CASE AUTH/2383/2/11

ANONYMOUS GENERAL PRACTITIONER v BAYER

Yasmin journal advertisement

An anonymous and non-contactable general practitioner alleged that a journal advertisement for the oral contraceptive Yasmin (ethinylestradiol and drospirenone) issued by Bayer Healthcare, was misleading and could put patients at unnecessary risk.

A bullet point stated that Yasmin had been shown to have a beneficial effect vs baseline on acne, fluid retention, hirsutism and premenstrual symptoms. The complainant was concerned that the advertisement read as if it were asking him to prescribe Yasmin in these conditions and noted that at least three of them were listed as adverse events in the Yasmin summary of product characteristics (SPC).

The detailed submission from Bayer is given below.

The Panel noted that the 'headline' claim 'Yasmin. It's for more women than you might imagine' was immediately followed by claims in much smaller type, the first two of which were that Yasmin was an effective and well-tolerated contraceptive and that 95% of users reported overall satisfaction. The claim at issue followed: 'Yasmin has also been shown to have a beneficial effect vs baseline on acne[5]*, fluid retention[6]*, hirsutism[7]* and premenstrual symptoms[8]*'. This was followed by the claim 'Yasmin is licensed for oral contraception' beneath which, in a smaller type size again, was the explanation '*Acne and fluid retention may be uncommon side effects of COC [combined oral contraceptive] use. Yasmin is not licensed as a treatment for acne, hirsutism, fluid retention or premenstrual symptoms. ^A non-comparative study'. The product logo to the right of the claim at issue included the strapline 'Contraception and more'.

The Panel noted that there was a difference between promoting a medicine for its licensed indication and promoting additional clinical benefits. Whilst the Panel considered that it was not unacceptable to refer to a medicine's additional clinical benefits, such benefits must be referred to within the context of the licensed indication and not presented such as to imply that they were the reason, *per se*, to prescribe. Statements to the contrary were unlikely to negate an otherwise misleading impression. The Panel considered that overall the claim that Yasmin was 'for more women than you might imagine' and the strapline 'Contraception and more' would encourage readers to consider prescribing Yasmin for more than just its oral contraceptive efficacy ie its positive effects on acne, fluid retention, hirsutism and premenstrual symptoms.

The acne claim was referenced to a study which demonstrated the non inferiority of Yasmin compared with Dianette (which was licensed for severe acne refractory to prolonged oral antibiotic therapy). The fluid retention claim was referenced to a non comparative prospective study which showed an improvement in abdominal bloating and breast tenderness. The claim for a beneficial effect on premenstrual symptoms was referenced to an in-house literature search in which thirteen studies were identified, five of which included an active or placebo comparator. All showed a positive trend on one or more premenstrual symptoms with Yasmin. Many showed statistically significant results. Conversely, the Panel noted that depressive mood, changes in libido and fluid retention were listed on the SPC as possible adverse reactions.

The Panel noted that the advertisement stated that 'acne and fluid retention *may* be uncommon side effects of COC use' (emphasis added). The Yasmin SPC stated that both effects had been reported during use with Yasmin. The Panel considered that the advertisement underplayed the side-effects of Yasmin. A breach of the Code was ruled.

The Panel noted Bayer's submission regarding the adverse reactions in the SPC and that these included treatment emergent adverse events irrespective of whether they were thought to be caused by the medicine. The Panel considered that the advertisement promoted clinical effects of Yasmin which were not licensed indications and the converse of which were listed as adverse reactions in the SPC. In the Panel's view the advertisement encouraged prescribers to consider these features as a reason to prescribe Yasmin. Further, some of the data referred to in the advertisement was non comparative. The Panel considered that overall the advertisement was misleading and inconsistent with the SPC. Breaches of the Code were ruled.

The Panel noted that prejudicing patient safety was an activity likely to be ruled in breach of Clause 2. The Panel noted that there was no evidence to show that patient safety had been adversely affected but considered that to imply possible clinical uses that were not licensed, such that a counter claim was considered necessary, was a serious matter. Further, citing possible clinical advantages the opposite of which were listed in the SPC as potential side effects was of serious concern. The Panel did not consider that the statement 'Acne and fluid retention may be uncommon side effects of COC use' negated the impression otherwise given. A breach of Clause 2 was ruled.

An anonymous and non-contactable general practitioner complained about an advertisement (ref UK.PH.WH.YSM.2010.119) for Yasmin

(ethinylestradiol and drospirenone) published in Pulse, 26 January 2011, by Bayer Healthcare. Yasmin was indicated for oral contraception.

COMPLAINT

The complainant stated that he regularly prescribed Yasmin for his patients.

The third bullet point in the advertisement stated that Yasmin had also been shown to have a beneficial effect vs baseline on acne, fluid retention, hirsutism and premenstrual symptoms.

The complainant was concerned firstly that the advertisement read as if it were asking him to prescribe Yasmin in the above mentioned conditions, and secondly that at least three of these were recognised adverse events of Yasmin and listed in the current summary of product characteristics (SPC).

The complainant believed it was highly unethical to put such misleading information into an advertisement and that it could put patients at unnecessary risk.

When writing to Bayer, the Authority asked it to respond in relation to Clauses 2, 3.2, 7.2 and 7.9 of the Code.

RESPONSE

Bayer noted that the advertisement read as follows:

- 'Yasmin is an effective and well-tolerated contraceptive
- 95% of users report overall satisfaction with Yasmin, the most widely used pill in Europe
- Yasmin has also been shown to have a beneficial effect vs baseline on acne, fluid retention, hirsutism and premenstrual symptoms
  Yasmin is licensed for oral contraception'.

Bayer submitted that it was clear, upfront, from the advertisement that Yasmin was a contraceptive. Moreover, the licensed indication was re-stated in the main bulk of the copy. The advertisement did not suggest that Yasmin was licensed for acne, fluid retention, hirsutism or premenstrual symptoms, and in fact this was explicitly stated in the adjacent text with the words 'Yasmin is not licensed as a treatment for acne, hirsutism, fluid retention or premenstrual symptoms'.

The language used in the advertisement was factual. It was intended to alert a potential prescriber to the properties of Yasmin with regard to these common co-morbid conditions, which was important when making a prescribing decision because combined oral contraceptives (COCs) could worsen some of these conditions. Yasmin had a positive effect on the listed conditions as a result of its antiandrogenic and mild antimineralocorticoid properties, which were described in Section 5.1 of the SPC. Clinical studies substantiating the beneficial effects were discussed below.
In addition, in 2009 the Medicines and Healthcare products Regulatory Agency (MHRA) reviewed the claim 'Drospirenone has a positive effect on acne and fluid retention' particularly with regard to whether the claim about fluid retention could be substantiated. Although the complaint was upheld, importantly, the MHRA allowed the claim regarding fluid retention to be made as long as a previously agreed claim from pre-vetting was used in future advertisements. Bayer had adhered to this.

In summary, Bayer believed its advertisement was consistent with the SPC and it therefore denied a breach of Clause 3.2.

Bayer noted that Yasmin had been on the UK market for 9 years and there was now a substantial body of evidence to support the beneficial effects on acne, fluid retention, hirsutism and premenstrual symptoms. The beneficial effects on acne were largely related to the antiandrogenic properties of drospirenone which were discussed further in the SPC. In the advertisement, the claim with regard to acne was referenced to a double blind study comparing Yasmin with Dianette (ethinylestradiol and cyproterone acetate) over 9 treatment cycles (van Vloten et al, 2002). One hundred and twenty-eight women with mild-to-moderate facial acne were randomized to receive either Yasmin or Dianette in a 2:1 ratio. The results showed that, from baseline, the reduction in acne lesions was 62.5% and 58.8% respectively for Yasmin and Dianette.

Statistical analysis demonstrated non-inferiority for Yasmin vs Dianette ($p=0.0006$) which indicated that Yasmin was at least as effective as Dianette in improving the acne lesion count at the end of 9 treatment cycles. The authors concluded that Yasmin was as effective for treating mild-to-moderate acne as Dianette. This was clinically relevant because Dianette was licensed for severe acne refractory to prolonged oral antibiotic therapy.

Bayer noted that a similar claim, 'A demonstrable positive effect on … skin condition', was considered in Case AUTH/1352/8/02; the Panel ruled no breach.

Yasmin's positive effects on fluid retention were largely related to the mild antimineralocorticoid effects of drospirenone, which were discussed further in the SPC and could be substantiated by Apter *et al*, (2003) and Endrikat *et al*, (2009).

Apter *et al* (reference number 6 in the advertisement), was a single-arm prospective study. General well-being and fluid-related symptoms were measured at baseline and again after 6 cycles of Yasmin. 177 women (77.3%) showed improvement in the severity of abdominal bloating during the luteal phase ($p<0.001$); 158 (69%) showed improvement in the severity of breast tension ($p<0.001$) and 119 (52% showed improvement in the severity of swelling of the extremities (p=ns). This study clearly demonstrated an improvement

between baseline and cycle 6 of treatment in two major somatic symptoms associated with fluid retention, with a non-significant positive trend in swelling of extremities. In keeping with what was agreed with the MHRA in 2009, the nature of this trial was clearly identified through the words 'a non-comparative study' in the advertisement.

Endrikat *et al* (part of reference number 8 in the advertisement) was a single-arm prospective study of 3,488 women. Outcomes including premenstrual symptoms of water retention were measured at baseline and after three and six cycles of Yasmin. The results, clearly demonstrated a statistically significant improvement in all fluid-related parameters vs baseline.

Reference number 8 'data on file' in the advertisement referred to the results of an in-house literature search to evaluate the body of evidence for the effects of Yasmin on fluid retention and premenstrual symptoms. There were many studies of differing designs. Many showed statistically significant results supporting the effect of Yasmin; the remainder generally showed positive trends. Therefore Bayer believed that Apter *et al* and Endrikat *et al* reflected the overall substantial existing body of evidence.

Bayer noted that premenstrual symptoms was the name given to the physical, psychological and behavioural symptoms that could occur in the two weeks before menstruation. Definition of premenstrual symptoms typically included breast tenderness, mood swings, irritability, loss of interest in sex and fluid retention'. Yasmin's positive effect on premenstrual symptoms was largely related to the mild antiandrogenic and antimineralocorticoid effects of drospirenone, which were discussed further in the SPC.

The beneficial effect of Yasmin on premenstrual symptoms was referenced in the advertisement to 'data on file'. This referred to the in-house literature search to evaluate the body of evidence for the effects of Yasmin on fluid retention and on premenstrual symptoms. Thirteen papers were identified, five of which were studies with an active or placebo comparator. All studies showed a positive trend on one or more symptoms with Yasmin.

Yasmin had also been recommended in several recognised clinical guidelines for the management of premenstrual symptoms and fluid retention, most notably in the National Association for Premenstrual Syndrome (NAPS) premenstrual symptoms treatment guideline.

Many of the studies referred to above showed statistically significant results supporting the effect of Yasmin. The principal ones were as follows:

- Guang-Sheng *et al* (2010), a randomised, open-label, multicentre study in 768 women, compared Yasmin with Marvelon (30mcg ethinylestradiol and 150mcg desogestrel), randomized 3:1. As part of the secondary endpoint, as well as a global assessment, the Menstrual Distress Questionnaire (MDQ) was administered at baseline, visit 3 (cycle 7) and visit 5 (after cycle 13). According to the MDQ subscale, water retention during the inter-menstrual period, and water retention and general well-being during the menstrual period in the Yasmin group (-0.297, -0.057, 0.033 and 0.150, respectively), were significantly improved compared with the Marvelon group (-0.108, 0.023, 0.231 and -0.023, respectively) [all $p<0.05$]. The authors concluded that Yasmin had a more favourable effect on premenstrual symptoms than Marvelon.

- Kelly *et al* (2010), a randomized, single blind, parallel-group, multicentre study in 280 women, compared Yasmin with Microgynon (30mcg ethinylestradiol and 150mcg levonorgestrel). The primary outcome measured was the change in the overall score for the MDQ from randomization to cycle 6. Secondary outcomes of menstrual symptoms, and subjective well-being were also measured. Treatment with Yasmin and Microgynon had similar beneficial effects on symptoms of fluid retention and impaired concentration. However Yasmin was significantly better in alleviating negative affect symptoms during the menstrual phase (median difference in MDQ T score -3; $p=0.027$). More subjects in the Yasmin group reported improved physical well-being (60% vs 46%; $p=0.035$).

- Sangthawan and Taneepanichskul (2005), a randomized, open-label study in 99 women, compared Yasmin with Microgynon. The primary outcome measured the prevalence of premenstrual symptoms at cycle 6, while the secondary outcome measured changes from baseline in the Women's Health Assessment Questionnaire (WHAQ) categories (a subset of items from the MDQ). At cycle 6, the prevalence of premenstrual symptoms in the Yasmin group was significantly lower than that of the Microgynon group (32% vs 61.2%; $p=0.005$). In the premenstrual phase, the Yasmin group showed a greater improvement of mean scores from baseline vs Microgynon on negative affect as seen in the items on anxiety, irritability, feeling sad or blue and weight gain in the category of water retention.

- Freeman *et al* (2001), a randomized, double-blind, multicentre, placebo-controlled study in 82 women, evaluated the efficacy of Yasmin in the treatment of premenstrual dysphoric disorder (PMDD), which was a severe form of premenstrual symptom, over 3 treatment cycles. The primary endpoint measured changes from baseline in scores on the Calendar of Premenstrual Experiences (COPE) scale. The study revealed greater improvement in the total COPE scores in the Yasmin group compared with the placebo group. The results of this study showed a consistent trend in reduction of

symptoms that suggested a beneficial effect of Yasmin for the treatment of PMDD, despite limitations of the study design.

- Apter *et al* showed a significant increase in overall Psychological General Well-Being Index (PGWBI) scores from baseline of 16.9 and 20.8 points at cycles 3 and 6, respectively ($p<0.0001$) in women suffering from PMS, demonstrating an improvement in psychological general well-being with treatment.

- Endrikat *et al* showed a statistically significant improvement in all of the satisfaction parameters measured:

Question	Strength of positive trend vs baseline
Are you satisfied with your body weight?	p<0.0001
How do you feel before menses?	p<0.0001
Your skin is…	p<0.0001
Do you have mood swings?	p<0.0001
Do you feel depressed?	p<0.0001
Do you have trouble sleeping?	p<0.0001
Do your breasts feel tender or uncomfortable?	p<0.0001
Do you feel physically attractive?	p<0.0001
Overall quality of life during the last month	p<0.0001

The remainder of the studies identified in Bayer's literature search showed either statistically significant results for improvements in premenstrual symptoms or positive trends. Consequently the body of evidence supported Bayer's statement that Yasmin had a beneficial effect vs baseline on premenstrual symptoms.

Bayer noted that a similar claim, 'demonstrable positive effect on PM (premenstrual) symptoms', had been at issue in Case AUTH/1352/8/02. The differences from the present case were that:

- Since the PMCPA's ruling in 2002 more studies had been published and there was now further substantial evidence to support the clinical effect of Yasmin in fluid retention and premenstrual symptoms.

- Since the 2002 PMCPA ruling, Yasmin had also been recommended in several recognised clinical guidelines for the management of premenstrual symptoms and fluid retention, most notably in the NAPS treatment guideline and suggested in a leading textbook for clinicians 'Contraception: Your Questions Answered'(Guillebaud).

Bayer noted that Yasmin's positive effects on hirsutism were, like acne, largely related to the antiandrogenic effects of drospirenone, which were discussed further in the SPC. In the advertisement the claim with regard to hirsutism was referenced to Batukan *et al*, (2007), a double blind study which compared Yasmin with Dianette over 12 months. Ninety-one women with moderate-to-severe hirsutism were randomized to receive either Yasmin or Dianette, which was licensed for moderately severe hirsutism. The results showed that the median reduction of total hirsutism score from baseline was 80% and 81% respectively for Yasmin and Dianette. The authors concluded that both treatments had a similar effect on reducing body hair growth.

The effect of Yasmin on hirsutism, specifically hair growth on the upper lip and chin, was also measured as a secondary outcome in van Vloten *et al*. During treatment hair growth decreased in both the Yasmin and Dianette treatment groups and completely resolved in most cases. By cycle 9, the percentage of subjects without upper lip hair had increased from 65.5% to 84.5% and 66.7% to 87.9% in the Yasmin and Dianette groups respectively. Similarly, the percentage of subjects without chin hair increased from 84.5% to 93.1% and 90.9% to 97.0% in the Yasmin and Dianette groups respectively.

In summary, Bayer submitted that the claims in the advertisement about Yasmin's non-contraceptive properties could be substantiated and were a fair reflection of the overall body of evidence supporting the beneficial effects of Yasmin. Bayer denied a breach of Clause 7.2.

With regard to adverse events, Bayer recognised that acne and fluid retention were listed in the current SPC as uncommon side effects. Given that this was explicitly stated in the advertisement Bayer considered that there was no danger that a prescriber would be misled.

Moreover, Bayer did not consider that the description of the non-contraceptive properties of Yasmin in the advertisement was incompatible with these being stated as possible uncommon side effects of Yasmin use. This was due to two key factors, namely the methodology of collecting and interpreting safety data for inclusion in the SPC; and secondly the 2009 correspondence with the MHRA about fluid retention.

Historically, inclusion of undesirable effects in Section 4.8 of the SPC was dependent on the frequency of adverse drug reactions (in which a causal relationship between the medicine and an adverse reaction was suspected). This was the methodology used for most other COCs currently on the UK market, most of which were licensed in the 1970s or early 80s. However, current methodology included all treatment emergent adverse events occurring at a particular frequency, irrespective of whether they were thought to be caused by the medicine. Adverse events were defined as any untoward event, regardless of whether it was thought to be causally related to the medicine. The Yasmin SPC was based on this modern methodology.

The listing of adverse events as opposed to just adverse reactions was considered safer, for

example because sometimes a previously unknown causal relationship could emerge only in hindsight. However, the downside was a potential listing of unrelated 'side effects', because although a condition might arise during treatment, this did not necessarily imply a causal relationship with the medicine; it might just be a common co-morbid condition that existed in the population receiving the medicine.

Moreover, despite the fact that fluid retention was listed as an uncommon side effect in the Yasmin SPC, in 2009 the MHRA accepted that the claim regarding a beneficial effect on fluid retention could still be used, as long as it was made clear that this could also be an uncommon side effect. Bayer had complied with this request. Therefore, there was no incompatibility with a non-contraceptive beneficial property also being listed as a side effect.

Therefore, Bayer did not consider the reference to the beneficial non-contraceptive properties of Yasmin was misleading or in breach of Clause 7.9.

In summary, Bayer did not consider the description of the additional non-contraceptive properties of Yasmin was misleading or unethical. Most importantly, Bayer strongly maintained that it had not put patients at risk. Bayer considered that it had acted in a highly ethical, balanced and transparent manner and it denied breaches of Clauses 2, 3.2, 7.2 or 7.9.

PANEL RULING

The Panel noted that the 'headline' claim in the advertisement was 'Yasmin. It's for more women than you might imagine'. This was immediately followed by claims in much smaller type, the first two of which were that Yasmin was an effective and well-tolerated contraceptive and that 95% of users reported overall satisfaction. The claim at issue followed: 'Yasmin has also been shown to have a beneficial effect vs baseline on acne5*, fluid retention6*, hirsutism7* and premenstrual symptoms8*'. This was followed by the claim 'Yasmin is licensed for oral contraception' beneath which, in a smaller type size again, was the explanation '*Acne and fluid retention may be uncommon side effects of COC use. Yasmin is not licensed as a treatment for acne, hirsutism, fluid retention or premenstrual symptoms. ^A non-comparative study'. The product logo to the right of the claim at issue included the strapline 'Contraception and more'.

The Panel noted that there was a difference between promoting a medicine for its licensed indication and promoting its additional clinical benefits. Whilst the Panel considered that it was not unacceptable to refer to a medicine's additional clinical benefits, such benefits must be referred to within the context of the licensed indication and not presented such as to imply that they were the reason, *per se*, to prescribe. Statements to the contrary were unlikely to negate an otherwise misleading impression. The Panel considered that overall the claim that Yasmin was 'for more women than you might imagine' and the strapline 'Contraception and more' would encourage readers to consider prescribing Yasmin for more than just its oral contraceptive efficacy ie its positive effects on acne, fluid retention, hirsutism and premenstrual symptoms.

The SPC stated in Section 4.8, Undesirable effects, that fluid retention and acne were uncommon adverse reactions (<1 in 100, ≥1 in 1000). Section 5.1 of the SPC, Pharmacodynamic properties, stated that in a therapeutic dosage, drospirenone possessed antiandrogenic and mild antimineralocorticoid properties and had a pharmacological profile closely resembling the natural hormone progesterone. This section also stated that there were indications from clinical studies that the mild antimineralocorticoid properties of Yasmin resulted in a mild antimineralocorticoid effect. There was no similar statement regarding the antiandrogenic properties of drospirenone and no reference in the SPC specifically about positive effects on acne, fluid retention, hirsutism or premenstrual symptoms.

The Panel noted that Clause 3.2 required the promotion of a medicine to be in accordance with the terms of its marketing authorization and not inconsistent with the particulars listed in the SPC.

The acne claim was referenced to van Vloten *et al* which demonstrated the non inferiority of Yasmin compared with Dianette (which was licensed for severe acne refractory to prolonged oral antibiotic therapy). The fluid retention claim was referenced to Apter *et al*, a non comparative prospective study which showed an improvement in abdominal bloating and breast tenderness. Endrikat *et al*, a single arm prospective study showed a statistically significant improvement in all fluid-related parameters (abdominal bloating, breast tenderness and swollen extremities) vs baseline. Thirteen studies were identified, five of which included an active or placebo comparator. All showed a positive trend on one or more premenstrual symptoms with Yasmin. Many showed statistically significant results.

The claim for a beneficial effect on premenstrual symptoms was based on a literature search by Bayer to evaluate all the evidence for the positive effects of Yasmin on breast tenderness, mood swings, irritability, loss of interest in sex and fluid retention. Conversely, depressive mood, changes in libido and fluid retention were listed on the SPC as possible adverse reactions.

The Panel noted that the advertisement stated that 'acne and fluid retention *may* be uncommon side effects of COC use' (emphasis added). The Yasmin SPC stated that both effects had been reported during use with Yasmin. The Panel considered that the advertisement underplayed the side-effects of Yasmin. A breach of Clause 7.9 was ruled.

The Panel noted Bayer's submission regarding the

adverse reactions in the SPC and that these included treatment emergent adverse events irrespective of whether they were thought to be caused by the medicine. The Panel considered that the advertisement promoted clinical effects of Yasmin which were not licensed indications and the converse of which were listed as adverse reactions in the SPC. In the Panel's view the advertisement encouraged prescribers to consider these features as a reason to prescribe Yasmin. Further, some of the data referred to in the advertisement was non comparative. The Panel considered that overall the advertisement was misleading and inconsistent with the SPC. Breaches of Clauses 3.2 and 7.2 were ruled.

With regard to Clause 2, the Panel noted that prejudicing patient safety was an activity likely to be ruled in breach of Clause 2. The Panel noted that there was no evidence to show that patient safety had been adversely affected but considered that to imply possible clinical uses that were not licensed, such that a counter claim was considered necessary, was a serious matter. Further, citing possible clinical advantages the opposite of which were listed in the SPC as potential side effects was of serious concern. The Panel did not consider that the statement 'Acne and fluid retention may be uncommon side effects of COC use' negated the impression otherwise given. A breach of Clause 2 was ruled.

Complaint received **7 February 2011**

Case completed **24 March 2011**