Generic Rifaximin [Reprint 2014]

DATASET · SEPTEMBER 2014

READS
380

4 AUTHORS, INCLUDING:

Giuseppe Viscomi
Alfa Wassermann
34 PUBLICATIONS  438 CITATIONS

Carmelo Scarpignato
Università degli studi di Parma
324 PUBLICATIONS  3,832 CITATIONS
Is generic rifaximin still a poorly absorbed antibiotic? A comparison of branded and generic formulations in healthy volunteers

Corrado Blandizzi\(^a\), Giuseppe Claudio Viscomi\(^b\), Antonio Marzo\(^c\), Carmelo Scarpignato\(^d,\)\* 

\(^a\) Division of Pharmacology, Department of Clinical & Experimental Medicine, University of Pisa, Via Roma 55, 56126 Pisa, Italy
\(^b\) Research and Development Division, Alfa Wassermann Pharmaceuticals, Via Ragazzi del 99 S, 40133 Bologna, Italy
\(^c\) Institute for Pharmacokinetic and Analytical Studies SA, Via Mavri 36, 6851 Ligornetto, Switzerland
\(^d\) Clinical Pharmacology and Digestive Pathophysiology Unit, Department of Clinical and Experimental Medicine, University of Parma, Cattani Pavilion, Maggiore University Hospital, Viale Gramsci 14, 43125 Parma, Italy

**A B S T R A C T**

Rifaximin is an antibiotic, locally acting in the gastrointestinal tract, which may exist in different crystal as well as amorphous forms. The branded rifaximin formulation contains the polymorph rifaximin-\(\alpha\), whose systemic bioavailability is very limited. This study was performed to compare the pharmacokinetics of this formulation with that of a generic product, whose composition in terms of solid state forms of the active pharmaceutical ingredient was found to be different. Two tablets (2 x 200 mg) of branded and generic formulations were given to 24 healthy volunteers of either sex, according to a single-blind, randomized, two-treatment, single-dose, two-period, cross-over design. Plasma and urinary samples were collected at preset times (for 24 h or 48 h, respectively) after dosing, and assayed for rifaximin concentrations by high-performance liquid chromatography–mass spectrometry. Rifaximin plasma and urine concentration–time profiles showed relevant differences when generic and branded rifaximin were compared. Most pharmacokinetic parameters were significantly higher after administration of generic rifaximin than after rifaximin-\(\alpha\). In particular, the differences for \(C_{\text{max}}\), AUC and cumulative urinary excretion between the generic formulation and the branded product ranged from 16% to 345%. The few adverse events recorded were not serious and not related to study medications. The results of the present investigation demonstrate different systemic bioavailability of generic and branded formulations of rifaximin. As a consequence, the therapeutic results obtained with rifaximin-\(\alpha\) should not be translated without consideration to the generic formulations of rifaximin, which do not claim containing only rifaximin-\(\alpha\) and will display significantly higher systemic absorption in both health and disease.

© 2014 Elsevier Ltd. All rights reserved.

**Introduction**

Generic medicinal products are 'copies' of patented drugs and can be marketed following patent expiration of the brand product [1]. Accordingly, regulatory authorities have issued guidelines dictating the terms and conditions under which generic drugs can be recognized as therapeutically equivalent to their branded counterparts [2–4].

Bioequivalence studies, consisting of single-dose pharmacokinetic (PK) evaluations, are required for registration of most generic formulations of systemically acting drugs, including antibacterial compounds, for which the therapeutic activity depends significantly on PK parameters [5,6]. For generic formulations of systemic antibiotics, differences in pharmaceutical properties might therefore result in changes of their PK profiles, with consequent alteration of PK/PD (pharmacodynamic) relationships, leading to variations in their clinical efficacy, as compared to the brand-name counterparts.

On the contrary, locally acting antibiotics, such as rifaximin, are medicinal products, which exert their effect at the site of application. In this setting, a systemic action, if any, would be considered as an undesirable effect, which could give rise to adverse events [4,7]. In these medicinal products, a change in formulation or dosage form may influence – through variations in local and/or systemic bioavailability – their efficacy and/or safety profiles.
Besides formulation, the physico-chemical characteristics of the active ingredient are also relevant to the local and/or systemic bioavailability [8,9]. In this context, crystal polymorphism is extremely important [10–12]. Polymorphism is the ability of a molecule to assemble into more than one crystal structure. Different polymorphs display different atom arrangements within the unit cell, and this can have a remarkable impact on the physico-chemical properties of the crystallized compound [11,12].

Different polymorphic forms of a drug can display different chemical and physical properties, including stability and chemical reactivity, dissolution rate and solubility, which can affect bioavailability, PK and, as a consequence, PD [10,13]. Several examples of polymorphism's impact on bioavailability have been reported [14–18]

Rifaximin (4-deoxy-4’-methylpyrido[1’,2’-1,2]imidazo[5,4-c]rifamycin SV) is a synthetic product designed to modify the parent compound, rifamycin, in order to achieve low gastrointestinal (GI) absorption while retaining good antibacterial activity [19]. Indeed, several studies have shown that rifaximin is a non-systemic antibiotic with a broad spectrum of antibacterial activity [20,21]. According to the European Pharmacopoeia, rifaximin shows crystal polymorphism [22] and five distinct crystal forms, namely α, β, γ, δ and ε, have been described [23]. In vitro studies have shown different dissolution and solubility rates of these polymorphs, and in vivo investigations in dogs found significantly different PK patterns amongst the various crystal forms, with the γ polymorph displaying the highest systemic bioavailability [23].

In addition to crystal polymorphs, an amorphous form of rifaximin can be also prepared. The amorphous form of a drug consists of disordered molecule arrangements and does not display a crystalline lattice [24,25]. Because of this peculiarity, there are significant stability differences between crystalline polymorphs and the amorphous form of a drug. In vitro dissolution tests on rifaximin do suggest for the amorphous form a PK behavior similar to that of polymorph-γ, thus implying a higher systemic bioavailability than that of polymorph-α [23]. And indeed, preliminary animal studies showed that this is the case [26].

A previous study [27] on healthy volunteers showed that the PK profile of amorphous rifaximin differs from that of polymorph-α (the crystal form present in the branded formulation), resulting in higher systemic bioavailability. These findings confirm that also in humans different solid-state forms of rifaximin show a different PK behavior.

Since some generic formulations of rifaximin have been marketed, we felt it worthwhile to evaluate their PK profile in comparison to that of the branded product. Indeed, while the summary of product characteristics of the branded rifaximin provides clear information about its specific crystal structure [28], this was not the case for the generic products, whose composition and – as a consequence – systemic absorption is unknown. Provided be it significant, clinical consequences could arise.

The aim of this study was therefore to evaluate the impact of the composition (in terms of crystalline polymorphs and/or amorphous from) of the active ingredient present in the generic formulation on the systemic bioavailability of rifaximin.

Methods

Healthy volunteers

Healthy adult volunteers of either sex (age range: 18–60 years) and Caucasian origin were invited to participate to the study. They were informed of the purpose, methods and potential hazards of the study, and were requested to sign a written informed consent. Clinical evaluations, performed to assess the health condition of volunteers, as well as inclusion and exclusion criteria have been previously described in details [29].

Design of the study

The study was performed in a single center (Institute for Pharmacokinetic and Analytical Studies S.A., Lugano, TI, Switzerland), in accordance with a single-blind, randomized, two-treatment, single-dose, two-period, cross-over design, with a wash-out period of 7 days [30]. The study was approved by the Ethics Committee of Canton Ticino and Swissmedic (Switzerland), and was conducted in accordance with ICH guidelines for Good Clinical Practice. The study procedures were performed in compliance with the Declaration of Helsinki.

Subjects were randomized to receive a 400-mg single-dose (2 × 200-mg tablets) of the generic rifaximin or branded formulation (rifaximin polymorph-α; Normix®). The tablets were administered with 250 ml of water at 08:00 AM, under fasting conditions. About 4, 8 and 12 h after drug intake, a lunch (1200 kcal), a snack (150 kcal) and a dinner (900 kcal) were served. After drug intake, subjects were requested to drink water as follows: 500 ml every hour of plain mineral water during each of the 4-h intervals from drug administration till 12 h after dosing; then, at will, until the end of urine collection (i.e. 48 h post-dosing).

Venous blood samples of 10 ml were collected into tubes (containing sodium heparin) kept on ice, at pre-set time intervals of 0 (pre-dosing) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post-dosing. Plasma was separated from blood within 20 min by centrifugation at 2000 × g (10 min at 4 °C). Each plasma sample was split into two aliquots and stored at −20 ± 5 °C. Urine was collected pre-dosing and at intervals of 0–4, 4–8, 8–12, 12–24, 24–48 h post-dosing into refrigerated flasks. The weight of each urine fraction was recorded, a sample of approximately 100 ml was split into two aliquots and frozen.

Study medications

The film-coated tablets (200 mg) of generic rifaximin (San- doz Biopharmaceuticals SpA) and those of branded rifaximin (Alfa Wassermann SpA) were from the same batch, which was n. 00307 and n. 8278 for generic formulation and Normix® respectively. The brand of generic rifaximin was selected amongst the products available in the Italian market at the time of the study. It is noteworthy that they were all manufactured by the same company (Special Product’s Line SpA, Pomezia, Italy) and contained the same active ingredient (Industrias GMB SA, Barcelona, Spain) [31]. Therefore, no specific criteria were needed to select a given generic formulation. The compositions of Normix® and generic rifaximin are displayed in Table 1.

X-ray power diffraction analysis of the generic formulation showed the presence of both amorphous rifaximin and rifaximin α. Quantitative estimation was not possible, due to interference of tablet excipients in this kind of analysis.

Safety evaluations

 Volunteers were enquired about the occurrence of any adverse event after their admission to the clinical unit, both before the administration of study drugs and throughout the study until discharge. Vital signs were monitored.

Rifaximin assay

Rifaximin concentration in plasma and urine samples was measured by liquid chromatography mass spectrometry (LC/MS-MS) as previously described [23], with a lower limit of quantification
Table 1
Chemical composition of the rifaximin formulations employed in the present pharmacokinetic study. The only difference between the branded and generic formulations concerns one excipient (highlighted in gray).

<table>
<thead>
<tr>
<th>Active ingredient (crystalline status)</th>
<th>Branded rifaximin (Normix® 200-mg film-coated tablet)</th>
<th>Generic rifaximin 200-mg film-coated tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>Sodium starch glycolate</td>
<td></td>
</tr>
<tr>
<td>Glycerol dioleatate</td>
<td>Glycerol monostearate</td>
<td></td>
</tr>
<tr>
<td>Colloidal anhydrous silica</td>
<td>Colloidal anhydrous silica</td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>Talc</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Microcrystalline cellulose</td>
<td></td>
</tr>
<tr>
<td>Coating components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyromellose</td>
<td>Hyromellose</td>
<td></td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>Titanium dioxide</td>
<td></td>
</tr>
<tr>
<td>Disodium edetate</td>
<td>Disodium edetate</td>
<td></td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
<td></td>
</tr>
<tr>
<td>Red iron oxide E172</td>
<td>Red iron oxide</td>
<td></td>
</tr>
</tbody>
</table>

(LLOQ) of 0.5 ng/mL in both the biological fluids analyzed. The intra-assay precision (CV%) for all quality control (QC) samples was < 7.2, and the mean accuracy (ACC%) ranged from −5.3 to −0.3 of the nominal concentration. The inter-assay precision (CV%) was < 5.1 and the mean accuracy (ACC%) ranged from −1.1 to +2.3 of the nominal concentration. No significant interfering peaks were found at the retention times of rifaximin and internal standard.

Pharmacokinetic evaluations
Non-compartmental PK analysis was carried out with WinNonLin® software (Pharsight, Mountain View, CA, U.S.A.). The highest concentration achieved in plasma (Cmax), the time needed to achieve Cmax (Tmax), the area under the drug plasma concentration–time curve from time 0 to infinity (AUC0–∞), the AUC from time 0 to the time of last quantifiable drug concentration (AUC0–t), the plasma drug elimination half-life (∝1/2), and the cumulative urinary excretion (AEx–∞) were estimated from individual concentration–time curves. The first order elimination rate constant was estimated by linear regression of the time versus the log of drug concentration using the terminal (log-linear) portion of the curve. AUC0–t was calculated by the linear trapezoidal rule. Extrapolation to infinity for the estimation of AUC0–∞ was obtained by dividing the last quantifiable drug concentration by the elimination rate constant and adding this value to AUC0–t [32].

Statistical analysis
Descriptive and summary statistics were used. All results are presented as means ± standard error of the mean (SEM). The significance of differences between mean values was calculated by means of Student’s t test for paired data. ANOVA was employed to evaluate the effect of period, sequence and formulations on PK parameters. p < 0.05 were considered significant. All calculations were performed with the Instat® software (GraphPad Software Inc., La Jolla, CA, USA).

Results
Demographic characteristics of healthy volunteers
Twenty-four subjects met the selection criteria and completed the experimental procedures. Their overall characteristics are displayed in Table 2.

Plasma and urinary PK profiles
The mean plasma and urinary excretion profiles of healthy volunteers, treated with generic rifaximin or rifaximin-α, are shown in Fig. 1. The respective values of estimated PK parameters are reported in Table 3. In most subjects, the first plasma rifaximin concentration could be detected at the first blood sampling (i.e. 30 min after dosing) for both rifaximin formulations. Plasma

Table 2
Demographic characteristics of subjects (n = 24).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>36.21</td>
<td>170.25</td>
<td>66.33</td>
</tr>
<tr>
<td>SEM</td>
<td>1.82</td>
<td>1.64</td>
<td>1.97</td>
</tr>
<tr>
<td>CV%</td>
<td>24.61</td>
<td>4.73</td>
<td>14.55</td>
</tr>
<tr>
<td>Min</td>
<td>19.00</td>
<td>156.00</td>
<td>53.00</td>
</tr>
<tr>
<td>Max</td>
<td>52.00</td>
<td>181.00</td>
<td>88.00</td>
</tr>
</tbody>
</table>

Table 3
Mean values of plasma and urine pharmacokinetic parameters of rifaximin estimated following the administration of generic rifaximin and rifaximin-α at the single dose of 400 mg (n = 24).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>400 mg</th>
<th>400 mg</th>
<th>400 mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifaximin-α</td>
<td>2.29 ± 0.28</td>
<td>6.89 ± 0.74</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.78 ± 0.46</td>
<td>1.98 ± 0.30</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>AUC0–x (ng/ml × h)</td>
<td>6.34 ± 0.99</td>
<td>28.26 ± 3.86</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>AUC0–∞ (ng/ml × h)</td>
<td>9.80 ± 1.23</td>
<td>32.24 ± 3.98</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>t½ (h)</td>
<td>2.8 ± 0.4</td>
<td>4.5 ± 0.4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>AEX–∞ (µg)</td>
<td>45.27 ± 4.61</td>
<td>120.13 ± 14.59</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
</tbody>
</table>
concentrations then increased up to the peak, which was achieved at 1.98 h (range: 0.50–6.0) in subjects treated with generic rifaximin, and 1.78 h (0.5–12.0) in subjects administered with rifaximin-α.

Plasma concentrations were lower after administration of rifaximin-α than generic rifaximin. Following treatment with rifaximin-α, the drug could be detected in plasma up to 8 h from dosing in 3/24 subjects, and up to 10 h from dosing in 2/24 subjects; rifaximin concentrations remained below the LLOQ after 16 h and 24 h from dosing. Upon administration of the generic product, rifaximin plasma concentrations could be measured up to 12 h from dosing in 6/24 subjects, up to 16 h from dosing in 7/24 subjects, and up to 24 h in 2/24 subjects.

Urine rifaximin concentrations could be detected at all collection intervals in all subjects after administration of generic rifaximin, and in 21/24 subjects after treatment with rifaximin-α. Following the administration of rifaximin-α or generic rifaximin, the highest urine concentration was measured at the first collection interval (0–4 h) in 16/24 subjects, and at the second collection interval (4–8 h) in 8/24 subjects.

Rifaximin plasma and urine concentration–time profiles and PK parameters showed marked differences when generic rifaximin and rifaximin-α were compared. As shown in Table 3, most PK parameters were significantly higher after administration of generic rifaximin than rifaximin-α. In particular, the differences for C_max, AUC_0-24, AUC_0-∞, and AUC_0-48, between the generic formulation and the product containing rifaximin-α ranged from 165% to 345%.

ANOVA evaluation of all parameters for cross-over design showed statistically significant differences between the two rifaximin products tested (Table 4). On the contrary, there were no statistically significant differences in relation to the period (period 1 versus period 2) or the sequence (brand–generic versus generic–brand) of administration of the two formulations.

**Table 4**

<table>
<thead>
<tr>
<th>Rifaximin</th>
<th>Period</th>
<th>Sequence</th>
<th>Formulation</th>
<th>F</th>
<th>p</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max</td>
<td>0.74</td>
<td>0.3975</td>
<td>0.62</td>
<td>0.4378</td>
<td>105.61</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>AUC_0-24</td>
<td>1.62</td>
<td>0.2160</td>
<td>0.97</td>
<td>0.3364</td>
<td>206.63</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>AUC_0-∞</td>
<td>3.10</td>
<td>0.0948</td>
<td>0.98</td>
<td>0.3336</td>
<td>162.28</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>AUC_0-48</td>
<td>1.66</td>
<td>0.2107</td>
<td>2.26</td>
<td>0.1473</td>
<td>83.00</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
</tbody>
</table>

In the present study, when generic rifaximin was compared with the branded formulation (containing the pure polymorph α), the findings were unexpected. Indeed, our results show that the PK profile of generic rifaximin differs significantly from that of branded rifaximin-α, while – according to regulatory requirements for equivalence [3] – the systemic bioavailability of the generic product should overlap that of the branded formulation. Indirect comparisons with data from a previous study [27] suggest that the PK of generic formulation also differs from that of the pure amorphous rifaximin. Indeed, since X-ray diffraction patterns showed that in the generic product both the amorphous form and polymorph α are present, it is conceivable that the systemic bioavailability of rifaximin depends on the composition (in terms of crystalline polymorphs and amorphous form) present in the formulation. The observed differences between branded rifaximin-α and its generic formulation cannot be ascribed to variations in the composition of non-active ingredients, since, as outlined in Table 1, both the excipients and coating components were virtually the same. In addition, despite the branded formulation employed in the present investigation belonged to a different batch of the product employed in our previous PK study [27], and despite the enrolled subjects were also different, the PK behavior of the active ingredient (polymorph-α) in both studies appears to be consistent, indicating its physico-chemical stability over time.

Drug polymorphs occur during the synthesis and purification of active ingredients. The occurrence of a given polymorph depends on the conditions of synthesis and crystallization [12,13]. The whole production process generally leads to the formation of a given polymorph rather than the amorphous form of a drug. X-ray diffraction studies revealed that rifaximin polymorphs are hydrates [34] and, since addition or removal of water can lead to changes in polymorphism, great attention should be paid also to any manipulation and storage of the drug (be it a branded or a generic formulation) to ensure stability of the desired crystal structure. Overall, it is possible that – for the generic formulation tested (i.e. a mixture of amorphous and crystalline rifaximin) – manufacturing and/or storage processes were different from those of the original molecule contained in the branded formulation. Being the polymorph content related to the manufacturing process, the same considerations should be applied to those medicinal products containing rifaximin, whose origin of the active ingredient is different from that of the molecule contained in the branded formulations (Normix®, Xifaxan®, Flonorm® and other brand names). In some South-American Countries (Argentina, Colombia, Venezuela and Peru) as well as in Egypt, Turkey, India and China there are indeed branded formulations of rifaximin whose summary of product characteristics provides no clear information about the specific crystal structure of the active ingredient.

The increased systemic bioavailability of the generic formulation raises some clinically relevant concerns. Indeed, for a poorly absorbed antibiotic, whose antimicrobial activity is intended to be topical (i.e. within the GI tract), systemic absorption might lead to reduced local bioavailability and potentially to systemic adverse events. In the case of rifaximin, a reduced intraluminal bioavailability might be without clinical consequences since its fecal concentrations are known to largely exceed the minimum inhibitory concentration (MIC) values of pathogenic enteric bacteria [21]. The risk of adverse events would be expected to correlate with blood levels [35,36]. With the polymorph-α, contained in the branded formulation, both the short- and long-term tolerability is extremely good [21,37,38], most likely because of the lack of systemic absorption. However, after 400-mg single-dose administration of the generic formulation, C_max increased by more than 200%. When translating these findings to the clinical setting, rifaximin blood levels would be expected to increase even more in patients with liver disease, in whom blood concentrations of
rifaximin-α are already 10–20 times higher, depending on the disease severity (Child–Pugh A–C classes) [38,39]. This is of particular concern since rifaximin received approval for “reduction in risk of overt hepatic encephalopathy recurrence in patients with advanced liver disease” [39]. Rifaximin is the most effective and widely used antibiotic for the treatment of SIBO (small intestine bacterial overgrowth) [40]. The recent discovery of an association between SIBO and functional gut symptoms, albeit controversial, has renewed interest in this mimicky. SIBO represents indeed an umbrella term, under which some different functional (e.g. irritable bowel syndrome, chronic constipation, diarrhea) or organic (e.g. inflammatory bowel disease, celiac disease, diverticular disease, etc.) conditions can be included, since – in each of them – bacterial proliferation (and consequent minimal inflammation) may, at least in part, trigger similar abdominal symptoms. In all these conditions, especially the organic ones, rifaximin is used long-term to get rid of pathogenic bacteria, reduce the inflammatory response and achieve symptom relief [41,42]. As for every drug used in the long-term, safety – besides efficacy – is of paramount importance. Rifaximin-α proved to be extremely safe, even given continuously (at standard therapeutic doses) for 6 months and its minimal, if any, systemic absorption (not exceeding 1%) accounts for the adverse event profile, which overlapped that of placebo [38]. The use of generic rifaximin formulation(s), whose absorption is higher and often unpredictable, might not guarantee the excellent tolerability of the branded medication.

A peculiar, potentially serious, adverse event, related to systemic rifaximin exposure, is the development of extra-GI cross-resistance. This is particularly relevant to M. tuberculosis and Neisseria meningitides since rifampicin (another member of the rifamycins’ family) is a pivotal antibiotic for the treatment of tuberculosis [43,44] and prevention of Neisseria meningitidis [45–47]. However, a 10-year survey [48] in Italy has shown that mycobacterial resistance to rifampicin has remained quite stable over time and a recent Italian study [49] found that all meningococci isolated from asymptomatic carriers were susceptible to rifampicin, despite the large consumption of rifaximin in our Country. The above-mentioned bacterial cross resistances are therefore very unlikely to occur with the polymorph-α, but – taking into account the present data on systemic bioavailability – it is plausible that the risk of resistance with the generic formulation of rifaximin might become clinically relevant.

Conclusions

The present results show different systemic bioavailability of generic and branded formulations of rifaximin. As a consequence, the therapeutic results obtained with the polymorph-α should not be translated sic et simpliciter to generic rifaximin formulations, which can display significant systemic absorption and can no longer be included in the class of poorly absorbable (locally acting) antibiotics.

Conflict of interest

Corrado Blandizzi has occasionally been involved as a speaker, in satellite symposia supported by Alfa Wassermann, the manufacturer of rifaximin. Giuseppe Claudio Viscomi is an employee of Alfa Wassermann. Antonio Marzo is an employee of the Institute for Pharmacokinetic and Analytical Studies SA, where the clinical study was conducted upon contract with Alfa Wassermann. Carmelo Scarpignato is member of the Speakers’ Bureau of Alfa Wassermann.

Acknowledgments

We are indebted to Professor Fabrizia Gregioni (Department of Chemistry “G. Ciamician”, University of Bologna, Italy) for performing and interpreting the XRDP analysis.

References


C. Blandizzi et al. / Pharmacological Research 85 (2014) 39–44 43


[28] Normix® Summary of Product Characteristics (Revision September 1, 2007), Section 5.1.


