Dear Sir/Madam

Re: Options for reform of the regulatory framework for pharmacy compounding

Norgine's submission relates to the potential public health risks of pharmacy compounded finished products. Norgine is the Australian sponsor of a number of medicines and devices. One of these products is Xifaxan (rifaximin) 550 mg tablets, which was added to the ARTG in May 2012.

Xifaxan 550 mg tablets are indicated for the prevention of the recurrence of hepatic encephalopathy where other treatments have failed or are contraindicated. Xifaxan has been recommended for listing on the Pharmaceutical Benefits Scheme (PBS) but has not yet been listed.

The active material in Xifaxan tablets is rifaximin, a semi-synthetic antibiotic that is a member of the rifamycin family. Rifaximin can exist in a number of polymorphic forms, as well as in an amorphous form.

Five crystalline polymorphic forms of rifaximin (α, β, γ, δ, ε), have been isolated and identified by X-ray powder diffraction (1). Many compounds exhibit polymorphism, and this is important for pharmaceuticals, as chemical and physical properties can vary between the polymorphic forms, potentially affecting efficacy and safety. This is true for rifaximin, as the different polymorphic forms show significant differences in the dissolution, absorption and bioavailability of rifaximin (1).

Xifaxan contains the α polymorph of rifaximin (2), which undergoes minimal absorption from the gastrointestinal tract (less than 1%), and essentially acts as a topical agent in the gut lumen. The β and ε forms also show low absorption, however the γ and δ forms exhibit significant systemic absorption (1). A bioavailability study of the 5 different rifaximin polymorphs in dogs shows the differences in pharmacokinetic parameters (1);
Table 1. Study of bioavailability of the crystalline forms of rifaximin in dogs. Mean ± S.E.M. of the pharmacokinetic parameters after oral administration of 100 mg/kg (n = 4)

<table>
<thead>
<tr>
<th>Rifaximin form</th>
<th>C_{max}^{a} (ng/mL)</th>
<th>t_{max}^{b} (h)</th>
<th>AUC_{0-24h}^{c} (ng h/mL)</th>
<th>AUC_{0-inf}^{d} (ng h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>2.6 ± 0.7</td>
<td>4</td>
<td>17 ± 7</td>
<td>17 ± 7</td>
</tr>
<tr>
<td>β</td>
<td>1.1 ± 0.6</td>
<td>4</td>
<td>10 ± 7</td>
<td>12 ± 8</td>
</tr>
<tr>
<td>γ</td>
<td>1,085.1 ± 78.7</td>
<td>2</td>
<td>4,795 ± 4,120</td>
<td>4,894 ± 4,107</td>
</tr>
<tr>
<td>δ</td>
<td>308.3 ± 224.1</td>
<td>2</td>
<td>801 ± 517</td>
<td>830 ± 515</td>
</tr>
<tr>
<td>ε</td>
<td>6.9 ± 5.1</td>
<td>4</td>
<td>42 ± 35</td>
<td>77 ± 42</td>
</tr>
</tbody>
</table>

*α* Maximum observed plasma concentration.

*β* Time from administration to obtain Cmax; the values are given as median.

*γ* Area under the concentration–time curve from time zero up to last sampling (24 h after administration).

*δ* Area under the concentration–time curve calculating the extrapolation to infinity.

A study in humans has also shown differences in *in vivo* absorption between rifaximin-α and an amorphous form of rifaximin (3). Twenty four healthy male and female volunteers were randomised to receive either 2 x 200 mg tablets of Normix® (rifaximin-α) or 2 x 200 mg of a generic brand containing amorphous rifaximin as a single oral dose in crossover, with a 7 days washout period in between. Rifaximin levels were measured in blood and urine. All pharmacokinetic parameters for the amorphous rifaximin were significantly higher than for rifaximin-α. There was a four-fold increase in Cmax and a six-fold increase in AUC.

Table 2. Comparison of pharmacokinetic parameters of rifaximin-α and amorphous rifaximin.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean (Test = Amorphous Rifaximin)</th>
<th>Mean (Reference = Normix®)</th>
<th>T&gt;R</th>
<th>T/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>15.01</td>
<td>3.54</td>
<td>324.0%</td>
<td>4.24</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>1.71</td>
<td>1.21</td>
<td>41.3%</td>
<td>1.41</td>
</tr>
<tr>
<td>AUC_{0-24h} (ng/mL·h)</td>
<td>63.38</td>
<td>10.38</td>
<td>510.6%</td>
<td>6.11</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng/mL·h)</td>
<td>68.80</td>
<td>13.03</td>
<td>426.0%</td>
<td>5.28</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>5.35</td>
<td>2.23</td>
<td>139.9%</td>
<td>2.40</td>
</tr>
<tr>
<td>CUE (µg)</td>
<td>441.93</td>
<td>88.34</td>
<td>400.3%</td>
<td>5.00</td>
</tr>
</tbody>
</table>

The TGA evaluators who assessed the Xifaxan marketing application noted that the 'benign toxicity profile' of the product was related to the minimal absorption of rifaximin, and that the use of the α polymorph of rifaximin was critical, as other polymorphic forms exhibit significant systemic absorption. The Australian Public Assessment Report (AusPAR) for Xifaxan tablets notes the following important points in regard to polymorphism (4);
• "Five crystalline polymorphic forms of rifaximin (α, β, γ, δ, and ε), have been isolated and identified by X-ray powder diffraction. However, only rifaximin α is obtained from the manufacturing procedure and is verified in the proposed drug substance specification using x-ray diffraction techniques. This is critical as forms γ and δ exhibit significant systemic absorption."

• "Overall, the nonclinical studies provide little evidence of potential adverse effects associated with rifaximin and it is likely that the few observed effects are secondary to the effect on the intestinal microflora. The benign toxicity profile refers to the poorly absorbed rifaximin α polymorphic form, which is the form proposed for manufacture, with apparently no propensity for interconversion."

• "Given the much greater oral bioavailability of other polymorphic forms, there is a need to ensure that the commercial preparation of rifaximin is the poorly-absorbed polymorphic form, rifaximin α."

• "Based on the low oral rifaximin bioavailability, it is likely that any systemic exposure of these impurities would be very low, with levels of any (theoretical) metabolites even lower. The risk of genotoxicity from potential exposure to these compounds is considered very unlikely."

Xifaxan 550 mg tablets were approved by the TGA on the basis of acceptable toxicological, quality and clinical data, all linked to the very low systemic absorption of the alpha polymorph of rifaximin present in Xifaxan tablets. The low risk of Xifaxan causing bacterial cross resistance is also due in part to the very low systemic absorption of rifaximin-α.

Norgine is aware that despite the commercial availability of TGA approved Xifaxan 550 mg tablets, unregistered preparations of rifaximin continue to be supplied in Australia by various parties. These include companies importing and supplying rifaximin tablets under the Special Access Scheme (one company advertises the SAS availability of rifaximin tablets on its Australian website), and the manufacture and supply by compounding pharmacies.

We are aware of one large compounding pharmacy in Sydney which advertises and supplies compounded rifaximin capsules to patients at a community and hospital level. The website of this pharmacy invites customers to fill out their symptoms on the website; they will then be contacted and a prescription written, filled and the medication posted. A list of available prescription medicines is also displayed on the website.

This compounding pharmacy also exhibits at specialist medical conferences to promote its compounded products to clinicians.

Norgine obtained a supply of 500 mg rifaximin capsules (dispensed on prescription) from this Sydney pharmacy and submitted them to Alfa Wassermann for analysis. Alfa Wassermann is the innovator company that discovered and developed rifaximin.

The results of the analysis are attached (Attachment 1). They can be summarized as follows;
• Rifaximin-α was not present. Both amorphous and an unidentified crystalline form of rifaximin were identified.

• There were unidentified impurities present at levels higher than permitted by the European Pharmacopoeia monograph for rifaximin. The levels were also at levels higher than the identification and qualification thresholds prescribed by ICH Guideline Q3B for impurities in drug product.

• Individual capsule contents ranging from 68 – 104% of the stated amount.

Based on the analysis of this batch, it can be concluded that;

• The consistency of manufacture of the batch is poor.

• The compounded rifaximin capsules did not comply with the relevant pharmacopoeial monographs for active substance or finished product.

• The presence of amorphous rifaximin and an unknown crystalline form of rifaximin (with unknown absorption characteristics) raises safety concerns, as does the high level of impurities.

• The active ingredient in the compounded capsules cannot be considered equivalent to the non-absorbed rifaximin-α present in the TGA approved Xifaxan.

Clearly the results from one batch of compounded rifaximin capsules from one pharmacy should not be used to judge all compounding pharmacies. However, in the case of rifaximin and other actives where the use of the correct polymorph is critical for product safety, this case illustrates the lack of controls applied to pharmaceutical ingredients by the compounders. In this case, the resulting compounded product supplied commercially to patients is not of acceptable quality and raises concern about safety.

Patients receiving this compounded product (and the prescribers) would be completely unaware of the quality issues and potential safety issues.

Norgine supports all of the steps outlined in proposal B, of the document “Options for reform of the regulatory framework for pharmacy compounding. Consultation regulation impact statement” and in particular that compounded medicines should only be excluded from the ARTG when there is no suitable and available medicine on the ARTG, and that the compounded product be clearly labeled to show that it has not been approved by the TGA.

Yours faithfully

Norgine Pty Ltd
References:


2. XIFAXAN 550 mg. TGA Approved Product Information. May 2012.

3. Marzo A, Ismaili S. P 256. A randomised crossover study to evaluate the safety and the pharmacokinetic profiles of a single oral dose (400 mg) of amorphous rifaximin in comparison with a single oral dose (400 mg) of Normix® (rifaximin polymorph-α) in healthy volunteers. Digestive and Liver Disease 2010;42(S2) S191-191