CASE AUTH/2087/1/08

# UCB PHARMA v FLYNN PHARMA

## Medikinet XL 'Dear Doctor' letter

**UCB Pharma complained about a 'Dear Doctor' promotional letter sent by Flynn Pharma in response to a supply problem with UCB's product Equasym (methylphenidate immediate release). The letter promoted Flynn's product Medikinet XL (methylphenidate modified release). UCB alleged that promoting medicines in such a way did not maintain high standards in breach of the Code.**

**Readers were told that to alleviate the supply problems with [Equasym] Flynn was trying to increase its supply of immediate release methylphenidate. The letter also stated that 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a b.d. dosage of immediate release methylphenidate'. UCB alleged that this claim could not be substantiated.**

**The Panel did not consider that issuing a letter referring to supply problems of a competitor product was necessarily a breach of the Code. There had been supply problems with UCB's product, Equasym when the letter was sent. The Panel did not consider that promoting in this way meant that high standards had not been maintained as alleged and no breach of the Code was ruled.**

**With regard to the claim 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a b.d. dosage of immediate release methylphenidate', the Panel noted that the Equasym XL Summary of Product Characteristics (SPC) stated that patients established on an immediate release methylphenidate formulation might be switched to the milligram equivalent daily dose of Equasym XL. The claim at issue was thus misleading; Medikinet XL was not the only sustained release methylphenidate available as a direct replacement for bd dosage of immediate release methylphenidate. Equasym XL could also be used. A breach of the Code was ruled.**

UCB Pharma Ltd explained that manufacturing issues had led to a temporary supply shortage of Equasym (methylphenidate immediate release) tablets. The supply issue occurred in November 2007 and was resolved by 14 December 2007. UCB had managed the issue according to the Department of Health (DoH) and the Association of the British Pharmaceutical Industry (ABPI) Best Practice Guidance 'Notification and Management of Medicines Shortages' (January 2007), and had contacted the DoH as part of the process.

UCB complained about a 'Dear Doctor' promotional letter sent by Flynn Pharma Ltd in response to the supply problem with Equasym. The letter had been sent on 18 November 2007 to paediatricians and child psychiatrists and was headed 'Shortage of methylphenidate immediate release tablets'. Readers were told that there were supply problems with the leading brand of immediate release methylphenidate (UCB's Equasym) and that to alleviate the problem Flynn was attempting to increase supply of its immediate release methylphenidate tablets, Medikinet. The letter also stated that 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a b.d. dosage of immediate release methylphenidate'.

UCB supplied Equasym XL (modified release methylphenidate). Methylphenidate, immediate or controlled release, was used as part of a comprehensive treatment plan in attention deficit/hyperactivity disorder (ADHD) in children over six when remedial measures alone proved insufficient.

### COMPLAINT

UCB stated that the letter came to its attention when it started receiving telephone calls from representatives and health professionals. The letter was sent to approximately 3,000 paediatricians and 800 child psychiatrists on 18 November 2007 and Flynn health specialists were also provided with a copy. The letter referred to a shortage of the leading brand of methylphenidate immediate release tablets which, as conceded by Flynn, was immediately identifiable as Equasym.

UCB understood that the DoH asked Flynn whether production of its immediate release methylphenidate tablet (Medikinet) could be increased. UCB believed that this discussion with the DoH resulted in the production of the 'Dear Doctor' letter. UCB alleged that promoting medicines in such a way was not maintaining high standards and in breach of Clause 9.1 of the Code.

With regard to the claim that 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a b.d. dosage of immediate release methylphenidate', the Equasym XL summary of product characteristics (SPC), Section 4.2 stated that individuals might be switched directly from immediate release methylphenidate to Equasym XL, or be started on Equasym XL as a direct alternative to methylphenidate immediate release. UCB alleged that the Equasym XL SPC demonstrated that the claim was not substantiable, in breach of Clause 7.2 of the Code.

## RESPONSE

Flynn submitted that the background context and stimulus to issue the letter was the supply of methylphenidate tablets (immediate release) in the UK. The product was available in 5mg, 10mg and 20mg, although in the case of the 5mg and 20mg Flynn and UCB were the only two suppliers. Flynn as a relatively recent market entrant (March 2007), supplied only a small proportion of the market. In contrast, UCB as the established player supplied an estimated 80% of demand for the 5mg and 20mg strengths and approximately 25% of demand for the 10mg strength where other suppliers also competed. Thus one could readily predict that any interruption in supply from the dominant supplier had every potential to impact on patient care. Without responsible communications, it was also improbable that a second minority supplier would be able to maintain continuity of supply for anything other than a very short period before its own supplies were exhausted.

Flynn submitted that these products were used in sensitive and vulnerable patients ie, juveniles and adolescents with ADHD. Further, the numbers of patients potentially affected were not trivial. Prescribing and Cost Analysis data for 2006 indicated a total of around 50,000 prescriptions for the 5mg strength and 7,000 for the 20mg strength in 2006 in the retail sector (primary healthcare). On a simple pro rata basis, this equated to about 1,000 scripts/patients per week for the 5mg and about 135 scripts/patients per week for the 20mg strength. Although more than 90% of supply occurred in primary care, the diagnosis and prescription (or revision/change of prescription) of medicine for ADHD occurred exclusively in primary (sic) care (hospital environment) through child psychiatrists and paediatricians with relevant experience.

Thus Flynn submitted that it had acted properly and responsibly in issuing the letter to clinicians in primary care. It was issued because of an interruption in supply by UCB, which prescribers and suppliers were not told about. From late October 2007 Flynn received calls and contacts from wholesalers, pharmacists and doctors who thought that methylphenidate (immediate release) was out of stock. In other words, they thought that none was available, and by inference, that both UCB and Flynn could not supply. This was not so.

Further, from 1 October 2007 for a period of 2 years, Flynn was awarded the national contract to supply hospitals in England with all of their methylphenidate immediate release 5mg, 10mg and 20mg. In other words, all requirements for these products in NHS hospitals in England should be met with the supply of Medikinet XL until September 2009 or some 22 months after the letter was issued. The substantial majority of the recipients of the letter in question were the prescribers in those hospitals and if copies of the letter still existed or were in circulation, they should not impact the prescribing practice of those particular doctors

Flynn alleged that UCB's communications had to date been ambiguous and incomplete as to the nature and extent of the shortage. UCB's letter of 30 November referred to 'potential shortages'. To be clear – this was approximately one month after Flynn had become aware of 'actual shortages'. UCB's letter of 20 December stated that 'the stock shortage….was a temporary one which has been completely resolved'. UCB's subsequent complaint to the Authority was more specific in stating 'The issue was resolved by 14 December 2007'. As of 8 February 2008, Flynn was still not confident that this was so. Flynn was advised by two of the main three wholesalers in the UK that Equasym 20mg continued to be unavailable. Flynn provided a recent out of stock report for one of the wholesalers as confirmation which implied a date of March (2008) for resolution of the problem. A significant percentage of pharmacists relied on either of the two wholesalers and therefore Flynn could not reconcile a statement that the situation was 'fully resolved' with this position.

The alleged breach of Clause 9.1 was a statement of opinion and was not supported by evidence or reasoned argument. Further the alleged breach of Clause 9.1 was a misapplication of both the letter and intent of that particular clause, which it understood was concerned primarily with matters of suitability and taste and the special nature of medicines. The letter itself might be considered in two parts – the first was a factual (trade) announcement as to the availability of methylphenidate immediate release tablets. That it did not mention Equasym by name was irrelevant, since the Code did not prohibit the use of competitor brand names. The second part of the letter referred to an 'alternative solution' (to the supply problem), offered by Medikinet XL, Flynn's modified release methylphenidate. This made a promotional claim and hence the use of an appropriate reference and prescribing information. The claim itself was subject to a separate allegation. If, however, the essence of UCB's concern was that it was inappropriate to mix statements of fact or trade announcements (eg pricing and availability information), with promotion, then it should state that. Regardless, it was Flynn's view that such practice was permissible, proper and consistent with the advertising and promotion of medicines in the UK for many years.

Flynn submitted that if however, UCB's concern was that it was not the responsibility of a company to communicate shortages or situations that might and did impact on markets in which it operated, then again it failed to see the reasoning behind this. The fact that a competitor took issue to such a situation being communicated was quite simply, not in breach of the Code. Nor, did the letter offend against the generally held standards and norms in pharmaceutical promotion; to state that a product was unavailable was as permissible as it was to make comparative claims of a clinical or pharmaceutical nature. Finally, the shortage itself was not disputed – in other words, there was a shortage, and indeed questions remained as to the

availability of the 20mg tablets.

With regard to the claim 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a b.d. dosage of immediate release methylphenidate' Flynn that SPCs were carefully crafted and important documents, the wording of which was assessed in detail and approved by the Medicines and Healthcare products Regulatory Agency (MHRA). It was appropriate therefore to refer to the precise language of this document. The Equasym XL SPC in Section 4.2 stated that, 'For example, 20mg of Equasym XL is intended to take the place of 10mg at breakfast and 10mg at lunchtime' and that 'Equasym XL 10mg once daily may be used in place of immediate release methylphenidate hydrochloride 5mg twice daily from the beginning of treatment …' UCB's use of the highlighted wording in its complaint was at variance with the SPC itself, and conveyed a degree of certainty not supported by the language therein. In Flynn's view, the SPC fell short of substantiating a claim that Equasym XL was a **direct** replacement for immediate release methylphenidate.

Flynn submitted that the equivalence of immediate release products and their modified release counterparts was frequently debated. Whereas in some instances, different brands of a modified release medicine were considered interchangeable (or direct replacements) with each other and their immediate release equivalents, methylphenidate was not one of them.

Flynn submitted that there was a clear and direct relationship between the pharmacokinetic and pharmacodynamic (clinical) response, such that formulation and release profile very much mattered. Indeed, the authoritative expert comment on the subject might be found in 'Long-acting medications for the hyperkinetic disorders – A systematic review and European treatment guideline' (Banaschewski *et al* 2006), which in reference to modified release products stated, 'all provide a mixture of immediate- and extended-release methylphenidate; they differ in the physics of the delayed release system and in the proportion of immediate to delayed'. It was this variation in the release profiles of the competing brands of modified release methylphenidate that demanded prescription by brand and in practice, the selection of different brands to suit individual patients. The clinical profile of the underlying hyperkinetic disorder and inter-subject variability was such that different patients exhibited symptoms to a greater or lesser degree in the morning or afternoon. Thus it was clinically useful and prudent when selecting and prescribing a modified release methylphenidate product, to select one with a release profile that matched the particular patient's underlying hyperkinetic profile. All brands were different and all had a place. Another common feature in clinical practice was the use of early morning/late afternoon, early evening 'top-up' doses to add-on to the release profile offered by a specific product. In regard to Equasym XL the same review stated that '30% of the dose is provided by the immediate release component and 70% of the dose is provided by the delayed release component'.

In relation to Medikinet XL, the European guideline stated '50% immediate with 50% extended'. Both Equasym XL and Medikinet XL were designed to release methylphenidate over an approximately 8 hour period, whereas the immediate release presentations provided release and clinical effect over an approximate 4 hour period.

Medikinet XL was the only modified release presentation that had been shown to be bioequivalent to a bd dosage (Döpfner *et al* 2003) cited in the letter at issue. That is to say, a single dose of Medikinet XL would produce plasma levels of methylphenidate equivalent to half the same mg dose taken twice daily (with a dosing interval of approximately four hours). Medikinet XL had also been shown to be clinically equivalent (Döpfner *et al* 2004). The same could not be said of Equasym XL.

The claim asserted that Medikinet XL was the only direct replacement for a bd dosage. In other words for example, that a dose of Medikinet XL 10mg once daily was the only direct replacement for a dosage of 5mg immediate release bd. Put simply, Flynn was stating that '5 + 5 = 10'. The essence of UCB's implied claim was that '3 + 7 = 10'. However, '5 + 5' was not the same as '3 + 7' – the two modified release products produced different pharmacokinetic and pharmacodynamic profiles and were not interchangeable or equivalent. For UCB's argument to hold true, namely that Equasym XL was also a direct replacement, would then suggest the contrary and that by inference, one (modified release) product could be substituted for the other. Flynn cited Döpfner *et al*, (2003), a bioequivalency study. To support the statement of clinical equivalence Flynn noted that Döpfner *et al*, (2004) reported a comparative efficacy of once-a-day extended release (Medikinet XL), twice-daily immediate-release methylphenidate, and placebo. This was a randomised double-blind crossover study with assessments of clinical response obtained five times over an eight hour period. This study provided robust evidence of the clinical equivalence of Medikinet XL and immediate release methylphenidate at daily dosages of 5mg, 10mg, 15mg and 20mg. On the basis of the above Flynn submitted that there was no breach of Clause 7.2.

## PANEL RULING

The Panel did not consider that issuing a letter referring to supply problems of a competitor product was necessarily a breach of the Code. There had been supply problems with UCB's product, Equasym when the letter had been sent. It stated that the leading brand might not be available for patients and offered two solutions, these being increasing supply of Medikinet or using Medikinet XL. The Panel did not consider that promoting in this way meant that high standards had not been maintained as alleged and no breach of Clause 9.1 was ruled.

With regard to the claim 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a bd dosage of immediate release methylphenidate', the Panel examined the Equasym XL SPC. Section 4.2, in a reference to patients currently using methylphenidate, stated that patients established on an immediate release methylphenidate formulation might be switched to the milligram equivalent daily dose of Equasym XL. A comparable statement appeared in the Medikinet XL SPC. The Panel considered that the claim at issue was misleading given the statements in the Equasym XL SPC.

Medikinet XL was not the only sustained release methylphenidate available as a direct replacement for bd dosage of immediate release methylphenidate. Equasym XL could also be used. The Panel did not consider that the claim related to changing from one modified release product to another as appeared to be implied from much of Flynn's response to this point. The Panel ruled a breach of Clause 7.2.

**Complaint received** **25 January 2008**

**Case completed** **4 March 2008**