin in case of ulcerations in the gastrointestinal mucosa.

### 3 TOXICOLOGY

Rifaximin drug substance used in all toxicological studies is most likely considered to be form α. The non-clinical studies have not demonstrated important toxicities of potential clinical relevance. Source and characterisation of the non-clinical batches have been provided. To address the possibility of interconversion between the different forms of rifaximin, the Applicant has provided a comparative table of the content of impurities in the tested non-clinical batches and the specifications for the commercial product. The impurity levels stated are within acceptable levels.

Acute toxicology studies with rifaximin administered by intravenous route were conducted in mice and rats. The lowest lethal intravenous dose to rats of rifaximin was 40 mg/kg and the toxicity was most likely due to the vehicle formulation of 50% PEG 400. The possibility that the mortality observed by intravenous is due to systemically available rifaximin cannot be excluded. Single oral dose of 2000 mg/kg of rifaximin was non-toxic to rats.

The repeat-dose toxicology studies were performed in rats, dogs and rabbits by the oral route proposed for human therapy. In rats given daily oral rifaximin for 6 months, except for a decrease in weight gain and a decrease in white cell count, no meaningful changes attributable to rifaximin were present in clinical condition, food consumption, clinical pathology parameters, or in organ weights or gross- and histopathology examinations. Based on these results, the NOAEL was 300 mg/kg/day was.

In a 39-week study in dogs, thymic atrophy/involution was seen in rifaximin-treated animals with evidence of reversibility following the recovery period. However, there were no histopathological changes in other lymphoid tissues such as the lymph nodes,
gastrointestinal tract or spleen. The thymus changes were considered not toxicologically relevant and, therefore, the NOAEL was 1000 mg/kg/day.

Due to the fact that rifaximin is insoluble in toxicity-free solvent at high dosages and that has a limited oral absorption capacity, the exposure levels reached in the toxicity studies account for a low safety margin. The NOAEL proposed by the non-clinical expert accounts for a systemic exposure up to 20 ng/ml approximately, which is only in line with the systemic clinical exposure in some patients.

An interspecies comparison table of the exposures, including the safety margin for the main toxicity and safety pharmacology studies, showed that systemic absorption is not dose-dependent and increasing the dose the exposure doesn’t increase in a proportional way. Toxicokinetics have not been performed in the safety pharmacology studies considering that the same animal species for toxicity studies were used, except mice. Due to the fact that rifaximin is insoluble in toxicity-free solvent at high dosages and that has a limited oral absorption capacity, the exposure levels reached in the toxicity studies account for a low safety margin. The limited exposure could limit the value of some results for extrapolation of the risk to humans.

The antibacterial activity of rifaximin restricted the maximum evaluable dose in the Ames test and the low oral absorption limited the exposure of the bone marrow in the micronucleus test in rats, thus reducing the sensitivity of the genotoxic battery tests. However, no evidence of genotoxic effects of rifaximin has been observed for gene mutation in yeast and CHO cells, and for chromosomal aberration in human lymphocytes. Therefore rifaximin is considered to be not genotoxic.

No carcinogenicity studies have been done with rifaximin. The lack of carcinogenicity studies is acceptable taking into account the negative results in the genotoxicity studies and the short-term treatment (3 days) for the proposed indication.

Rifaximin at a dose level up to 300 mg/kg did not cause adverse effects on the fertility of treated male and female rats, and on the postnatal development and reproductive performance of the offspring. However, adverse effects on morphological development of the foetuses were seen in the 150 and 300 mg/kg treated groups. Foetal effects may be caused by the action on the intestinal flora and inhibition of nutrient absorption. The antibacterial effects on the intestinal flora could an inhibition in maternal nutrient absorption, especially at higher dosage, that may have been responsible for the foetal effects in rabbits. However, morphological alterations have been observed in the foetuses of rifaximin orally administered rats (150 to 300 mg/kg; study T19) and rabbits (62.5 to 1000 mg/kg) at doses that did show no or little maternal toxicity, respectively. There also is an inter-species concordance in the occurrence of skeletal abnormalities that seem to be indicative of developmental toxicity. Therefore, the studies in the two species tested have shown reproductive toxicity, regardless of the classification of the skeletal findings as malformations or variations. The non-clinical information in section 4.6 and the section 5.3 of the SmPC has been worded to reflect the toxicity to reproduction observed in animals and according to the Guideline on the Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling EMEA/CHMP/203927/05. Studies on juvenile animals have not been performed and are not required since rifaximin is not indicated in children.
The local tolerance of oral rifaximin has not been evaluated. Antigenicity studies have not been performed and are not required. Potential cross-hypersensitivity to rifamycin derivatives is not excluded.

The administration of rifaximin, at dosages up to 500 mg/kg/day, produced no effects on the immune system of toxicological significance in an immunotoxicity study. However, taking into account all the experimental results, including haematological, histological and functional changes (e.g. decreases in circulating lymphocytes and decreases in spleen and thymus weights decrease in the production interleukin IL-2, IL-12, and IFN-γ levels) observed in treated animals, an immunomodulatory effect of rifaximin on the cellular immune system cannot be excluded.

No studies on dependence have been conducted and are not required since no signs of dependence or withdrawal have been observed in the toxicity studies and the short-term treatment for the proposed indication.

25 desacetyl-rifaximin is the only metabolite of rifaximin identified in human faeces. Rifaximin appears to be more active than its derivative 25-desacetyl rifaximin against Enterobacteriaceae, *Staphylococcus* spp. and *Enterococcus* spp.

### 4 ECOTOXICITY/ENVIRONMENTAL RISK ASSESSMENT

The Applicant has conducted Phase II tier A studies. The worst case Predicted Environmental Concentration (PEC) for rifaximin, assuming no degradation or removal in sewage treatment is 4 μg/l. The worst case PEC/Predicted No-effect Concentration (PNEC) ratio for rifaximin to groundwater and micro-organisms are both below the respective trigger values, indicating that it does not present a risk to these. The worst-case PEC/PNEC ratio for surface water was above the respective trigger value based on the No-Observed-Effect-Concentration (NOEC) for the blue-green alga *Anabaena sp*. So the PEC_{SURFACE WATER} was further refined by Sewage Treatment Plant (STP) simulation by using the Simple Treat model. The results of adsorption:desorption (OECD 106) and sediment water fate (OECD 308) studies showed that rifaximin was readily adsorbed onto sewage sludge and was readily hydrolysed both in aqueous solution and on sediments.

The PEC_{SURFACE WATER} and PNEC_{SURFACE WATER} of rifaximin, taking into account adsorption onto sewage sludge and hydrolysis, were estimate to be 0.02 μg/l and 0.24 μg/l, respectively, and the PEC_{SURFACE WATER}/PNEC ratio for surface water, 0.08. Rifaximin is not, therefore, likely to present a risk to organisms in surface waters.

Rifaximin and its degradates are likely to progressively partition to sewage solids and sediments, where they are stable and predominantly unextractable.

The assessments conducted on the fate and effects of rifaximin encompass both the parent substance and its degradation products, because its rapid rate of hydrolysis gives rise to the presence of both in test media within the first 24 hours of exposure. It can be concluded from the studies conducted that neither rifaximin nor its hydrolysis products are toxic to microorganisms, nor are they toxic to aquatic organisms as a result of exposure in aqueous solution or (because food is administered in the Daphnia and Fish early life stage test) by ingestion of adsorbed material.
In conclusion, rifaximin is not considered to present a potential risk to micro-organisms, surface water or ground water.

5 NON-CLINICAL EXPERT REPORT
The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical data submitted.

6 CONCLUSIONS
The grant of marketing authorisations is recommended for these products.
1 CLINICAL PHARMACOLOGY
1.1 PHARMACOKINETICS

In Study BA 9701, the small concentrations of both radioactivity and rifaximin in plasma indicated little systemic availability of $^{14}$C-rifaximin and of its metabolites. The amount of radioactivity in urine (<0.4% dose) also indicated that $^{14}$C-rifaximin was poorly absorbed from the gastrointestinal tract. The fact that most faecal radioactivity was associated with $^{14}$C-rifaximin supports a conclusion of poor absorption, since the small fraction of the dose that was absorbed was extensively metabolised (about 18% of radioactivity in plasma was associated with rifaximin and rifaximin accounted for 4-15% of urine radioactivity). Therefore, if there had been considerable absorption then biliary excretion would be expected to result in the presence of metabolites of $^{14}$C-rifaximin in faeces. Finally, since 168 hours after administration > 96% of the dose was recovered in faeces as parent drug, it appears that rifaximin is not metabolised by the gut microflora.

The findings of BA 9701 are supported by the other studies in which the oral bioavailability of rifaximin was studied in healthy volunteers and in patients with diarrhoeal disease. The actual maximum concentrations observed have varied between studies and sometimes considerably between individuals. However, even with single doses of 400 mg in healthy volunteers, $C_{\text{max}}$ has generally been < 10 ng/ml and the amounts of the oral dose recovered from urine have been < 1%. While taking rifaximin with a high-fat meal increased $C_{\text{max}}$ and AUC by approximately three-fold, systemic exposure was still low. In patients with diarrhoeal disease taking at least 200 mg three times daily, maximal plasma levels were < 25 ng/ml and urinary recovery was < 1%.

Faecal concentrations of rifaximin in patients treated with 400 mg twice daily for 3 days in Study ESID 9701 declined over 7 days post treatment to very low levels. On the first post therapy day the mean concentration was approximately 8 mg/g, declining to about 2 mg/g by the 5th day.

*In vitro*, rifaximin did not appear to inhibit the range of CYP isoenzymes tested, but it did induce CYP3A4, albeit less efficiently than rifampicin. *In vivo*, rifaximin did not appear to affect plasma levels of ethinyl oestradiol, norgestrel or 17-deacetylnorgestimate, when a single dose of ethinyl oestradiol and norgestimate was administered on the last day of a rifaximin 200 mg q8h regimen. Also, a 7-day regimen of rifaximin 200 mg q8h did not affect plasma concentrations of midazolam or 1'-OHmidazolam after intravenous or oral dosing. Midazolam (IV or PO) slightly reduced systemic exposure to rifaximin.

Overall, the plasma concentrations of rifaximin that seem to be achieved in man are very low and, despite the theoretical potential for drug-drug interactions to occur, there would seem to be a low potential for clinically significant interactions.
1.2 PHARMACODYNAMICS

The mechanism of action of rifaximin does appear to be similar to that of rifampicin. Data on cross-resistance between rifaximin and other rifamycins, and investigation of the most likely mechanism of acquired resistance to rifaximin that may be encountered, are important omissions from the dossier. However, the assessor identified a recent (2007) publication that describes the mechanism of resistance to rifaximin in a laboratory-selected mutant strain of Bifidobacterium infantis. A mis-sense mutation at codon 513 of the rpoB gene was evident when the rifaximin-resistant mutant was compared with the fully susceptible parent strain. Without any further data, the assessor assumes that the major mechanisms of resistance to rifaximin would be similar to those for other rifamycins and that cross-resistance between rifaximin and other rifamycins should be expected.

In the in vitro studies of antimicrobial activity of rifaximin, MIC50 values ranged from 0.001-128 μg/mL and MIC90 from 0.005-256 μg/mL. The data indicate that several potentially important species in diarrhoeal disease may not be very susceptible to rifaximin (e.g. Salmonellae and some Shigella spp.), whereas others were likely normally susceptible, but included isolates that had acquired resistance. The latter seem to include C. difficile. However, the relationship between MICs of rifaximin and clinical outcomes when it is used for the treatment of travellers’ diarrhoea is unknown and cannot be predicted due to the fact that local gut concentrations of rifaximin may be very high during therapy and may serve to overcome at least some degree of acquired resistance mechanisms.

Several studies have demonstrated the considerable potential for exposure to rifaximin to select for resistance in the endogenous intestinal flora. However, once the selection pressure is withdrawn (i.e. after stopping therapy) there seems to be a reasonably rapid drop in detection of resistant strains over a period of about 2 weeks.

There has to be a particular concern regarding whether exposure to rifaximin in patients harbouring Mycobacterium tuberculosis could select for mutants resistant to rifampicin. Thus far it seems likely that with very low systemic exposure to rifaximin the potential for this to happen is very low. Nevertheless, the assessor considers that rifaximin should not anyway be administered to patients who are taking other rifamycins (e.g. rifampicin, rifabutin and rifapentine) due to the unknown potential for pharmacodynamic interactions to occur in the gut. Therefore, patients who are being treated for mycobacterial disease would not anyway receive rifaximin.

2 CLINICAL EFFICACY

DOSE FINDING

The Phase II dose-finding study (ESID 9601) evaluated the 200 mg t.i.d. rifaximin regimen in comparison with higher doses but administration was over 5 days. There was no placebo group in this study and the active comparative regimen (sulphamethoxazole - trimethoprim) would not be considered optimal in 2007. The results of this study do not clearly support a conclusion that 200 mg t.i.d. was an optimal choice for the Phase III studies (in which it was given for only 3 days).

Nevertheless, it is important to take into account that 50-80% of untreated cases of travellers’ diarrhoea have resolved within 5 days (and often within 2-3 days) and that only 1-3 days of treatment with various fluoroquinolones has been shown to shorten...
the duration of symptoms. In addition, study 9802 compared 200 mg and 400 mg t.i.d. over 3 days with placebo and these data need to be taken into account.

Overall the assessor considers that the choice of 200 mg three times daily for 3 days as the regimen of rifaximin used in two Phase 3 studies was not unreasonable. The investigation of 400 mg twice daily in the third study is also not unreasonable given that rifaximin exerts its antibacterial action locally within the gut. Indeed, a once daily dose, if sufficient, might be expected to be efficacious.

**Efficacy of 200 mg three times daily for 3 days**

Of the three Phase III studies the assessor considers that the two that compared rifaximin 200 mg t.i.d for 3 days with placebo (0201 and 9802) are pivotal. In addition, the assessor considers that most weight should be placed on the more recent Study 0201, in which placebo and active control groups were employed.

The selection criteria in ESID 0201 and 9802 seem to have been appropriate. However, it is worth pointing out that in Study 0201 < 20% of subjects had fever and < 17% had blood and/or mucus in stool at baseline. In 9802, 20-25% had fever, but only 1-2% reported blood in the stool. Therefore, the majority of subjects did not have a systemic illness or evidence of dysenteric diarrhoea.

ESID 0201 demonstrated that rifaximin shortened the median TLUS from about 66 hours (2.75 days) to 32 hours (1.3 days), with only a small numerical difference between rifaximin and ciprofloxacin in the ITT population. The findings were very consistent with those for the ITT population in ESID 9802, in which rifaximin 200 mg t.i.d. shortened the median TLUS from about 60 hours (2.5 days) to 33 hours (1.4 days), with no detectable difference between this dose and the rifaximin 400 mg t.i.d. regimen. The issue regarding the Goa site was found to affect results for rifaximin and ciprofloxacin in a similar fashion. After excluding data from Goa, the median TLUS values in all three treatment groups were lower than in the primary analysis, but there was still a two-fold difference between each of the rifaximin and ciprofloxacin groups (both 24 hours) and the placebo group (48 hours).

It is appropriate that the ITT populations were used for the primary analysis that compared rifaximin with placebo. In the EE populations (met the inclusion/exclusion criteria, took at least 2 days of assigned therapy, completed daily diaries for at least 2 days and did not take any prohibited medications), the median TLUS in the active and placebo groups were shorter and the actual differences between rifaximin and placebo were smaller (31 hours vs 48 hours in 0201 and 33 hours vs 57 hours in 9802), although they still reached significance.

Therefore, based on TLUS results in the populations enrolled into these studies, the proposed rifaximin regimen may reduce the time that a traveller is incapacitated by diarrhoea. The median benefit may be somewhere in the region of 1 to 1.5 days. This difference might be viewed as being potentially useful, especially to persons on business trips or on short-break holidays.

However, in the ITT population of 0201, the proportion of treatment failures in the rifaximin group was twice that in the ciprofloxacin group (14.7% versus 6.9%). This merits further exploration.
It was noted that 11/17 (65%) rifaximin-treated subjects who discontinued study drug due to lack of efficacy had fever and/or blood in the stool at baseline, compared to 4/12 such subjects in the placebo group and 1 of 2 in the ciprofloxacin group. When the subjects with fever or blood in the stool at baseline were excluded (leaving 241 subjects across the three groups), the proportions of treatment failures in the rifaximin and ciprofloxacin groups were similar (8.6% versus 7.7%).

The logistic regression analyses showed that gross blood in stool at baseline (p=0.0041), occult blood in stool at baseline (p=0.0005) and ≥8 unformed stools in the 24 hours preceding treatment (p=0.0033) were significantly associated with the presence of inflammatory/invasive pathogens. Efficacy for subjects with inflammatory/invasive pathogens (including \textit{C. jejuni}) was poor. In this subgroup more than half the subjects treated with rifaximin failed to achieve wellness and the median TLUS could not be calculated. The median TLUS in the placebo and ciprofloxacin groups were calculated at ≥ 65 hours for these subjects. Also, the median TLUS for rifaximin-treated subjects with \textit{Shigella spp.} was much longer than for those with \textit{E. coli}.

It is also relevant to note that the sub-group analyses of TLUS suggested an overall advantage for ciprofloxacin in subjects with a demonstrated pathogen, whether or not an inflammatory/invasive pathogen in type, and with leucocyte positive stool. In contrast, there was no advantage apparent for ciprofloxacin over rifaximin among those with ETEC.

Most of those who achieved wellness had an overall microbiological response of eradication. Therefore it is pertinent to note that the eradication rate was 81% for ciprofloxacin compared to 62% for rifaximin and 52% for placebo. Also, 18 subjects treated with rifaximin who were culture-positive with \textit{C. jejuni} or \textit{Salmonella} were deemed to be clinical failures, while only six achieved clinical wellness. Pathogen persistence was noted in 83.3% (15/18) of these failures. Note also that at the post treatment visit, overall 53% followed-up in the rifaximin group, 39% in the placebo group and 71% in the ciprofloxacin group had no post-treatment pathogen detected.

On pooling data from 0201 and 9802, it was observed that among subjects culture-positive for diarrhoeagenic \textit{E. coli}, clinical wellness was achieved in 122 and treatment failure was noted in 17 subjects. For the 122 clinical successes, pathogen eradication was reported in 95 (77.9%) cases, while eradication was observed in 12/17 (70.6%) of the failures. Also, among the 15 rifaximin-treated subjects that were culture positive for \textit{Shigella} spp. at baseline all achieved clinical wellness and 13/15 (86.7%) achieved eradication.

In contrast, among subjects culture-positive with invasive pathogens \textit{C. jejuni} and \textit{Salmonella} species 19 were reported as clinical failures and only 9 achieved clinical wellness with rifaximin therapy. Pathogen persistence was noted in 16/19 (84.2%) of the failures. In the MITT population, one or more new pathogens were isolated post treatment in 25.4% (49/193) of rifaximin-treated subjects, 23.9% (28/117) of placebo-treated subjects and 13.7% (14/102) of ciprofloxacin-treated subjects. The applicant acknowledges that the lower rate of newly isolated post treatment pathogens
in ciprofloxacin-treated subjects would be consistent with the higher level of pathogen eradication produced by this agent.

Despite the overall TLUS results, these additional findings indicate that rifaximin may provide a useful benefit over placebo only in specific types of travellers’ diarrhoea, and that it is not as suitable for this use as ciprofloxacin.

**Efficacy of 400 mg twice daily for 3 days**

The only study that evaluated the alternative dose regimen proposed in the draft SmPC (400 mg twice daily) was 9701.

The median TLUS for the ITT population was 25.7 hours for rifaximin and 25 hours for ciprofloxacin, and the sponsor concluded that the treatment groups were equivalent. However, the estimated hazard ratio for comparing rifaximin to ciprofloxacin was 0.82 (95% confidence interval: 0.60 – 1.11). The 95% confidence interval for the difference in median TLUS (rifaximin group – ciprofloxacin group) calculated using a bootstrap procedure was (-16.7, 5.6). A TLUS of 0 hours, indicating that subjects had met the criteria for wellness immediately after initiation of treatment, was noted for 7/93 subjects (7.5%) in the rifaximin group and 20/94 subjects (21.3%) in the ciprofloxacin group. There were nine treatment failures (9.7%) in the rifaximin group and three (5.7%) in the ciprofloxacin group. A “bacteriological cure” was noted for 30/43 subjects (69.8%) in the rifaximin group and 39/48 subjects (81.3%) in the ciprofloxacin group with at least one pathogen isolated in the pre-treatment culture. Pathogens isolated in the post-treatment culture that were not present in the pre-treatment culture were noted for 11 subjects in the rifaximin group and one subject in the ciprofloxacin group.

Despite the TLUS findings, the study pointed very much towards a greater benefit of ciprofloxacin over rifaximin. The data from 0201 and the pooled analyses across 0201 and 9802 (as described above) also pointed to a greater benefit for ciprofloxacin over rifaximin in several secondary analyses. With no placebo control group in Study 9701 to allow for an assessment of the benefit of rifaximin over no antibacterial therapy, it is not possible to conclude that the 400 mg b.i.d. regimen is appropriate. Therefore, the assessor does not consider that this alternative dose regimen can be allowed in the SmPC.

**Assessor’s overall conclusions**

The primary analysis results based on median TLUS demonstrate a benefit of rifaximin over placebo that is similar in magnitude to that conferred by ciprofloxacin. While rifaximin may shorten the median TLUS by about 1 to 1.5 days, this seemingly quite modest benefit could be useful to those who most need to recover quickly while travelling. However, more detailed analyses from 0201 and 9802 have indicated that rifaximin is unlikely to confer any useful benefit in those who have *Campylobacter*, *Shigella* or *Salmonella* infections. The difficulty is that it is not at all likely that subjects who are provided with a course of rifaximin to take on a trip would have access to rapid diagnostic facilities, and it is not possible to come to any firm conclusions regarding the most likely pathogen based on symptoms and stool appearance that might be used to qualify an indication for use.
There is also the issue that the results of 0201 and 9701 indicate that rifaximin is generally less suitable for the management of travellers’ diarrhoea than ciprofloxacin. The limited data suggest that the systemic availability of ciprofloxacin may be associated with a more reliable effect in infections due to invasive pathogens, albeit less than in other types of infections. Also, ciprofloxacin was more likely to achieve pathogen eradication and was associated with a lower rate of detection of “new” pathogens than rifaximin. The assessor accepts that finding pathogens in post treatment stools did not necessarily correlate with symptoms at the time the sample was obtained. Nevertheless, none of the studies followed-up subjects beyond 3 days post therapy and so it is not known if there were any later clinical consequences of the differences in eradication rates, and appearance of “new” pathogens, between the rifaximin and ciprofloxacin groups.

The data suggest that rifaximin may provide a useful benefit over placebo and comparable efficacy to ciprofloxacin only when travellers’ diarrhoea is not associated with invasive bacterial species. Clinical signs and symptoms alone are not reliable to exclude the use of rifaximin in patients who are unlikely to benefit from it and who should be receiving another agent from the outset, if specific antibacterial therapy is deemed to be necessary. However, the data point to the possibility of precluding use of rifaximin in patients with:

- Fever
- Bloody diarrhoea
- ≥ eight unformed stools in the previous 24 hours
- Occult blood or leucocytes in the stool (if testing available).

These features will not entirely select out patients with infections that may show a response to rifaximin and, indeed, might prevent some patients who could benefit from receiving the agent.

3 CLINICAL SAFETY

The most relevant data come from the 591 subjects with travellers’ diarrhoea who were treated with rifaximin in four Phase II/III studies, of which 320 were treated in the two placebo-controlled studies. In the two placebo-controlled studies (ESID 0201 and 9802), there was no excess of adverse events or drug-related adverse events in the rifaximin group compared to the placebo group. Also, in ESID 0201 the adverse event profiles of rifaximin and ciprofloxacin were similar.

Overall, the safety profile of rifaximin during 3 days’ treatment for travellers’ diarrhoea has been unremarkable, as would be expected for an agent that is hardly absorbed. However, even with low systemic availability, allergic reactions have occurred that seem to have been due to rifaximin.

It should be noted that, with a last visit at only 3 days post-therapy, the safety databases from the traveller’s diarrhoea studies do not allow for any judgement to be made about longer-term safety, most particularly whether there is any potential for rifaximin to select for *C. difficile* enterocolitis. Patients with hepatic encephalopathy, and with other conditions in which rifaximin has been studied, have received longer courses (e.g. 14 days every month for up to 6 months in hepatic encephalopathy), but the collection of safety data in these studies was generally inadequate and patients were not followed-up appropriately.
In addition, despite the apparent lack of major safety issues, the number of post marketing adverse drug reaction reports received is astonishingly small. It can only be surmised that with > 9 million of the estimated total 9.7 million doses distributed having been administered in Italy, there are some major deficiencies in spontaneous reporting attitudes in that country. Of these Italian reports, it was clear that rashes and urticaria predominated together with various gastrointestinal complaints. In 2008 there were five subjects with rashes, plus seven with urticaria, so that 12/17 subjects had some sort of potential hypersensitivity reaction. In 2007, 4/7 subjects had events that might represent hypersensitivity and 3/5 in 2006.

In addition to this, an updated Periodic Safety Update Review has been provided, including Food and Drug Administration Health Professional confirmed cases from May 2004 to April 2009. A total of 71 cases reports (65 spontaneous medically confirmed cases, 3 cases with trade name unknown, 1 case from literature and 2 cases from consumers) have been received. The frequency of these events is very low (0.001%) considering the number of patients potentially treated during the reporting period (conservative estimate of 5 million patients). In addition, during the period under review, 29 serious cases, 32 non-serious unlisted and 26 non-serious listed cases medically confirmed (for a total of 185 adverse reactions) plus 88 cases reported by consumers occurred in the USA and were notified by other manufacturers.

The applicant has made sufficient changes to the SmPC and the Risk Management Plan to reflect all possible adverse drug reactions.

4 PHARMACOVIGILANCE
4.1 PHARMACOVIGILANCE SYSTEM
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

4.2 RISK MANAGEMENT PLAN
A satisfactory Risk Management Plan has been provided, which suitably evaluates the need for risk minimisation activities. Based on this, the following safety concerns have been identified and additional activities outlined for each:

i. Potential for new drug-drug interactions:
   - Continuous and close monitoring of safety signals deriving from PM data for potential new drug-drug interactions
   - Post authorisation drug utilisation study proposed

ii. Potential off-label paediatric use:
   - Appropriate labelling
   - Readability testing of PIL
   - Post authorisation drug utilisation study proposed

The post authorisation drug utilisation study is to assess the potential risk for drug-drug interactions with rifaximin to occur at the level of gut transporter systems, and to assess off-label use of rifaximin, including duration of use and use in children by collecting prescribing data from the UK general Practice Research Database.
5 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for the UK brand leaders. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

6 CLINICAL EXPERT REPORT
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical data submitted.

7 CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Abimix 200 mg film-coated tablets and Normicron 200 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
Suitable non-clinical data have been submitted with these applications. The relevant sections of the SmPC have been updated to reflect the non-clinical data submitted. A suitable Environmental Risk Assessment has been submitted, showing that rifaximin is not considered to present a potential risk to micro-organisms, surface water or ground water.

EFFICACY
Suitable data have been submitted to show that these products are efficacious for the indications that are stated. The safety data, although limited, shows that the adverse reactions frequency with these products is low. Sufficient changes have been made to the SmPC and the Risk Management Plan to reflect all possible adverse drug reactions.

A suitable Pharmacovigilance System and Risk Management Plan have been submitted.

The SmPC, PIL and labelling are satisfactory and consistent with the data that have been submitted.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable and evidence of efficacy has been provided. The adverse event profile for these products is suitable for its use. The benefit/risk is, therefore, considered to be positive.
ABIMIX 200 MG FILM-COATED TABLETS
NORMICRON 200 MG FILM-COATED TABLETS
PL 19364/0030 and 0033

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation applications on 11th October 2007

2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 31st October 2007

3. Following assessment of the applications, the MHRA requested further information relating to the pharmaceutical/non-clinical on 12th March 2008, and clinical dossiers on 30th October 2008

4. The applicant responded to the MHRA’s requests, providing further information on 4th May 2010

5. The applications were determined on 2nd December 2010
ABIMIX 200 MG FILM-COATED TABLETS  
NORMICRON 200 MG FILM-COATED TABLETS  
PL 19364/0030 and 0033

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
</table>
1 NAME OF THE MEDICINAL PRODUCT
   ▼ Abimix 200 mg film-coated tablets
   ▼ Normicron 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
   One film-coated tablet contains:
   Rifaximin 200 mg

   Excipients:
   For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
   Film-coated tablet
   Pink circular biconvex film-coated tablets, with “RFX” debossed on one side.

4 CLINICAL PARTICULARS
   4.1 Therapeutic indications
   Abimix/Normicron is indicated for the treatment of traveller’s diarrhoea that is not associated
   with any of:
   Fever
   Bloody diarrhoea
   Eight or more unformed stools in the previous 24 h
   Occult blood or leucocytes in the stool.

   Abimix/Normicron may shorten the duration of diarrhoea when this is associated with non-
   invasive strains of E.coli (see sections 4.4 and 5.1).

   4.2 Posology and method of administration
      Posology
      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 (see section 4.4).

      Rifaximin can be administered with or without food.

      Paediatric population
      The safety and efficacy of Abimix/Normicron 200 mg film-coated tablets in children (aged
      less than 18 years) have not been established.

      A dosage adjustment for patients with hepatic or renal insufficiency is not necessary.

      Method of administration
      Orally with a glass of water.

   4.3 Contraindications
   Hypersensitivity to the active substance, to any rifamycin (e.g. rifampicin or rifabutin) or to
   any of the excipients.

   4.4 Special warnings and precautions for use
   Clinical data have shown that Rifaximin is not effective in the treatment of traveller’s
   diarrhoea caused by invasive enteric pathogens such as Campylobacter, Salmonella and
   Shigella, which typically produce dysentery-like diarrhoea characterised by fever, blood in
   the stool and high stool frequency.

      If symptoms worsen treatment with Rifaximin should be interrupted.

      If symptoms have not resolved after 3 days of treatment, or recur shortly afterwards, a second
      course of Rifaximin should not be administered.
**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.

**Paediatric population**
Abimix/Normicron 200 mg film-coated tablets are not recommended for use in children (<18 years old).

### 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. Due to the lack of data and the potential for severe disruption of gut flora with unknown consequences rifaximin should not be administered concomitantly with other rifamycins.

Due to the negligible gastrointestinal absorption of orally administered Rifaximin (less than 1%), the systemic drug interaction potential is low.

*In vitro* data show that Rifaximin is a weak inducer of the CYP3A4 isoenzyme of the P450 cytochrome. Drug-drug interaction studies investigating the clinical interaction between Rifaximin and drugs metabolised by the human cytochrome P450 isoenzymes demonstrated that Rifaximin did not significantly affect the pharmacokinetics of midazolam or an oral contraceptive containing ethinyl estradiol and norgestimate. Therefore, clinical interactions with drugs metabolised by these isoenzymes are not expected.

The potential for drug-drug interactions to occur at the level of gut transporter systems has not been evaluated and cannot be ruled out.

No drug interaction studies investigating the concomitant intake of Rifaximin and other drugs that might be used during an episode of traveller’s diarrhoea (e.g. loperamide, charcoal) are available. Patients should take Rifaximin at least 2 hours after the administration of charcoal.

### 4.6 Pregnancy and lactation

For Rifaximin no clinical data on exposed pregnancies are available.

Animal studies have shown reproductive toxicity (see 5.3).

Rifaximin is not recommended during pregnancy and in women of childbearing potential not using contraception (see Section 5.3).

It is not known whether rifaximin is excreted in human milk. A decision should be taken whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

In clinical controlled trials dizziness has been reported but rifaximin has negligible influence on the ability to drive and use machines.
## Undesirable effects

In clinical studies in subjects who received Rifaximin for treatment of traveller’s diarrhoea Adverse Reactions considered as being at least possibly related to Rifaximin have been categorised by organ system and frequency.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class (ver. 12.1)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1000 to &lt;1/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Candidiasis, Herpes simplex, Nasopharyngitis, Pharyngitis, Upper respiratory tract infection</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorder</td>
<td>Lymphocytosis, Monocytosis, Neutropenia</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite, Dehydration</td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Abnormal dreams, Depressed mood, Insomnia, Nervousness</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, Headache, Hypoesthesia, Migraine, Paraesthesia, Sinus headache, Somnolence</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Diplopia</td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Ear pain, Vertigo</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Blood pressure increased, Hot flush</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Cough, Dry throat, Dyspnoea, Nasal congestion, Oropharyngeal pain, Rhinorrhea</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, Constipation, Defecation urgency, Diarrhoea, Flatulence, bloating and distension, Nausea and vomiting symptoms, Rectal tenesmus, Abdominal pain upper, Dry lips, Dyspepsia, Gastrointestinal motility disorder, Faeces hard, Haematochezia, Mucous stools, Taste disorders</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Aspartate aminotransferase increased</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rashes, eruptions and exanthemas NEC, Sunburn</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain, Muscle spasms, Muscular weakness, Myalgia Neck pain</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Blood in urine present Glycosuria, Pollakiuria, Polyuria Proteinuria</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Polymenorrhoea</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia, Asthenic conditions, Chills, Cold sweat, Hyperhidrosis, Influenza like illness, Oedema peripheral, Pain and discomfort NEC</td>
<td></td>
</tr>
</tbody>
</table>
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).

<table>
<thead>
<tr>
<th>MedDRA System Organ Class (ver. 12.1)</th>
<th>Frequency not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Clostridial infections</td>
</tr>
<tr>
<td>Blood and lymphatic system disorder</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic responses, Angioedemas, Hypersensitivity</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Presyncope</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Liver function tests abnormalities</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dermatitis, Eczema, Erythemas, Pruritus NEC, Urticarias</td>
</tr>
<tr>
<td>Investigations</td>
<td>International normalised ratio abnormalities</td>
</tr>
</tbody>
</table>

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 signs.

In case of overdose gastric emptying and administration of appropriate supportive treatment are recommended.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: intestinal anti-infective agents, antibiotics. ATC code: A07AA11

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

Mechanism of resistance
The main mechanism of acquiring resistance to rifaximin appears to involve: a mutation in the rpoB gene encoding the bacterial RNA polymerase.

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.

5.2 Pharmacokinetic properties
Absorption
Pharmacokinetic studies in rats, dogs and humans demonstrated that after oral administration Rifaximin in the polymorph α form is virtually not absorbed (less than 1%). Following the 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). Systemic absorption of Rifaximin is increased but not by a clinically relevant extent by administration within 30 minutes of a high-fat breakfast.

Elimination
The urinary recovery of Rifaximin does not exceed 0.4% of the administered dose.

Special Populations
No clinical data are available on the use of Rifaximin in patients with impaired renal function.
In patients with hepatic encephalopathy mean peak plasma concentrations of 13.5 ng/mL Rifaximin were detected after administration of 800 mg Rifaximin three times daily for 7 days. Less than 0.1% of the administered dose was recovered after 7 days. Because of the limited systemic absorption of Rifaximin, no specific dosing adjustments are recommended for patients with hepatic insufficiency.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Morphological alterations have been observed in the foetuses of Rifaximin orally administered rats and rabbits.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core:
- Sodium starch glycolate type A
- Glycerol distearate
- Colloidal anhydrous silica
- Talc
- Microcrystalline cellulose

Tablet coating:
- Hypromellose,
- Titanium dioxide
- Disodium edetate
- Propylene glycol
- Red iron oxide E172.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Original packing: 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
PVC-Aluminium blister pack containing 9 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
UKR Regulatory Affairs Ltd.
Chiltern House
Thame Road
Haddenham
Bucks.
HP17 8BY

8 MARKETING AUTHORISATION NUMBER(S)
PL 19364/0030
PL 19364/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/12/2010

10 DATE OF REVISION OF THE TEXT
02/12/2010
UKPAR Abimix/Normicon 200 mg film-coated tablets

PL 19364/0030 and 033

PACKAGE LEAFLET: INFORMATION FOR THE USER

Abimix 200 mg film-coated tablets
Rifaximin

Read all of this leaflet carefully before you start taking this medicine.

Keep this leaflet. You may need to read it again.

- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Abimix 200 mg film-coated tablets are and what they are used for
2. Before you take Abimix 200 mg film-coated tablets
3. How to take Abimix 200 mg film-coated tablets
4. Possible side effects
5. How to store Abimix 200 mg film-coated tablets
6. Further information

1. WHAT ABIMIX 200 MG FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Abimix 200 mg film-coated tablets are an intestinal antibiotic and are used to treat:
- Traveller’s diarrhoea in adults when the diarrhoea is not accompanied by fever or blood in the stools, or if more than unformed (soft or liquid) stools in the last 24 hours.

Abimix 200 mg film-coated tablets are not recommended for use in children (aged less than 18 years).

2. BEFORE YOU TAKE ABIMIX 200 MG FILM-COATED TABLETS

Do not take Abimix 200 mg film-coated tablets:
- If you are allergic (hypersensitive) to rifaximin, to similar types of antibiotics (such as trimethoprim or rifabutin) or to any of the other ingredients (see section 6) of Abimix film-coated tablets.
- If you have a fever.
- If you have blood in your stools.
- If you passed 8 or more unformed stools in the last 24 hours.

Take special care with Abimix 200 mg film-coated tablets:
- If, after days of treatment, your symptoms continue or re-appear shortly afterwards do NOT take a second course of Abimix 200 mg film-coated tablets, see a doctor.
- If your symptoms get worse during treatment stop taking Abimix 200 mg film-coated tablets and consult a doctor.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. If you are using activated charcoal (for example to treat wind or diarrhoea) please take Abimix 200 mg film-coated tablets at least 2 hours after taking charcoal.

Taking Abimix 200 mg film-coated tablets with food and drink

Abimix 200 mg film-coated tablets can be taken with or without food.

Pregnancy and breast-feeding

Abimix 200 mg film-coated tablets are NOT recommended during pregnancy or in fertile women not using contraception.

Inform your doctor:
- If you are pregnant or think you may be pregnant or are thinking of becoming pregnant.
- If you are breast-feeding or planning to start breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Abimix 200 mg film-coated tablets are unlikely to affect your reactions when driving or using machines.

3. HOW TO TAKE ABIMIX 200 MG FILM-COATED TABLETS

Always take Abimix 200 mg film-coated tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- Unless otherwise prescribed by your doctor, the usual dose is 1 tablet every 8 hours (200mg/day). You should continue taking Abimix 200 mg film-coated tablets for three days even if your symptoms have improved.
- Unless otherwise prescribed by your doctor, the duration of the treatment should not exceed three days. If your symptoms persist for more than three days please see a doctor.

If you take more Abimix 200 mg film-coated tablets than you should:
- If you take more than the recommended number of tablets, please contact a doctor.
- If you forget to take Abimix 200 mg film-coated tablets:
- Take the missed dose as soon as you remember and then the next scheduled dose at its regular time.

If you stop taking Abimix 200 mg film-coated tablets:

If you do not complete the three days of treatment recommended, your symptoms may return. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Abimix 200 mg film-coated tablets can cause side effects, although not everybody gets them.

Common side effects (1 in 10 - 100 patients):
- Diarrhoea, headache
- Wind, abdominal bloating, abdominal pain, constriction, diarrhoea, urgency to evacuate faeces, nausea, involuntary and painful or ineffective straining, vomiting
- Fever.

Uncommon side effects (1 in 100 - 1,000 patients):
- Throat, cold sore, swollen throat, inflammation or infection of the nose and throat
- Abnormal blood test results (increased lymphocytes, increased monocytes, reduced neutrophil granulocytes)
- Loss of appetite, loss of body fluid (dehydration)
- Abnormal dreams, depressed mood, sleeplessness, nervousness
- Numbness, migraine, pins and needles, sinus headache, drowsiness
- Dental pain
- Earache, sensation of the room going round (vertigo)
- Heart racing
- Increased blood pressure, hot flushes
- Cough, dry throat, shortness of breath, blocked nose, sore throat, runny nose
- Upper abdominal pain, indigestion, intestinal movement disorder, dry lips, hard stools, blood in the stools, mucus in stools, tailbone disorders
- Increased liver enzymes values (aspartate-aminotransferase), alanine-aminotransferase
- Rash, pruritus, skin itch, sunburn
- Back pain, muscle aches, muscle weakness, muscle pain, neck pain
- Blood in urine, sugar in urine (glycosuria), frequent urination, excessive urination (polyuria), protein in urine, frequent periods of diarrhoea
- Loss of strength, chills, cold sweat, increased perspiration, flu-like illness, swollen arm, pain

The following side effects have been reported, however their frequency cannot be estimated from the available data:
- Bacterial infections (Escherichia coli, Shigella flexneri, Campylobacter jejuni)
- Abnormal blood tests (reduced platelets, liver function tests outside of normal range, normalised ratio abnormalities)
- Severe acute reactions to the drug, allergic reactions to the drug
- Heart race
- Giant hives
- Skin roughness, skin rash, itching, wheals

Treatment with any antibiotic may cause Clostridium difficile associated diarrhoea (CDAD).

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ABIMIX 200 MG FILM-COATED TABLETS

Keep out of the reach and sight of children.

Abimix 200 mg film-coated tablets do not require any special storage conditions.

Do not use Abimix 200 mg film-coated tablets after the expiry date which is stated on the carton and the blister. The expiry date refers to the last day of that month.

Medicines should not be disposed of via waste disposal or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Abimix 200 mg film-coated tablets contain:
- The active substance is rifaximin. Each film-coated tablet contains: 200 mg of rifaximin.

What other ingredients are in the tablets:
- The other ingredients are: Povidone, magnesium stearate, talc, hydroxypropyl cellulose, yellow lacquer coating.

What Abimix 200 mg film-coated tablets look like and contents of the pack:
- Abimix 200 mg film-coated tablets are pink circular biocoat coated tablets, with "RFX" indented on one side.
- They are provided in blister packs containing 9 tablets.
- Marketing Authorisation Holder and Manufacturer:
- Marketing Authorisation holder: UKR Regulatory Affairs Ltd., Haddingham, Bucks, HP17 8BY
- Manufacturer: Atlas Waehrwein S.P.A., Via E. Fermi, 1 — 03020 Alzano (PG) ITALY

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UKPAR Abimix/Normicon 200 mg film-coated tablets

PL 19364/0030 and 033

If you forget to take Normicon 200 mg film-coated tablets:
- take the missed dose as soon as you remember and take the next scheduled dose at its regular time.
- if you stop taking Normicon 200 mg film-coated tablets:
  - you do not complete the three days of treatment recommended, your symptoms may worsen.
  - if you have any further questions on the use of this product, ask your doctor or pharmacist.

6. POSSIBLE SIDE EFFECTS

Like all medicines, Normicon 200 mg film-coated tablets can cause side effects, although not everybody gets them.

Common side effects (1 in 10 – 100 patients):
- dizziness, headache
- stomach ache, abdominal bloating, abdominal pain, nausea, diarrhoea, fever, vomiting, unusual tiredness or weakness, loss of appetite, dry mouth, feeling generally unwell

Uncommon side effects (1 in 100 – 1,000 patients):
- skin rash, fever, swelling of the hands and feet, breathing difficulties (wheezing/coughing), severe skin rash, angioedema (swelling of lips, tongue, throat), eye problems, changes in taste, impaired vision, increased liver enzymes (particular: transaminases)
- increased blood pressure, hot flashes
- cough, shortness of breath, blocked nose, sore throat, runny nose
- water retention, swelling in the legs, ankles, hand and feet

The following side effects have been reported, however their frequency cannot be estimated from the available data:
- bacterial infections (e.g. urinary tract infections)
- abnormal blood tests (reduced platelets, liver function tests out of normal range, international normalised ratio (INR) abnormalities)
- severe acute reactions to the drug, allergic reactions to the drug
- dizziness, fainting
- skin rashes, skin redness, itching, swelling, wheals
- treatment with any antibiotics may cause Clostridium difficile associated diarrhoea (CDAD)
- if any of the side effects get worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NORMICON 200 MG FILM-COATED TABLETS

Keep out of reach and sight of children.

Normicon 200 mg film-coated tablets do not require any special storage conditions.

Do not use Normicon 200 mg film-coated tablets after the expiry date which is stated on the carton and the blister. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Normicon 200 mg film-coated tablets contain:
- The active substance is Rifaximin. Each film-coated tablet contains: 200 mg of Rifaximin. The other ingredients are: Tablet core: starch, hydroxypropyl methylcellulose, hypromellose, titanium dioxide, talc, ferric oxide (violet, red), iron oxide (yellow).
- Normicon 200 mg film-coated tablets look like and contain:
  - Normicon 200 mg film-coated tablets are pink circular prism coated tablets, with "FAX" indented on one side.
  - They are provided in blister pack containing 9 tablets.

Marketing Authorisation Holder and Manufacturer:
Marketing Authorisation holder: UKPR Regulatory Affairs Ltd., Huddersfield, Huddersfield, HD1 1SY
Manufacturer: Alfa Wasserman S.p.A., Via E. Fermi, 1 – 65020 Alanno (PD) ITALY

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