CASE AUTH/2472/1/12

# SHIRE v FLYNN PHARMA

## Medikinet leavepiece

**Shire Pharmaceuticals complained about a Medikinet XL (methylphenidate prolonged release) leavepiece issued by Flynn Pharma. Medikinet was indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years and over when remedial measures alone proved insufficient.**

**Shire noted that the second page of the leavepiece (headed 'Extended Release Methylphenidate (MPH) Preparations Exhibit Different Pharmacokinetic Profiles') featured plasma concentration-time curves from two comparative pharmacokinetic studies conducted in adults (Equasym XL vs Medikinet XL (Schütz *et al* 2009) and Equasym XL vs Concerta XL (González *et al* 2002)). There was no contextual information about the relevance of these comparative studies to the treatment of ADHD in children or any comment on the clinical significance of the data. Shire alleged that the graphs, with Equasym XL as the common comparator, invited readers to extrapolate a favourable but misleading comparison between the pharmacokinetic profiles of Medikinet XL and Concerta XL, when in fact there were no data to support this.**

**The front page of the leavepiece set the clinical question 'How do you achieve a good start to the day for children and adolescents with severe ADHD who are hyperactive and/or inattentive at the start of the school day?' and proposed Medikinet and Medikinet XL as the answer with only comparative pharmacokinetic data from adult studies to support it. Shire alleged that this presentation of adult pharmacokinetic data breached the Code as it was misleading and did not enable readers to form a rational opinion of the therapeutic value of Medikinet XL.**

**Shire alleged a further breach as the inclusion of comparative adult pharmacokinetic data implied that Medikinet XL had a superior clinical profile compared with Equasym XL and Concerta XL although no clinical studies had shown this to be so.**

**The detailed response from Flynn is given below.**

**The Panel noted that the front page of the leavepiece posed the question 'How do you achieve a good start to the day for children and adolescents with severe ADHD who are hyperactive and/or inattentive at the start of the school day?' Page 2 was headed 'Extended Release Methylphenidate (MPH) Preparations Exhibit Different Pharmacokinetic Profiles' and featured two graphs which showed the mean methylphenidate plasma concentration-time profiles in healthy adult volunteers for three different medicines. The first graph (Medikinet XL 20mg vs Equasym XL 20mg (adapted from Schütz *et al*)) clearly showed that at 2 hours post-dose, Medikinet XL 20mg achieved higher methylphenidate plasma concentrations than Equasym XL 20mg. The second graph (Equasym XL 20mg vs Concerta XL 18mg (adapted from González *et al*)) also showed that 2 hours post-dose, Equasym XL 20mg achieved higher methylphenidate plasma concentrations than Concerta XL 18mg.**

**In the Panel's view, the graphs encouraged readers to compare the plasma concentration-time profiles of Medikinet XL, Equasym XL and Concerta XL and concluded that, in the first few hours post-dose, Medikinet XL achieved a higher methylphenidate plasma concentration than the other medicines. In that regard the Panel considered that some readers might assume that this resulted in a clinical advantage for children who were hyperactive and/or inattentive at the start of a school day thus answering the question posed on the front page of the leavepiece.**

**The Panel noted that although the leavepiece did not refer to any clinical data, it did not state that the depicted pharmacokinetic differences in healthy adult volunteers had not been shown to have consequential differences in clinical outcome when used to treat ADHD in children. The Panel noted Shire's submission that there were no clinical studies to show that Medikinet XL had a superior clinical profile to either Equasym XL or Concerta XL.**

**The Panel considered that the presentation of the pharmacokinetic data was such that the comparisons of Medikinet XL with Equasym XL and Concerta XL were misleading as alleged. A breach of the Code was ruled.**

Shire Pharmaceuticals Limited complained about a four page, A5 Medikinet XL (methylphenidate prolonged release) leavepiece (ref MXL/LVP/11/0038) issued by Flynn Pharma Limited. Medikinet was indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years and over when remedial measures alone proved insufficient. Shire marketed Equasym XL (methylphenidate prolonged release) for the same indication.

**COMPLAINT**

Shire alleged that use of adult pharmacokinetic data in the leavepiece was misleading. During inter-company dialogue Flynn submitted that the leavepiece had been withdrawn but did not accept Shire's arguments in relation to the pharmacokinetic data, and provided no reassurance that similar claims and graphs would not be used in future material.

Shire noted that the second page of the leavepiece (headed 'Extended Release Methylphenidate (MPH) Preparations Exhibit Different Pharmacokinetic Profiles') featured graphs of plasma concentration-time curves from two comparative pharmacokinetic studies conducted in adults (one comparing Equasym XL and Medikinet XL (Schütz *et al* 2009), and the other comparing Equasym XL and Concerta XL [methylphenidate marketed by Janssen Cilag] (González *et al* 2002)). There was no contextual information provided about the relevance of these comparative studies to the treatment of ADHD in children or indeed any comment on the clinical significance of the data. There was no discussion or presentation of any therapeutic studies comparing these products. In the absence of any explanatory text or guidance Shire alleged that the graphs, with Equasym XL as the common comparator, invited readers to extrapolate a favourable but misleading comparison between the pharmacokinetic profiles of Medikinet XL and Concerta XL, when in fact there were no data to support this.

Shire alleged that this was compounded by the fact that the only part of the leavepiece that provided any information about the clinical performance of Medikinet XL was the statement on the opposite page (page three) that the release profile had been designed to mimic two equal doses of methylphenidate given four hours apart.

Shire alleged that this presentation of adult pharmacokinetic data was in breach of Clause 7.2. This clause required that promotional material was not misleading and that it was sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine. The front page of the leavepiece set the clinical question 'How do you achieve a good start to the day for children and adolescents with severe ADHD who are hyperactive and/or inattentive at the start of the school day?' and proposed Medikinet and Medikinet XL as the answer. However, it provided only comparative pharmacokinetic data from adult studies to support this. Shire considered that this was misleading and did not enable readers to form a rational opinion of the therapeutic value of Medikinet XL.

Shire further alleged that this presentation of data was in breach of Clause 7.3 which allowed comparisons provided they were not misleading. The inclusion of comparative adult pharmacokinetic data implied that Medikinet XL had a superior clinical profile compared with Equasym XL and Concerta XL. However, no clinical studies had shown this to be so.

Shire submitted that it had consistently maintained that the presentation of pharmacokinetic differences between products in a manner which inferred a clinical difference was misleading. In particular, Shire disagreed with Flynn's continued assertion that it was acceptable to use comparative pharmacokinetic data from healthy, adult volunteers to highlight differences between Medikinet XL and Equasym XL for use in children and adolescents with ADHD. Shire did not consider Flynn's presentation of pharmacokinetic data was acceptable or legitimate and had clearly stated its position in inter-company dialogue in relation to the leavepiece and similar previous items.

**RESPONSE**

Flynn submitted that both Shire and the PMCPA, in its letter notifying Flynn of the complaint, acknowledged that the leavepiece had been voluntarily withdrawn and to this extent Flynn understood that inter-company dialogue had been successful. The basis and the subject of the complaint was thus not entirely clear. The leavepiece at issue had been withdrawn and was pending revision. However, the same information was used in a Medikinet detail aid that was pending revision. A copy of the draft detail aid was provided. It had not yet been approved for use, however the presentation of pharmacokinetic data was essentially the same as that in the leavepiece at issue.

Flynn submitted that whilst Shire's complaint about the presentation of pharmacokinetic data characterised the issues as the absence of contextual information provided about the relevance of these comparative studies to the treatment of ADHD in children, or indeed any comment at all on the significance of these data, Shire's letter to Flynn during inter-company dialogue stated 'you continue to believe and repeatedly assert that the use of adult pharmacokinetic data in the leavepiece is balanced and not misleading' and that 'we disagree with your argument that it is acceptable to use comparative pharmacokinetic data from healthy adult volunteers to highlight differences.... in children and adolescents'. Flynn thus queried whether it was the use of adult pharmacokinetic data *per se* that Shire took issue with, and/or the absence of any comment as to its significance.

In inter-company dialogue in 2010 about a different leavepiece, Shire commented on the use of the pharmacokinetic data now at issue. Specifically, Shire had complained about the claim that Medikinet XL had a higher bioavailability than Equasym XL which was based on Schütz *et al*. Shire had stated that the clinical relevance of this finding to the treatment of children with ADHD was unknown but that there was a clear implication that the pharmacokinetic difference was clinically relevant. In later correspondence about the use of the same data, Shire had agreed there was no clinical comparator data for Medikinet XL and Equasym XL and that pharmacokinetic data and understanding of pharmacodynamics was both intuitive and important. Flynn submitted that it found the situation somewhat perverse – whereas previously Shire had objected to any inference or suggestion as to the significance or clinical meaning of pharmacokinetic data (a complaint Flynn accepted and took into full consideration in the production of the leavepiece now at issue), Shire now objected to the absence of such an extrapolation.

Flynn submitted that in inter-company dialogue Shire had emphatically challenged the use of adult pharmacokinetic data whereas now it challenged the

absence of contextual information where such data were used. Flynn submitted that Shire had previously questioned the use of contextual information, to which Flynn responded by its removal. What was it to be?

Flynn submitted that González *et al* reported a study of methylphenidate bioavailability from two extended-release formulations (Equasym XL and Concerta XL). The study was sponsored by Celltech and three of the authors were employees of that company. Celltech (UCB) was the original developer and licence holder for Equasym XL before divesting rights to Shire. Pharmacokinetic data from González *et al* was reproduced as one of the two graphs in the leavepiece at issue. The study was clearly referenced and relied on Gonzalez *et al* by way of supporting information. The 'Discussion and conclusions' section of Gonzalez *et al* stated:

> 'The objective of these studies was to compare the rate and extent of MPH [methlyphenidate] absorption from single doses of two extended-release MPH formulations. Whilst both formulations contain an immediate release as well as extended release MPH components, **it is important for clinicians to be aware of the similarities and differences in the plasma profile** resulting from dosing of these formulations….' (emphasis added)
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> 'The majority of ADHD patients that receive MPH treatment are children or adolescents. However, we chose adult subjects for these studies because of ethical considerations regarding the enrolment of children into clinical studies that involve invasive procedures with little expectation of clinical benefit. Despite the limitation, we believe the results presented have potential significance for children and adolescents. Thus, although the absolute plasma levels of MPH resulting from any given dose are generally higher in children than adults – most likely due to differences in dose-weight ratio – **the pharmacokinetic profiles of MPH in adults and children are qualitatively similar and there are no age-related differences in absorption, distribution, metabolism or excretion of MPH**.' (emphasis added)

Flynn submitted, and considered it was entirely supported by Gonzalez *et al*, that it was entirely reasonable and justified to make use of adult pharmacokinetic data in these circumstances.

However, during inter-company dialogue, Shire strongly challenged the use of adult pharmacokinetic data. Flynn found the position disingenuous if not duplicitous given than Shire also used adult pharmacokinetic data in the same therapy area. In its leavepiece, a whole page was devoted to presentation of the same González *et al* pharmacokinetic comparison of Concerta XL and Equasym XL under the heading 'Equasym XL delivers higher plasma concentrations versus Concerta XL during the early part of the school day'. In a later leavepiece Shire took a further step, albeit backwards in Flynn's view, in making claims of clinical relevance in connection with a statement as to Equasym XL's 'unique dose-ratio designed to make the most of the school day'. In that case the ratio referred to (30/70 immediate/delayed release components) was a reference to the pharmaceutical *in vitro* release of methylphenidate. Notwithstanding, Shire seemed comfortable to extrapolate to the clinical situation.

Flynn suggested that, for the purposes of argument however, it accepted that the use of adult pharmacokinetic data in this therapy area was meaningful and acceptable. Flynn was then left to consider the alleged breach of Clause 7.2 on the grounds that the presentation of both González *et al* and Schütz *et al* pharmacokinetic data in separate graphs was misleading and invited readers to extrapolate a favourable (but misleading) comparison between the pharmacokinetic profiles of Medikinet XL and Concerta XL. Flynn submitted that this was patently not the case and required readers to make a lateral jump in thinking that, in Flynn's view, they would not make. These were two separate published pharmacokinetic comparisons of two products in each, and Equasym XL was common to both studies. Shire asked Flynn to believe that readers might extrapolate a favourable but misleading comparison between Medikinet XL and Concerta XL. Flynn submitted that the audience, informed and expert child psychiatrists and paediatricians, was more than familiar with the therapy area, the use of stimulants and the extensive literature describing pharmacokinetic and pharmacodynamics correlation. In particular, they would not be misled or accept a suggested or claimed clinical advantage of one product over another based only on pharmacokinetic differences. Further, they would not naturally be drawn to superimpose in their mind's eye the two graphs. The two graphs were given equal prominence, were clearly and separately referenced (as originating from two different studies) and were presented in such a way as to invite readers to consider the two pieces of information separately. They were presented in the context of the heading of 'Extended Release Methylphenidate (MPH) Preparations Exhibit Different Pharmacokinetic Profiles'. Flynn submitted that similarly, on the opposite page, it presented information on the *in vitro* release profiles and product pricing for the three different extended release preparations. Flynn considered the piece was a balanced presentation of salient differences between the products in terms of pharmacokinetics, pharmaceutics and price.

Flynn therefore denied the alleged breaches of Clauses 7.2 and 7.3.

**PANEL RULING**

The Panel noted that although the leavepiece at issue had been withdrawn as a result of successful inter-company dialogue on other matters raised by Shire, the same pharmacokinetic information was to be used in a Medikinet detail aid which was currently under revision. In that regard there appeared to be a clear intent to continue using the data. The Panel therefore considered that inter-company dialogue in relation to the use of this data had been unsuccessful.

The Panel noted that the front page of the leavepiece posed the question 'How do you achieve a good start to the day for children and adolescents with severe ADHD who are hyperactive and/or inattentive at the start of the school day?' Page 2 was headed 'Extended Release Methylphenidate (MPH) Preparations Exhibit Different Pharmacokinetic Profiles' and featured two graphs which compared the mean methylphenidate plasma concentration-time profiles in healthy adult volunteers for Medikinet XL 20mg and Equasym XL 20mg (adapted from Schütz *et al*) and for Equasym XL 20mg and Concerta XL 18mg (adapted from González *et al*). The Panel noted that the first graph clearly showed that at 2 hours post-dose, Medikinet XL 20mg achieved higher methylphenidate plasma concentrations than Equasym XL 20mg. The peak plasma concentration achieved with Medikinet (4½ hours post-dose) was just under 4.5ng/ml.

The second graph (adapted from González *et al*) compared the plasma concentration-time curves for Equasym XL 20mg and Concerta XL 18mg. The results from this study showed a slightly different plasma concentration-time profile for Equasym XL compared with the results reported by Schütz *et al*, nonetheless the graph showed that 2 hours post-dose, Equasym XL 20mg achieved higher methylphenidate plasma concentrations than Concerta XL 18mg (approximately 3ng/ml and 2ng/ml, respectively). Peak plasma levels for Concerta (approximately 3.7ng/ml) were not achieved until 6 hours post-dose.

The Panel disagreed with Flynn's submission that readers would not be drawn to superimpose in their mind's eye the two graphs. The graphs were positioned next to each other, and both used Equasym XL as the comparator. The dosage of Equasym XL used in both studies was 20mg and the line depicting the plasma concentration of methylphenidate for Equasym XL was the same colour in each graph. In the Panel's view, the graphs encouraged readers to compare the plasma concentration-time profiles of Medikinet XL, Equasym XL and Concerta XL and conclude that, in the first few hours post-dose, Medikinet XL achieved a higher methylphenidate plasma concentration than the other medicines. In that regard the Panel considered that some readers might assume that this resulted in a clinical advantage for children who were hyperactive and/or inattentive at the start of a school day thus answering the question posed on the front page of the leavepiece.

The Panel considered that whilst readers might find pharmacokinetic data useful, care must be taken not to present such data in a way which implied consequential clinical benefit unless a direct link between the two had been established. The Panel noted that the data depicted was from healthy adult volunteers and that the absolute plasma levels of methylphenidate resulting from any given dose were generally higher in children than adults. This was not stated in the leavepiece nor was any indication given of the methylphenidate plasma concentration needed for a therapeutic effect in ADHD in children.

The Panel noted that although the leavepiece did not refer to any clinical data, it did not state that the depicted pharmacokinetic differences in healthy adult volunteers had not been shown to have consequential differences in clinical outcome when used to treat ADHD in children. The Panel noted Shire's submission that there were no clinical studies to show that Medikinet XL had a superior clinical profile to either Equasym XL or Concerta XL.

The Panel considered that the presentation of the pharmacokinetic data was such that readers would not be able to understand the significance of the data or form their own opinion of the therapeutic value of Medikinet XL vs Equasym XL or Concerta XL. A breach of Clause 7.2 was ruled. The comparisons of Medikinet XL with Equasym XL and Concerta XL were misleading as alleged in that regard. A breach of Clause 7.3 was ruled.

**Complaint received** **11 January 2012**

**Case completed** **22 February 2012**