CASE AUTH/3227/7/19

FERRING v PHARMASURE

Promotion of Meriofert

Ferring Pharmaceuticals Ltd complained about a Meriofert (menotrophin) detail aid issued by Pharmasure Limited. Meriofert was used to induce ovulation in women undergoing *in vitro* fertilization (IVF). Ferring marketed Menopur (menotrophin for injection) which was similarly used in fertility treatment.

Ferring's concerns related to 'urinary gonadotrophins' which were essential in IVF treatment. Gonadotrophins were a class of hormones which included follicle stimulating hormone (FSH), luteinising hormone (LH) and human chorionic gonadotrophin (hCG). Gonadotrophins were manufactured either from the urine of postmenopausal or pregnant women or through recombinant technology and used for controlled ovarian stimulation, a technique used in IVF to stimulate the ovaries to produce multiple ovarian follicles. The goal was to harvest an optimal number of eggs from the woman's ovaries to maximize the chances that the eggs could be fertilized *in vitro*, and that an embryo could be implanted back into the uterus and develop into a healthy baby.

In a typical healthy pregnancy, hCG was secreted by cells from the placenta of the implanting conceptus from week 2, supporting the ovarian corpus luteum, which in turn supported the endometrial lining and therefore maintained pregnancy. In postmenopausal women, hCG was secreted from the pituitary gland. Whether secreted from the placenta or the pituitary gland, hCG was excreted in the urine.

Meriofert and Menopur were both urinary gonadotrophins (human menopausal gonadotrophin, hMG) containing menotrophin, which was extracted from the urine of postmenopausal women (for Menopur) and also from pregnant women (for Meriofert). Menotrophin consisted of FSH, LH and hCG components, providing FSH and LH hormone activity in a 1:1 ratio. The LH activity was provided by the hCG hormone component.

Menopur received a marketing authorization in 1999 and the marketing authorization for Meriofert was obtained in 2014 using its similarity to published Menopur data. The Public Assessment Report clearly stated 'Overall, the Applicant has provided data to support that hMG-IBSA (Meriofert) is no different from the active comparator Menopur in any way that could lead to differences in efficacy between the two products'.

Ferring alleged that Pharmasure had attempted to differentiate its product Meriofert, on the grounds that it contained a high concentration of placental hCG, implying that this difference led to clinical differentiation in terms of better efficacy and efficiency. Ferring objected to Pharmasure's claims that Meriofert was superior to Menopur substantiated by Lockwood *et al* (2017) and Alviggi *et al* (2013).

Lockwood *et al* was a non-inferiority study. The primary endpoint was to show the non-inferiority of Meriofert to Menopur in respect of the primary endpoint – total number of oocytes retrieved.

Ferring submitted that when there was one primary endpoint, findings of secondary outcomes were considered subsidiary and exploratory, rather than confirmatory, so no claims could be made on these secondary endpoints, unless the statistical analysis was predefined to proceed hierarchically or adjusted for multiplicity. No such plan was stated in Lockwood *et al*, although the promotional material at issue contained a number of claims based on secondary endpoints.

Alviggi *et al* was also a non-inferiority study, where the primary endpoint was the total number of oocytes retrieved. Again, for the secondary endpoints the statistical analysis was not predefined to proceed hierarchically or adjusted for multiplicity. It was thus misleading to imply statistically significant differences for secondary endpoints between the comparators based on this study. Ferring noted a number of limitations with regard to Alviggi *et al* which restricted the citation of the study for substantiation of promotional claims.

The detailed response from Pharmasure is given below.

1 Claim 'Higher mature oocyte yield than Menopur'

The first claim on page 2 of the detail aid read, 'The aim of ovarian stimulation in IVF is to produce an optimum number of mature oocytes and embryos available for transfer', followed by the brand name (Meriofert) above two bullet points:

- **Contains predominantly placental hCG**
- **Higher mature oocyte yield than Menopur.**

Ferring alleged that the clear aim was to imply that Meriofert could produce a higher oocyte yield than Menopur, and therefore that Menopur was less effective than Meriofert. Ferring alleged that the claim was misleading and could not be substantiated.

Ferring noted that the claim in question was referenced to Lockwood *et al*. However, maturity of the oocytes was not a primary endpoint in that study. The primary endpoint was to show the non-inferiority of Meriofert to Menopur in respect of the total number of oocytes retrieved and the study was powered to demonstrate non-inferiority. Further, there was no indication of the amount of placental hCG present in Meriofert; and no indication of the amount of placental hCG that might be of clinical relevance in oocyte production.

Ferring further noted that Lockwood *et al* under-dosed Menopur compared with the UK licence and although the study design was included in small print beneath the bullet points, case precedent was clear that misleading claims could not be corrected by footnotes.

The Panel noted that the first claim on page 2 'The aim of ovarian stimulation in IVF is to produce an optimum number of mature oocytes and embryos available for transfer' and the second bullet point below this (the claim in question) were both referenced to

Lockwood *et al*. The Panel noted that Lockwood *et al* was powered as a non-inferiority study, to confirm the non-inferiority of Meriofert compared with Menopur with regard to clinical outcome (the primary end point being the total number of oocytes retrieved).

The Panel noted that in general terms non-inferiority trials demonstrated that a test product was no worse than a comparator by more than a pre-specified, small amount.

It was unclear to the Panel whether the secondary end points had been clearly pre-specified within Lockwood *et al* in the study design section, however, it appeared from the results and discussion section that the study authors considered the secondary endpoints were powered to show significance; the authors did not mention any limitations to the contrary.

The Panel considered that the presentation of positive secondary endpoint data (without reference to the primary endpoint) in a non-inferiority trial was not necessarily unacceptable so long as such references complied with the Code and were not otherwise misleading. In the Panel's view, page 2 of the leavepiece implied that Meriofert was more efficacious than Menopur, it referred to the inclusion of predominantly placental hCG and a higher mature oocyte yield thereby satisfying the aim of ovarian stimulation as described in the statement which introduced the page 'The aim of ovarian stimulation in IVF is to produce an optimum number of mature oocytes and embryos available for transfer'. The Panel was concerned that the impression of clinical superiority given by the page was inconsistent with Lockwood *et al* which concluded that Meriofert was non-inferior to Menopur in terms of its primary endpoint, the total number of oocytes retrieved. The Panel further noted that Lockwood *et al* found that no statistically significant differences between Meriofert and Menopur were reported for most of the clinically significant end-points including embryo quality, fertilization rate, implementation rate, ongoing pregnancy rate and live birth rate and noted the author's views that IVF efficacy corelated with the number of fertilized oocytes obtained.

The Panel further noted that according to the companies Lockwood *et al* was designed in such a way that Menopur treatment was stopped earlier than recommended in its SPC. According to both companies the Menopur SPC recommended that there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500pmol/L (920 picograms/ml); Human chorionic gonadotrophin should not be administered if these criteria have not been met, whereas Lockwood *et al* was designed in a way that daily gonadotrophin administration was continued until at least two follicles had a mean diameter greater than 16mm, serum oestradiol levels greater than 400pg/ml (or 1500pmol/l), or both.

The Panel queried whether the number of oocytes or MII (mature) oocytes retrieved for Menopur would have been different had the recommendation as referred to by both companies been followed. The Panel noted that although it was stated in small font in a footnote at the bottom of the page that the study was a non-inferiority study designed in such a way that it was not in line with the recommendation in the Menopur SPC, it noted the advice contained in the supplementary information to the Code that claims should be able to stand alone and in general should not be qualified by footnotes and the like.

The Panel noted its comments above and considered that given the unambiguous nature of the comparative claim in question 'Higher mature oocyte yield than Menopur' within

the context of the page and its overall implication of clinical superiority, the reader was not provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Meriofert vs Menopur. The Panel noted its comments above and considered that the claim in question within the overall implication of the page in question was misleading and not capable of substantiation; breaches of the Code were ruled.

2 Claim 'Contains predominantly placental hCG'

This claim appeared as a bullet point on page 2 of the detail aid as described above.

In Ferring's view, the secondary aim of page 2 was to imply that the type of hCG within Meriofert had a direct impact on the production of oocytes and embryos available for transfer. Ferring alleged that the claim that Meriofert 'Contains predominantly placental hCG' was misleading as it implied some special merit to placental hCG and also that Menopur was therefore somehow inferior to Meriofert.

Ferring stated that there was no indication of the amount of placental hCG present in Meriofert; and no indication of the amount of placental hCG that might be of clinical relevance in oocyte production. The layout of the page meant that the claim 'Contains predominantly placental hCG' implied that placental hCG had an impact on oocyte production. Ferring alleged that this could not be substantiated. The Panel noted that the claim 'Contains predominantly placental hCG' was referenced to the Meriofert SPC, IBSA data on file (hCG content) and Birken *et al*.

The Panel disagreed with Pharmasure's submission that it had not claimed or implied any clinical benefit regarding the difference in the type of hCG present in Meriofert or that the type of hCG had a direct impact on the production of oocytes and embryos available for transfer. Pharmasure stated that it had summarised the two key differences on page 2 but had not linked them. The Panel noted that the claim in question was the first bullet point below the more prominent and first claim on the page 'The aim of ovarian stimulation in IVF is to produce an optimum number of mature oocytes and embryos available for transfer' and above the second bullet point which read 'Higher mature oocyte yield than Menopur'. In the Panel's view, the claim in question would be read in light of what the Panel considered to be the headline claim and the claim below and thus would be considered to result in a clinical benefit in relation the production of mature oocytes and embryos available for transfer. In the Panel's view, readers would assume that there was a clinical benefit unless clearly told otherwise.

In the Panel's view, the reader was not provided with sufficient information to properly assess the claim 'Contains predominantly placental hCG' and form his/her own opinion of its therapeutic impact. The claim in question, as it appeared within the context of the page and its overall implication of clinical superiority was therefore misleading and could not be substantiated and breaches of the Code were ruled.

3 Page 3 featured a table which compared the oligosaccharide composition, relative amount (%), of Fostimon (urofollitropin), Puregon (follitropin beta) and Gonal-F (follitropin alfa). The table was adapted from Lombardi *et al* (2013).

Ferring alleged that the page purported to show that study results for Fostimon were somehow transferable to Meriofert. However, the active ingredient in Meriofert was menotrophin (a combination of FSH and LH in a 1:1 ratio), whereas the active ingredient in Fostimon was urofollitropin (FSH); to claim similarity between the two was misleading. There was no data or evidence provided to demonstrate any similarity between Meriofert and Fostimon in terms of composition, acidic FSH, sialylated and branched carbohydrate moieties.

The Panel noted that page 3 of the leavepiece was headed 'Meriofert Acidic FSH' and below it was stated that 'Meriofert, like Fostimon (urofollitropin) contains acidic FSH'. The page went on to describe a study that compared Fostimon with Puregon and Gonal-F and which demonstrated the prevalence in Fostimon of more acidic isoforms, which corresponded to species containing more sialylated and branched carbohydrate moieties. The Panel noted Pharmasure's submission that the table was included as a comparison against recombinant products such as follitropin alpha and follitropin beta and not Menopur.

The Panel noted Pharmasure's submission that the FSH in both Meriofert and Fostimon was extracted from the same source of postmenopausal urine using similar techniques, and in addition Meriofert had LH activity (by way of hCG) added. The Panel noted that it was not clear from the page at issue that Fostimon contained only FSH whereas Meriofert contained both FSH and LH activities.

It was not clear from the page what the differences in the table meant in terms of clinical relevance; the Panel noted Pharmasure's submission that no definitive clinical outcome was claimed but rather an important product characteristic had been presented.

The Panel noted Pharmasure's submission that the biological nature of these products including differences in extraction, raw material used and purification techniques might all have an impact on why one performed differently to another. This was why Pharmasure considered it was essential to provide a context that informed clinicians of the nature of these products and that each active was not a single molecule but a family of differently glycosylated or sulphated molecules, each variant having differences in biological activity and clearance rate. In this regard the Panel noted that Ferring had provided a comparative evaluation of the quality characteristics of FSH contained in Fostimon vs Meriofert. The evaluation concluded that the characteristics of FSH contained in Fostimon and Meriofert were similar. The authors stated that the result was expected since the purification process was very similar.

The Panel noted that whilst it was clear that the page discussed Meriofert and acidic FSH, it was not clear that Meriofert contained both FSH and LH activities whilst Fostimon contained only FSH as alleged, and the implication that the results of Lombardi *et al* in relation to the structure of the isoforms and corresponding moieties would equally apply without any qualification to both products meant that the reader was not provided with sufficient information to properly assess the information and form his/her own opinion of its therapeutic impact. A breach of the Code was ruled.

4 Claim 'LH activity in Meriofert is predominantly from placental hCG which is mainly comprised of glycosylated hCG' and the associated graphic.

The claim was at the top of page 4 and Ferring noted that the page focussed on the source and activity of LH and attempted to imply that the source of hCG to provide LH bioactivity in Meriofert and Menopur somehow conferred a clinical relevance and an advantage for Meriofert.

Ferring noted that the headline claim appeared immediately above a graphical representation of the source of LH activity for Meriofert and Menopur, below which a table compared sulphate content of pituitary and placental hCG subunits; then further bullet points about placental vs pituitary hCG. The graphic compared LH activity and source (pregnancy urine and menopausal urine for Meriofert and menopausal urine only for Menopur).

Ferring alleged that the combined effect of the headline statement and the graphic implied that Menopur was inferior to Meriofert which was not so.

Ferring alleged that the graphic itself was also misleading because it implied that Menopur was inferior to Meriofert which was not so.

There was no indication of the amount of placental hCG present in Meriofert; and no indication of the amount of placental hCG that might be clinically relevant. The graphic showed that the LH activity for Meriofert was from pregnancy urine, but the relevance of this was not clear; nor was the relationship between pregnancy urine and placental hCG. In the context of the text 'LH activity in Meriofert is predominantly from placental hCG', the reader was not given information to understand any relevance to the data.

The Panel noted that the graphical representation of the source of LH activity for Meriofert and Menopur appeared below the claim 'LH activity in Meriofert is predominantly from placental hCG which is mainly comprised of glycosylated hCG'. Below the graphic it stated 'Menopur is derived from menopausal urine which contains mainly pituitary hCG' followed by a table which compared the sulphate content of pituitary and placental hCG subunits which was referenced to Birken *et al*. Below this were three bullet points beneath the heading 'Placental hCG vs pituitary hCG': in vivo clearance is lower (longer half-life: placental hCG 36h, pituitary hCG 20h, LH 26 minutes); in vitro biological activity is higher and receptor binding affinity is higher. The first bullet point was referenced to Birken *et al* and Cole *et al*, whereas the second and third bullet points were only referenced to Birken *et al*.

The Panel noted that the graphic in question showed the pregnancy urine for Meriofert LH activity in red. All other components for FSH and LH activity including Meriofert menopausal urine for LH activity were coloured blue. In the Panel's view, the reader's eye was likely to link the red graphic for pregnancy urine with the three red bullet points at the bottom of the page the claims adjacent to which favourably compared placental hCG with pituitary hCG. This point had not been raised by Ferring. The Panel noted that the allegation in relation to the graphic appeared to be that it, as a stand alone matter, was in breach of the Code as the amount and clinically relevant amount of pregnancy urine was unclear, the relevance of this was not clear; nor was the relationship between pregnancy urine and placental hCG. In the context of the text 'LH activity in Meriofert is predominantly from placental hCG', the reader was not given information to understand any relevance to the data. The Panel did not consider that the reader would consider the graphic in isolation from the rest of the page nonetheless that was the allegation before

it. The Panel did not consider that the graphical representation of the source of LH activity for Meriofert and Menopur, when considered in isolation, misleadingly implied that Menopur was inferior to Meriofert as alleged. Whilst pregnancy urine was highlighted in red, the graphic in isolation made no claim based on this difference. In the Panel's view, Ferring had not established, on the balance of probabilities, that the graphic in isolation, including the amount of placental hCG present in Meriofert depicted, was misleading. No breach of the Code was ruled based on the very narrow allegation.

The Panel noted that Ferring also referred to the three bullet points at the bottom of the page described above and alleged that page 4 implied that the source of hCG to provide LH bioactivity in Meriofert and Menopur somehow conferred a clinical relevance and an advantage for Meriofert. The Panel noted that the three bullets were in the same red colour as the pregnancy urine depicted in the graphical representation of the source of LH activity for Meriofert and Menopur and thereby implied that the lower *in vivo* clearance (longer half-life: placental hCG 36h, pituitary hCG 20h, LH 26min) the higher *in vitro* biological activity, and the higher receptor binding affinity of placental hCG vs pituitary hCG referred to in the bullet points was due to the source of hCG and the tertiary structure of placental vs pituitary hCG . The Panel noted Ferring's submission that the tertiary structure of hCG isoforms (how glycosylated they were) had a direct bearing on the half-life of the molecule and activity at the receptor. Each active was not a single molecule but a family of differently glycosylated or sulphated molecules, each variant having differences in biological activity and clearance rate.

The Panel noted that whilst the table and bullet points were referenced to a second Birken *et al* study, 'Metabolism of hCG and hLH to multiple urinary forms', there was no direct reference to their content within that study. The Panel noted that the original Birken *et al* study, 'Isolation and Characterization of Human Pituitary Chorionic Gonadotrophin' stated that the presence of sulphate on pituitary hCG might play a role in its reduced *in vitro* biological activity but that this was not clear with regard to earlier studies of Baenziger. The sulphate content of pituitary hCG would be expected to lead to a rapid clearance *in vivo* by a liver receptor specific for the sulphate-4-GalNAc-GlcNAc-M structure.

The Panel further noted that the first Birken *et al* study isolated and characterised human pituitary hCG by analysing hCG content from pituitary glands and compared it with hCG purified from the urine of pregnant woman. The study undertook a series of analyses for sulphate and included the original table in question. The second Birken *et al* study stated that since many of the molecular forms of the two hormones (hCG and hLH) in urine differed from their forms in blood, it might be necessary to produce new immunoassays as well as novel urinary reference preparations to accurately measure these molecules within their urinary matrix.

The Panel noted that according to the first Birken study there were some differences between placental hCG vs pituitary hCG. The Panel noted its comments above and considered that the overall implication of page 4 was that Menopur was inferior to Meriofert based on its LH activity being predominantly from placental hCG which was mainly comprised of glycosylated hCG and its low sulphate content. The Panel noted that it appeared that the bullet points on page 4 had been referenced to the incorrect Birken *et al* study and, in the Panel's view, the reader should have been provided with details of the original Birken *et al* study. The Panel noted its comments at point 1 above

about Lockwood *et al* and non-inferiority. Further information should have been provided to enable the reader to properly assess the information on page 4 including in relation to the claim 'Menopur is derived from menopausal urine which contains mainly pituitary hCG' and form his/her own opinion of the relative clinical value of Meriofert compared with Menopur. The Panel noted its comments above and ruled a breach of the Code.

5 Table: Comparative sulphate content of pituitary and placental hCG subunits

This table appeared on page 4 and was referenced to Birken *et al* (1996).

Ferring alleged that the table of data was misleading. Birken *et al* analysed hCG content from pituitary glands and not from urine. As Meriofert contained hCG derived from the urine of postmenopausal and pregnant women, the data for sulphate content from Birken *et al* could not be extrapolated to Meriofert. Even Birken *et al* explained that many of the molecular forms of hCG in urine differed from their forms in blood. As far as Ferring knew, there was no evidence to show that data from pituitary extract could be extrapolated to products containing urinary human menopausal gonadotropins (hMG).

Ferring also noted that the table was incorrectly referenced to Birken *et al*, 'Metabolism of hCG and hLH to multiple urinary forms', however, this was only a secondary reference and the original data and table was from another Birken *et al* paper, 'Isolation and Characterization of Human Pituitary Chorionic Gonadotrophin', also published in 1996. Ferring also noted that the descriptions beneath the heading 'protein' had been altered and were not the same as in the original article.

The Panel did not consider that it was necessarily unacceptable to use data from the second Birken *et al* publication and reference it to that publication rather than the original provided the way in which it was used complied with the Code.

The first Birken study, 'Isolation and Characterization of Human Pituitary Chorionic Gonadotrophin', isolated and characterised human pituitary hCG by analysing hCG content from pituitary glands and compared it with hCG purified from the urine of pregnant woman.

The second Birken study was entitled 'Metabolism of hCG and hLH to multiple urinary forms'. The table as reproduced in the detail aid was present in both studies. The second Birken study stated that the table in question was reproduced from the first Birken study.

The Panel noted that the table in both Birken studies referred to pituitary $hCG_{\tilde{\alpha}}$ and hCG_{β} and urinary $hCG_{\tilde{\alpha}}$ and hCG_{β}, whereas the detail aid referred to pituitary $hCG_{\tilde{\alpha}}$ and hCG_{β} and placental $hCG_{\tilde{\alpha}}$ and hCG_{β}. The Panel noted Pharmasure's submission that purified hCG from pregnant women's urine was also called placental hCG. The first Birken *et al* trial stated that the hCG excreted by pregnant woman into urine was designated urinary hCG in the report, and thus it appeared to the Panel that the urinary $hCG_{\tilde{\alpha}}$ and hCG_{β} referred to in the table was from the urine of pregnant women.

In the Panel's view, whilst the table appeared in both Birken studies, the reader would need to look at the original study, 'Isolation and Characterization of Human Pituitary

Chorionic Gonadotrophin', in order to fully understand the implication of the table at issue. The Panel considered that it was therefore misleading not to reference the first Birken study in this regard and a breach of the Code was ruled.

The Panel did not accept Pharmasure's submission that it had 'not extrapolated the Birken *et al* data to apply to Meriofert'. The table appeared prominently on a page headed 'Meriofert LH Activity from Placental hCG' which then referred to Meriofert and placental hCG, illustrating the proportion of LH activity derived from pregnancy urine. The table then presented data for placental hCG. It was difficult to understand how the table including placental hCG could be viewed in isolation from the claims for Meriofert on the page. In the Panel's view, a reader would relate the data to Meriofert.

The Panel noted Ferring's submission that Birken *et al* analysed hCG content from pituitary glands and not from urine and as Meriofert contained hCG derived from the urine of postmenopausal and pregnant women, the data for sulphate content from Birken *et al* could not be extrapolated to Meriofert as had been done in the detail aid. Pharmasure stated that it had used Birken *et al* to illustrate the difference between placental and pituitary hCG, which was one way in which Meriofert and Menopur were different and that it was clear from Birken *et al* that a pituitary form of hCG, which was sulphated, was in postmenopausal women's urine.

The Panel further noted that the second Birken *et al* study stated that since many of the molecular forms of the two hormones (hCG and hLH) in urine differed from their forms in blood, it might be necessary to produce new immunoassays as well as novel urinary reference preparations to accurately measure these molecules within their urinary matrix.

The Panel noted that it was not clear that the data within the table on page 4 of the leavepiece was from the second Birken *et al* study rather than the original and referred to hCG content isolated from pituitary glands rather than from urine. In the Panel's view, the reader did not have sufficient information to form his/her own opinion of the relevance of the data which was misleading and a breach of the Code was ruled.

6 Claim 'On average for each patient TWO more mature oocytes were retrieved and ONE more cleaved embryo on day 2 was observed during a shorter period of stimulation in the Meriofert group'

This was the main claim on page 5 which was headed 'Meriofert High Ovarian Yield'.

Ferring alleged that the claim, which was referenced to Lockwood *et al*, was misleading. Differences in oocyte maturity, embryo cleavage or duration of stimulation were not primary endpoints of the study. To imply a clinically meaningful difference was therefore misleading, especially in the context of the capitalised 'TWO' and 'ONE'. The statistical analysis was not planned to proceed hierarchically or adjusted for multiplicity, therefore it was misleading to refer to secondary endpoints and attempt to imply clinical differences.

Ferring alleged that to imply clinical differences between Meriofert and a dose of Menopur which was less than that licensed in the UK was misleading. Lockwood *et al* prematurely discontinued the administration of Menopur compared with the licensed

Menopur dose – thus patients were triggered earlier than recommended in the Menopur SPC which stated 'It is recommended there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500pmol/L (920picograms/ml; Human chorionic gonadotrophin should not be administered if these criteria have not been met'.

Ferring noted that the Menopur SPC was mentioned in the small print at the foot of the page, however, case precedent had clearly established that misleading claims could not be corrected by a footnote.

The Panel considered that its comments at Point 1 above were relevant. Page 5 of the leavepiece implied that Meriofert was more efficacious than Menopur based on the higher mature oocytes retrieved and the number of cleaved embryos on day 2 as well as the total oocytes retrieved and inseminated injected oocytes and the duration of stimulation. The page did not state that Lockwood *et al* concluded that Meriofert was non-inferior to Menopur in terms of clinical efficacy or the author's views that IVF efficacy corelated with the number of fertilized oocytes obtained and no statistically significant differences between Meriofert and Menopur were reported for most of the clinically significant endpoints including embryo quality, fertilization rate, implementation rate, ongoing pregnancy rate and live birth rate.

The Panel further noted that according to both companies Lockwood *et al* was designed in such a way that Menopur was stopped earlier than recommended in its SPC. The Panel queried whether the number of oocytes or MII (mature) oocytes retrieved for Menopur would have been different had the recommendation as referred to by both companies had been followed.

The Panel noted that the trial design of Lockwood *et al* appeared at the top of the page and it was stated in small font in a footnote at the bottom of the page the recommendation in the Menopur SPC as referred to by both companies. The Panel noted, however, that unlike the footnote on page 2, the footnote on page 5 did not specifically state that the study had been designed in such a way that the Menopur SPC recommendation as referred to by both companies was not followed.

The Panel considered that the reader was not provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Meriofert vs Menopur. The Panel noted its comments above and considered that the claim in question was misleading and a breach of the Code was ruled.

7 Claim 'Efficiency of (Meriofert) appears to be higher due to reduced quantity of drug used and the higher yield of mature oocytes retrieved'

This claim, referenced to Alviggi *et al*, appeared on page 6, beneath a figure which compared results of the primary endpoint (mean number of total collected oocytes) and secondary endpoints (ratio of MII/total oocytes retrieved, controlled ovarian stimulation (COS) duration, total HMG units) using Menopur and Meriofert. The page was titled Meriofert High Efficiency followed by a description of the study design and a claim in the largest blue font on the page that '7% more mature oocytes were obtained with 14% less gonadotrophin being administered during a shorter period of stimulation in the Meriofert group'.

Ferring alleged that the claim was misleading. Alviggi *et al* was a non-inferiority study for the primary endpoint of total number of oocytes retrieved, with no statistical adjustment for hierarchical analysis or multiplicity on the depicted secondary endpoints (ratio metaphase II (MII) oocytes retrieved, controlled ovarian stimulation (COS) duration, total HMG units). Ferring reiterated that it was thus misleading to imply statistically significant differences between the comparators.

Ferring added that Alviggi *et al* stopped Menopur earlier than recommended in the SPC. This had clinical relevance because if the product was not used as per the SPC, the outcomes shown might not be those obtained in clinical practice and therefore they formed the basis of misleading claims.

The Panel noted that Alviggi *et al* was a prospective, randomised, investigator-blind, controlled non-inferiority clinical trial to evaluate the clinical efficacy and tolerability of a highly purified human menopausal gonadotrophin preparation (Merional-HG) and Menopur when administered to patients undergoing controlled ovarian stimulation (COS) for IVF procedure. The study authors stated that Merional-HG and Menopur were proven to be equally effective to achieve proper outcome of assisted reproductive technology (ART). In this regard, the Panel noted its understanding of a non-inferiority trial as referred to at Point 1 above.

The Panel noted that according to the authors Merional-HG appeared to be more efficient than Menopur in this setting as it allowed reducing drug consumption and might provide additional practical advantages in the management of ART procedures; not the higher yield of mature oocytes as implied by the page at issue.

The Panel further noted that Alviggi *et al* was designed in such a way that Menopur was stopped earlier than recommended in its SPC. The Panel queried whether the number of oocytes or MII (mature) oocytes retrieved for Menopur would have been different had the recommendation as referred to by both companies had been followed.

The Panel noted that although it was stated in small font in a footnote at the bottom of the page the recommendation in the Menopur SPC and the trial design of Alviggi *et al* appeared at the top of the page, unlike the footnote on page 2, it was unclear that the study design was such that the Menopur SPC recommendation as referred to by both companies was not followed. The Panel considered that the reader was not provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Meriofert vs Menopur. The Panel noted its comments above and considered that the claim in question was misleading and a breach of the Code was ruled.

8 Safety claim table on Page 7

Ferring noted that page 7 compared the safety of Meriofert and Menopur. The second table on page 7 depicted several adverse events including injection site pain, persistent redness, tenderness and itching. Ferring alleged that the table was misleading. Neither table had explanatory text to accompany the numbers.

Ferring submitted that the table showed the total number and percentage of specified adverse events. The information could easily be read as though Menopur had higher numbers than Meriofert and therefore had a worse adverse event profile, which was not so. The lack of p values on the table could be read as implying no statistically significant difference between the two products in terms of side-effects, however, this was also not the case as the table was selective in its presentation.

Ferring noted that the cited publication (Lockwood *et al*) was a non-inferiority study for total number of oocytes retrieved; it was not powered to show differences in adverse events. It was stated in the paper that 'No difference was reported in the frequency of the adverse events with the exception of vascular disorders (hot flushes) that were reported more often in the Meriofert group (8.2% vs 1.5%, p=0.02)'. The paper therefore clearly showed no clinically relevant differences between the products except for hot flushes. Ferring was particularly concerned that the important and clinically relevant adverse event of hot flushes, which was reported more frequently in the Meriofert group was omitted from the table, although a statement about hot flushes appeared beneath it. However, it did not state the numerical differences, as was done for the other stated adverse events in the table. The statement also appeared at the end of a paragraph that began 'Meriofert has good tolerability'. Given that hot flushes were the only adverse event that was significantly different, this appeared to be a deliberate attempt to hide this information from the reader.

The Panel noted that below the table at issue it was stated that Meriofert had good tolerability and that cases of injection site pain were mainly mild and did not last after the time of injection followed by hot flushes were reported more frequently in the Meriofert group. The Panel noted that it was misleading to provide data showing the difference between Meriofert and Menopur with regards to injection site pain and persistent redness, tenderness and itching which implied that there was a difference without including the p number or stating that tolerability at the injection site was found to be very good in both groups as stated in Lockwood *et al*. The table did not give a clear, fair, balanced view of the data and breaches of the Code were ruled.

The Panel considered that it was misleading to state that hot flushes were reported more frequently in the Meriofert group without stating that there was a significant difference in the reporting of hot flushes (8.2% vs 1.5%, p = 0.02).

In the Panel's view, the safety data was not adequately reflected in the leavepiece and a breach of the Code was ruled.

Ferring Pharmaceuticals Ltd complained about claims in a Meriofert (menotrophin) detail aid (ref UK/201809/00001/01) issued by Pharmasure Limited and noted that similar claims displayed on the Pharmasure UK website (UK/201810/00005/01). Meriofert was used to induce ovulation in women undergoing assisted reproduction techniques such as *in vitro* fertilization (IVF). Ferring marketed Menopur (menotrophin for injection) which was similarly used to induce ovulation in women undergoing fertility treatment.

Background – Ferring

Ferring explained that its concerns related to the use of fertility medicines called 'urinary gonadotrophins' which were essential in IVF treatment. Gonadotrophins were a class of

hormones which included follicle stimulating hormone (FSH), luteinising hormone (LH) and human chorionic gonadotrophin (hCG). Gonadotrophins were manufactured using a urinary source (from postmenopausal or pregnant female urine) or recombinant technology and used for controlled ovarian stimulation, a technique used in IVF to stimulate the ovaries to produce multiple ovarian follicles. The goal was to harvest an optimal number of eggs from the woman's ovaries to maximize the chances that the eggs could be fertilized *in vitro*, and that an embryo could be implanted back into the uterus and develop into a healthy baby.

In a typical healthy pregnancy, hCG was secreted from the placenta of the implanting conceptus from week 2, supporting the ovarian corpus luteum, which in turn supported the endometrial lining and therefore maintained pregnancy. In postmenopausal women, hCG was secreted from the pituitary gland. Whether secreted from the placenta or the pituitary gland, hCG was excreted in the urine.

Meriofert and Menopur were both urinary gonadotrophins (human menopausal gonadotrophin, hMG) containing menotrophin, which was extracted from the urine of postmenopausal women (for Menopur) and also from pregnant women (for Meriofert). Menotrophin consisted of FSH, LH and hCG components, providing FSH and LH hormone activity in a 1:1 ratio. The LH activity was provided by the hCG hormone component.

Meriofert and Menopur were licensed for treatment of various aspects of female infertility. Menopur received a marketing authorization in 1999 and the marketing authorization for Meriofert was obtained in 2014 using its similarity to published Menopur data. The Public Assessment Report (scientific discussion) clearly stated ‘Overall, the Applicant has provided data to support that hMG-IBSA (Meriofert) is no different from the active comparator Menopur in any way that could lead to differences in efficacy between the two products’.

Pharmasure had tried to differentiate its product Meriofert, on the grounds that it contained a high concentration of placental hCG, implying that this led to better efficacy and efficiency. Ferring objected to Pharmasure’s claims that Meriofert was superior to Menopur substantiated by Lockwood *et al* (2017) and Alviggi *et al* (2013) (copies provided).

Ferring noted that in studies when there was one primary endpoint, findings of secondary outcomes were considered subsidiary and exploratory, rather than confirmatory, so no claims could be made on these secondary endpoints, unless the statistical analysis was predefined to proceed hierarchically or adjustments for multiplicity made. No such statistical plan was stated in either Lockwood *et al* or in Alviggi *et al* although the detail aid at issue contained a number of claims based on secondary endpoints.

Lockwood *et al* was a non-inferiority study. The primary endpoint was to show the non-inferiority of Meriofert to Menopur in respect of the primary endpoint – total number of oocytes retrieved. For the secondary endpoints, $p<0.05$ was considered statistically significant; F-test (analysis of variance) was performed for continuous variables, and Fisher’s exact test for categorical variables.

Ferring noted that the supplementary information to Clause 7.2, Statistical information, clearly stated that care must be taken to ensure that there was a sound statistical basis for all information, claims and comparisons. Differences which did not reach statistical significance must not be presented in such a way as to mislead.Further, Ferring noted that Lockwood *et al* used an unlicensed dose of Menopur. The Menopur summary of product characteristics (SPC)

clearly stated: ‘It is recommended there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500 pmol/L (920 picograms/ml); Human chorionic gonadotrophin should not be administered if these criteria have not been met’.

Lockwood *et al* stopped Menopur earlier than recommended in the SPC – daily gonadotrophin administration was continued only until at least two follicles had a mean diameter greater than 16mm, serum oestradiol levels greater than 400pg/ml (or 1500pmol/l), or both. This was clinically relevant because if the product was not used as per the SPC, the outcomes shown might not be those obtained in clinical practice and they therefore formed the basis of misleading claims.

Alviggi *et al* was also a non-inferiority study, where the primary endpoint was the total number of oocytes retrieved. Again, for the secondary endpoints (ratio MII/oocytes retrieved, COS duration, total HMG units), the statistical analysis was not predefined to proceed hierarchically or adjusted for multiplicity. It was thus misleading to imply statistically significant differences for secondary endpoints between the comparators based on this study.Ferring stated that it was also relevant that the Alviggi *et al* study compared Merional HG to Menopur. The similarity between Meriofert and Merional HG had been discussed in inter-company dialogue and although Pharmasure contended that Meriofert and Merional HG were the same product, Ferring had established with the Medicines and Healthcare products Regulatory Agency (MHRA), that the two were different based on the source of hCG and purification processes. Moreover, Merional HG was available before the Meriofert licence was granted, as Alviggi *et al* was published in May 2013, and the approval procedure for Meriofert was finalised on 18 December 2014.

Ferring submitted that there were several limitations of the Alviggi *et al* study, which restricted the citation of the study for substantiation of promotional claims:

1 It was a small, non-inferiority study and randomised 157 women to receive either Menopur (n=79) or Merional HG (n=78); the study was not adequately powered to make comparisons of secondary endpoints (daily and the total dose of hMG (IU and vials), the stimulation duration, the number of mature oocytes etc.), so any claims of significant differences in secondary endpoints between Merional HG vs Menopur were unsubstantiated.

2 It was claimed that the study demonstrated reduced total medicine used and shorter duration of treatment with Merional HG compared with Menopur; however, it was difficult to compare gonadotrophin dosing due to high inter-patient heterogeneity – the dosage and schedule of treatment must be determined according to each patient’s needs.

The study used an unlicensed dose of Menopur as the Menopur SPC clearly stated: ‘It is recommended there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500pmol/L (920 picograms/ml; Human chorionic gonadotrophin should not be administered if these criteria have not been met’.

Alviggi *et al* stopped Menopur earlier than recommended in the SPC - the authors stated ‘Daily gonadotrophin administration was continued only until at least two follicles had a mean diameter greater than 16 mm’. This had clinical relevance

because if the product was not used as per the SPC, the outcomes shown might not be those obtained in clinical practice and they therefore formed the basis of misleading claims.

3 Alviggi *et al* was conducted in Italy in compliance with the Italian legislation, where no more than 3 oocytes per patient could be inseminated and all the available embryos transferred. Only 5 patients (7.5%) in the Merional HG group and 7 (11.1%) in the Menopur group received a single embryo transfer; all the other patients had 2 or 3 embryos transferred. This was not in line with UK guidelines from the National Institute for Health and Care Excellence (NICE) or the Human Fertilization and Embryology Authority (HFEA), which recommend a single embryo transfer, so it was not clear how results from this study could be generalised to UK clinical practice.

Ferring stated that the detail aid clearly attempted to differentiate Meriofert from Menopur.

Background – Pharmasure

Pharmasure noted that Ferring referred to correspondence between Ferring and the MHRA regarding the names of various products that was not presented to Pharmasure and Ferring appeared to be confusing Merional and Merional HG. Pharmasure noted that Alviggi *et al* referred to Merional HG which was the name given to Meriofert in Switzerland. The product was named differently in some countries, as was often the case with products available internationally. Merional HG was different to Merional. The correspondence with the MHRA had no bearing on the fact that Merional HG was the name given to Meriofert in Switzerland. The name Merional HG had never been used in the UK. The claims used for Meriofert were supported by Alviggi *et al* which used the product 'Merional HG' which was Meriofert.

Pharmasure noted that the products being discussed were biological extracts from human urine which did not contain just molecules of FSH, LH or hCG but a wide range of isoforms of each peptide. The tertiary structure of these FSH and hCG isoforms (how glycosylated they were) had a direct bearing on the half-life of the molecule and activity at the receptor.

For clarification, Menopur contained follicle stimulating hormone (FSH) activity and luteinising hormone (LH) activity. The bulk of LH activity was provided by human chorionic gonadotrophin (hCG), yet the hCG was not obtained from the urine of pregnant women but from that of postmenopausal women who excreted hCG of pituitary origin. In the case of Meriofert, the FSH was obtained from the urine of postmenopausal women but the majority of the hCG was extracted from the urine of pregnant women. That was why the hCG element within the products differed significantly.

Pharmasure stated that it was trying to differentiate Meriofert from Menopur. The biological nature of these products including differences in extraction, raw material used and purification techniques might all have an impact on why one performed differently to the another. This was why Pharmasure considered it was essential to provide a context that informed clinicians of the nature of these products and that each active was not a single molecule but a family of differently glycosylated or sulphated molecules, each variant having differences in biological activity and clearance rate. Thus, a significant difference in the population of these molecules (isoforms) might affect the performance of the product. Pharmasure noted that its claims only

related to product differences (whether clinical or otherwise) where those claims were statistically supported by robust evidence.

Ferring's complaint appeared to rest largely on its assertion that it was inappropriate and misleading to use Lockwood *et al* and Alviggi *et al* to present secondary endpoint data. Ferring also noted that both studies used a different cut-off for triggering final maturation of the oocytes compared with the Menopur SPC recommendations.

Pharmasure noted that it had stated the primary endpoints of the studies concerned (of which one was significantly in favour of Meriofert) and the secondary endpoints where statistically significant differences were reported. Furthermore, Pharmasure had also noted that the studies used cut-off criteria that were different to the recommendations in the Ferring SPC that were agreed with the Danish authority and accepted by the UK authority. These criteria were also based on the standard practice in each site.
In response to a request for further information Pharmasure clarified that it was its understanding that the leavepiece in question was the 'Oyster' detail aid/leave piece (ref UK/201809/00001/01). For the briefing of the sales team, Pharmasure used copies of the approved artwork in a PowerPoint presentation (copy provided); however the final certification reference numbers for the piece and 'data on file references' were not included until the following Monday, after which the piece was released to the sales team.

1 Claim 'Higher mature oocyte yield than Menopur'

The first claim on page 2 of the detail aid read, 'The aim of ovarian stimulation in IVF is to produce an optimum number of mature oocytes and embryos available for transfer', followed by the brand name (Meriofert) above two bullet points:

- Contains predominantly placental hCG
- Higher mature oocyte yield than Menopur.

the first claim and the latter bullet point were referenced to Lockwood *et al*.

COMPLAINT

Ferring alleged that the clear aim was to imply that Meriofert could produce a higher oocyte yield than Menopur, and therefore that Menopur was less effective than Meriofert. Ferring alleged that the claim was misleading and could not be substantiated, in breach of Clauses 7.2, and 7.4.

The claim in question was referenced to Lockwood *et al*. However, maturity of the oocytes was not a primary endpoint in that study. The primary endpoint was to show the non-inferiority of Meriofert to Menopur in respect of the total number of oocytes retrieved and the study was powered to demonstrate non-inferiority. Further, there was no indication of the amount of placental hCG present in Meriofert; and no indication of the amount of placental hCG that might be of clinical relevance in oocyte production.

There was no clear evidence that placental hCG had an impact on oocyte production. Lockwood *et al* was a non-inferiority study – it was misleading to use it to claim or imply differences between the studied products.

Lockwood *et al* under-dosed Menopur compared with the UK licence, thus it was misleading to use it to imply differences in oocyte yield.

While Ferring noted that the study design was included in small print beneath the bullet points, case precedent was clear that misleading claims could not be corrected by footnotes.

As stated above, maturity of the oocytes was not a primary endpoint in this study. The primary (non-inferiority) endpoint was total number of oocytes. Therefore, it was misleading to claim about oocyte maturity out of context as the reader did not have sufficient information to make an informed decision.

Ferring added that the literature demonstrated that during stimulated IVF cycles, up to 15-30% of oocytes retrieved were immature (Lee *et al* 2011 and Lee *et al* 2012) and only 63% were mature (Shapiro *et al* 2011) and so the total number of oocytes retrieved was not the same as the number of mature oocytes.

RESPONSE

Pharmasure noted that it had listed the key facts for Meriofert, which included the origin of the LH activity and the outcome of clinical studies compared with Menopur. It was reasonable to make doctors aware of the key differences with respect to both product characteristics and clinical outcomes. Pharmasure stated that it had not asserted or claimed that there was a link between the key messages on page 2 and definitive clinical outcomes, it had simply presented the two key scientific facts.

A Contains predominantly placental hCG

To manufacture Meriofert, purified hCG from pregnant women's urine (also called placental hCG) was added, as stated in the Meriofert SPC, which provided more than 50% of the total LH activity. IBSA data on file demonstrated that the LH activity depended mainly on hCG hormone (13-15 IU/vial) and the LH hormone quantity was about 0.3-0.5 IU/vial. It had been established that the hCG excreted from pregnant women's urine was of placental origin (Birken *et al* 1996, copy provided).

B Higher mature oocyte yield than Menopur

This claim was made because both the primary endpoint (total oocyte number retrieved) and secondary endpoint (mature oocyte yield) were significantly higher in the Meriofert group; this claim was supported by Lockwood *et al*.

Pharmasure considered that it was appropriate to use Lockwood *et al* to differentiate Meriofert from Menopur. Pharmasure stood by its claim that Meriofert could produce a higher mature oocyte yield than Menopur and it justified its claims below and denied breaches of Clauses 7.2 and 7.4.

Lockwood *et al* was a regulatory study, used for the submission of the dossier in the EU; of the 6 study sites, 2 were in Denmark and 1 each in Hungary, the UK, Switzerland and France. It was a robust study and the results were well known and established throughout the fertility clinical community. No other major studies provided contradictory comparative results and so it was reasonable to base claims on this data.

Although it was designed as a non-inferiority study, both the primary endpoint and secondary endpoints showed significant differences between Meriofert and Menopur. The primary endpoint of the study was the total number of oocytes retrieved. Meriofert achieved a significantly higher number of retrieved oocytes than Menopur (p=0.012). There were also secondary endpoints showing significant differences between Meriofert and Menopur. Meriofert achieved more mature oocytes (p=0.002), more inseminated-injected oocytes (p<0.001) and cleaved embryos (p=0.04) on day 2 than Menopur. Meriofert also achieved a shorter duration of stimulation than Menopur (p=0.02). Pharmasure noted that it had presented both primary and secondary endpoints in its materials and only made claims where p values showed significant differences.

The Menopur dosage within the study was agreed with the Danish authority and accepted by the UK authority, which was also based on the standard practice in each site. Pharmasure noted that it had clearly stated in its materials that the study was designed slightly differently to the recommendations in the Menopur SPC ie 'This finding is from a prospective, controlled, randomised, multicentre, non-inferiority study which was designed in a way that daily gonadotrophin administration was continued until at least two follicles had a mean diameter greater than 16mm, serum oestradiol levels greater than 400pg/ml (or 1500pmol/l), or both. While in Menopur's SPC, it is recommended there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 350 pmol/L (920 picograms/ml)'. This statement appeared wherever claims were referenced to Lockwood *et al*. Importantly, although the Menopur SPC recommended this approach, it did not mandate it, so Lockwood *et al* used Menopur 'on-licence' in line with the SPC.

PANEL RULING

The Panel noted that the claim 'The aim of ovarian stimulation in IVF is to produce an optimum number of mature oocytes and embryos available for transfer' and the second bullet point below this (the claim in question) which referred to Meriofert having a 'higher mature oocyte yield than Menopur' were both referenced to Lockwood *et al.*

The Panel noted that in general terms non-inferiority trials demonstrated that a test product was no worse than a comparator by more than a pre-specified, small amount known as the non-inferiority margin.

The Panel noted that Lockwood *et al* was powered as a non-inferiority study, to confirm the non-inferiority of Meriofert compared with Menopur with regard to clinical outcome (the primary end point being the total number of oocytes retrieved). If the lower bound of the 95% confidence interval of the differences between the means (Meriofert minus Menopur) was greater than -2.1 then Meriofert was considered to be non-inferior to Menopur.

The Panel noted that in the intention to treat (ITT) population, the mean (±SD) number of oocytes retrieved was significantly higher (p=0.012) in women stimulated with Meriofert (11.6 ± 6.6) than in those stimulated with Menopur (9.7 ± 5.9). The difference in mean number of oocytes retrieved was +1.9, with a 95% CI of the difference equal +0.43 to 3.43, ie a 95% CI lower limit greater than the pre-defined clinically significant difference of -2.1.

The Panel noted that the first bullet point 'Contains predominantly placental hCG' was referenced to the Meriofert SPC, IBSA data on file (hCG content) and Birken *et al*.

The Panel noted Ferring's statement that there was no indication of the amount of placental hCG present in Meriofert and no indication of the amount of placental hCG that might be of clinical relevance in oocyte production. The Panel noted that Lockwood *et al* stated that the use of a new HMG preparation (Meriofert) containing highly purified FSH and highly purified hCG of chorionic origin, led to retrieval of more oocytes, MII oocytes and cleaved embryos in IVF than an established HMG reference comparator (Menopur).

The Panel noted Ferring's submission regarding the status of the secondary endpoints in Lockwood *et al.* Ferring submitted that the statistical analysis was not predefined to proceed hierarchically or adjusted for multiplicity and therefore findings of the secondary outcomes were considered subsidiary and exploratory rather than confirmatory. Pharmasure had not responded specifically on this point but stated that it had presented both primary and secondary endpoints in its materials and had only made claims where p values showed significant differences. It was unclear to the Panel whether the secondary endpoints had been clearly pre-specified within Lockwood *et al* in the study design section, however, it appeared from the results and discussion section that the study authors considered the secondary endpoints were powered to show significance; the authors did not mention any limitations to the contrary.

The Panel considered that the presentation of positive secondary endpoint data (without reference to the primary endpoint) in a non-inferiority trial was not necessarily unacceptable so long as such references complied with the Code and were not otherwise misleading. In the Panel's view, page 2 of the leavepiece implied that Meriofert was more efficacious than Menopur, it referred to the inclusion of predominantly placental hCG and a higher mature oocyte yield thereby satisfying the aim of ovarian stimulation as described in the statement which introduced the page 'The aim of ovarian stimulation in IVF is to produce an optimum number of mature oocytes and embryos available for transfer'. The Panel was concerned that the impression of clinical superiority given by the page was inconsistent with Lockwood *et al* which concluded that Meriofert was non-inferior to Menopur in terms of its primary endpoint, the total number of oocytes retrieved. The Panel further noted that Lockwood *et al* found that no statistically significant differences between Meriofert and Menopurr were reported for most of the clinically significant end-points including embryo quality, fertilization rate, implementation rate, ongoing pregnancy rate and live birth rate and noted the author's views that IVF efficacy corelated with the number of fertilized oocytes obtained.

The Panel further noted that according to the companies, Lockwood *et al* was designed in such a way that Menopur treatment was stopped earlier than recommended in its SPC. According to both companies the Menopur SPC recommended that there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500pmol/L (920 picograms/ml); Human chorionic gonadotrophin should not be administered if these criteria had not been met, whereas Lockwood *et al* was designed in a way that daily gonadotrophin administration was continued until at least two follicles had a mean diameter greater than 16mm, serum oestradiol levels greater than 400pg/ml (or 1500pmol/l), or both.

The Panel noted that neither company had provided a copy of the Menopur SPC and the Panel was unable to find reference to the specific recommendation referred to by both companies in the Menopur SPCs available on the electronic medicines compendium (eMC) when the case was considered. The Panel noted that the different strength Menopur SPCs available on eMC stated that 'when a suitable number of follicles have reached an appropriate size a single

injection of 5,000 IU up to 10,000 IU hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval'.

The Panel queried whether the number of oocytes or MII (mature) oocytes retrieved for Menopur would have been different had the recommendation as referred to by both companies been followed. The Panel noted that although it was stated in small font in a footnote at the bottom of the page that the study was a non-inferiority study designed in such a way that it was not in line with the recommendation in the Menopur SPC, it noted the advice contained in the supplementary information to Clause 7.2 that claims should be able to stand alone and in general should not be qualified by footnotes and the like.

The Panel noted its comments above and considered that given the unambiguous nature of the comparative claim in question 'Higher mature oocyte yield than Menopur' within the context of the page and its overall implication of clinical superiority, the reader was not provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Meriofert vs Menopur. The Panel noted its comments above and considered that the claim, within the overall implication of the page on which it appeared, was misleading and not capable of substantiation, a breach of Clauses 7.2 and 7.4 was ruled.

2 Claim 'Contains predominantly placental hCG'

This claim appeared as a bullet point on page 2 of the detail aid as described above.

COMPLAINT

In Ferring's view, the secondary aim of page 2 was to imply that the type of hCG within Meriofert had a direct impact on the production of oocytes and embryos available for transfer. Ferring alleged that the claim that Meriofert 'Contains predominantly placental hCG' was misleading in breach of Clause 7.2 as it implied some special merit to placental hCG and also that Menopur was therefore somehow inferior to Meriofert.

There was no indication of the amount of placental hCG present in Meriofert; and no indication of the amount of placental hCG that might be of clinical relevance in oocyte production.

The layout of the page meant that the claim 'Contains predominantly placental hCG' implied that placental hCG had an impact on oocyte production. Ferring alleged that this could not be substantiated, in breach of Clause 7.4.

Ferring further noted that beneath the graphic on page 5 was the claim 'Menopur is derived from menopausal urine, which contains mainly pituitary hCG'. There was again no indication of the clinical relevance of menopausal urine or pituitary hCG, thus Ferring alleged that in context, the claim was misleading and implied that Menopur was inferior to Meriofert.

RESPONSE

Pharmasure stated that it had not intended to claim or imply any clinical benefit regarding the difference in the type of hCG present in Meriofert or that the type of hCG had a direct impact on the production of oocytes and embryos available for transfer. Pharmasure stated that it had summarised the two key differences on page 2 but had not linked them. The company had considered using numbering to separate the two summary claims but decided that this might

imply a sequential and causative link between the two, so it used bullet points instead. The product characteristics were described on pages 3 and 4 and were not linked with the claim of higher ovarian yield, which was separate on page 5.

Pharmasure noted that Ferring had repeatedly claimed that it had deliberately implied that these claims were linked. This was not the intention and Pharmasure was happy to alter the materials to more clearly separate the important product characteristic from the clinical claims.

It was a feature of Meriofert that its LH-like activity was predominantly from placental hCG and no clinical benefit was claimed or implied. This did, however, show a difference between these two biological, extracted products.

Pharmasure stated that in its view, clinicians wanted information on the characterisation of the products and how they might be different. Pharmasure had differentiated the characterisation of Meriofert from that of Menopur. Although the products were the same class of product, they were extracted biological products and differed in how they were extracted, the raw materials used for extraction and how they were purified. Pharmasure denied breaches of Clauses 7.2 and 7.4.

Pharmasure explained that to manufacture Meriofert, purified hCG from pregnant women's urine (also called placental hCG) was added, as stated in the Meriofert SPC, which provided more than 50% of the total LH activity. In the case of LH activity, this was supplied in both products by hCG. In Menopur, the hCG was extracted only from the urine of menopausal women. Such women, by definition, could not be pregnant, therefore the hCG they had in their urine was of pituitary, not placental, origin. Conversely, Meriofert had its hCG extracted from the urine of pregnant women, who produced large quantities of hCG from their placenta. Again, there was no suggestion of a clinical claim that placental hCG specifically impacted oocyte production. Pharmasure denied a breach of Clause 7.4.

Pharmasure noted that it was clearly stated in the Menopur SPC that 'Menotrophin is a gonadotrophin extracted from the urine of postmenopausal women ...'. Menopausal urine contained elevated pituitary sulphated hCG. HCG produced by non-pregnant women, such as postmenopausal women, was pituitary in origin. There was no suggestion of a clinical consequence of this fact or that it made Menopur in some way inferior to Meriofert, it simply showed a difference. Pharmasure denied a breach of Clause 7.4.

PANEL RULING

The Panel noted that the claim 'Contains predominantly placental hCG' was referenced to the Meriofert SPC, IBSA data on file (hCG content) and Birken *et al.*

The Panel disagreed with Pharmasure's submission that it had not claimed or implied any clinical benefit regarding the difference in the type of hCG present in Meriofert or that the type of hCG had a direct impact on the production of oocytes and embryos available for transfer. Pharmasure stated that it had summarised the two key differences on page 2 but had not linked them. The Panel noted that the claim in question was the first bullet point below the more prominent and first claim on the page 'The aim of ovarian stimulation in IVF is to produce an optimum number of mature oocytes and embryos available for transfer' and above the second bullet point which read 'Higher mature oocyte yield than Menopur'. In the Panel's view, the claim in question would be read in light of what the Panel considered to be the headline claim

and the claim below and thus would be considered to result in a clinical benefit in relation to the production of mature oocytes and embryos available for transfer. In the Panel's view, readers would assume that there was a clinical benefit unless they were clearly told to the contrary.

In the Panel's view, the reader was not provided with sufficient information to properly assess the claim 'Contains predominantly placental hCG' and form his/her own opinion of its therapeutic impact. The claim in question, as it appeared within the context of the page and its overall implication of clinical superiority was therefore misleading and could not be substantiated, a breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that the complainant raised concerns about the phrase 'Menopur is derived from menopausal urine, which contains mainly pituitary hCG' which appeared beneath the graphic on page 4 and not page 5 as referred to by the complainant. The Panel noted that this matter was dealt with at Point 4 below.

3 Table on Page 3

Page 3 headed 'Meriofert Acidic FSH' above the claim 'Meriofert, like Fostimon (Urofollitropin), contains acidic FSH.' featured a table which compared the oligosaccharide composition, relative amount (%), of Fostimon (urofollitropin), Puregon (follitropin beta) and Gonal-F (follitropin alfa).

COMPLAINT

Ferring alleged that the table was misleading, in breach of Clause 7.2.

The page purported to show that study results for Fostimon were somehow transferable to Meriofert. The table was adapted from Lombardi *et al* (2013) (copy provided) and purported to present Meriofert as being similar to Fostimon. However, the active ingredient in Meriofert was menotrophin (a combination of FSH and LH in a 1:1 ratio), whereas the active ingredient in Fostimon was urofollitropin (FSH); to claim similarity between the two was misleading.

Lombardi *et al* compared Fostimon with Puregon and Gonal F for: composition, acidic FSH, sialylated and branched carbohydrate moieties. There was no data or evidence provided to demonstrate any similarity between Meriofert and Fostimon in terms of composition, acidic FSH, sialylated and branched carbohydrate moieties.

RESPONSE

Pharmasure submitted that as a menotrophin product, Meriofert contained both FSH and LH activities.

The FSH in both Meriofert and Fostimon was extracted from the same source of postmenopausal urine using similar techniques. Fostimon (urofollitropin) contained only FSH, whereas Meriofert had LH activity (by way of hCG) added.

IBSA data on file demonstrated, as expected, comparable FSH isoforms distribution between Meriofert and Fostimon.

Pharmasure stated that it was important that clinicians knew what was in these biological products and how they might differ. Like Fostimon, Meriofert contained a high proportion of highly acidic (highly glycosylated) FSH isoforms and in the natural menstrual cycle, these isoforms predominated in the early-mid follicular phase. Acidic FSH isoforms had different biological activities and different half-lives compared with less acidic FSH isoforms. Pharmasure stated that it had previously referred to the isoform profile of Fostimon compared with recombinant FSH products (Lombardi *et al*) and wanted to continue with this theme for Meriofert. The reason this was presented was for comparison against recombinant products (ie not Menopur) such as follitropin alpha and follitropin beta, which was why the comparison was included. No definitive clinical outcome was claimed, simply an important product characteristic had been presented.

PANEL RULING

The Panel noted that page 3 of the leavepiece was headed 'Meriofert Acidic FSH' and below it was stated that 'Meriofert, like Fostimon (urofollitropin) contains acidic FSH'. The page went on to describe a study that compared Fostimon with Puregon and Gonal-F and which demonstrated the prevalence in Fostimon of more acidic isoforms, which corresponded to species containing more sialylated and branched carbohydrate moieties.

The Panel noted Pharmasure's submission that the table was included as a comparison against recombinant products such as follitropin alpha and follitropin beta and not Menopur.

The Panel noted Ferring's submission that the data in the table on page 3 compared the oligosaccharide composition, relative amount (%), of Fostimon (urofollitropin), Puregon and Gonal-F (follitropin alfa) and its allegation that the page purported to show that study results for Fostimon were somehow transferable to Meriofert.

The Panel noted Pharmasure's submission that the FSH in both Meriofert and Fostimon was extracted from the same source of postmenopausal urine using similar techniques, and in addition Meriofert had LH activity (by way of hCG) added. The Panel noted that it was not clear from the page at issue that Fostimon contained only FSH whereas Meriofert contained both FSH and LH activities.

It was not clear from the page what the differences in the table meant in terms of clinical relevance; the Panel noted Pharmasure's submission that no definitive clinical outcome was claimed but rather an important product characteristic had been presented.

The Panel noted Pharmasure's submission that the biological nature of these products, including differences in extraction, raw material used and purification techniques, might all have an impact on why one product performed differently to another. That was why Pharmasure considered it was essential to provide a context that informed clinicians of the nature of these products and that each active was not a single molecule but a family of differently glycosylated or sulphated molecules, each variant having differences in biological activity and clearance rate. In this regard the Panel noted that Ferring had provided a comparative evaluation of the quality characteristics of FSH contained in Fostimon vs Meriofert. The evaluation concluded that the characteristics of FSH contained in Fostimon and Meriofert were similar. The authors stated that the result was expected since the purification process was very similar.

The Panel noted that in response to a request for further information Pharmasure stated that for briefing the sales team in relation to the leavepiece at issue, it used copies of the approved artwork in a power point presentation. The Panel noted that this presentation included slides of the pages of the leavepiece but did not detail how representatives should use or discuss each page with health professionals. It therefore did not appear to be briefing material.

The Panel noted that whilst it was clear from the page that it was discussing Meriofert and acidic FSH, it was not clear from the page that Meriofert contained both FSH and LH activities whilst Fostimon contained only FSH as alleged, and the implication that that the results of Lombardi *et al* in relation to the structure of the isoforms and corresponding moieties would equally apply without any qualification to both products meant that readers not provided with sufficient information to properly assess the information and form their own opinions of its therapeutic impact and a breach of Clause 7.2 was ruled.

4 Claim 'LH activity in Meriofert is predominantly from placental hCG which is mainly comprised of glycosylated hCG' and the associated graphic.

The claim was at the top of page 4 beneath the heading 'Meriofert LH Activity from Placental hCG' and above the graphic in question which showed the source of FSH activity and LH activity for Meriofert and Menopur.

COMPLAINT

Ferring noted that page 4 focussed on the source and activity of LH and implied that the source of hCG to provide LH bioactivity in Meriofert and Menopur somehow conferred a clinical relevance and an advantage for Meriofert.

The headline claim appeared immediately above a graphical representation of the source of LH activity for Meriofert and Menopur, below which a table compared sulphate content of pituitary and placental hCG subunits; then further bullet points about placental vs pituitary hCG. The graphic compared LH activity and source (pregnancy urine and menopausal urine for Meriofert and menopausal urine only for Menopur).

Ferring contended that the combined effect of the headline statement and the graphic was in breach of Clause 7.2 because it implied that Menopur was inferior to Meriofert which was not so.

The graphic itself was also directly misleading in breach of Clause 7.8 because it implied that Menopur was inferior to Meriofert which was not so.

There was no indication of the amount of placental hCG present in Meriofert; and no indication of the amount of placental hCG that might be clinically relevant.

The graphic showed that the LH activity for Meriofert was from pregnancy urine, but the relevance of this was not clear; nor was the relationship between pregnancy urine and placental hCG. In the context of the text 'LH activity in Meriofert is predominantly from placental hCG', the reader was not given information to understand any relevance to the data.

RESPONSE

Pharmasure stated that page 4 did not focus on the source and activity of LH, but the source and activity of the hCG, which provided the LH activity in Menopur and Meriofert. Pharmasure referred to its response to Point 2 above. No claims were made as to the clinical benefit of the hCG content of Meriofert. There was clearly a difference in the type of hCG contained in Meriofert compared with Menopur. There was no suggestion of inferiority of Menopur compared with Meriofert in relation to hCG content, simply a difference. Pharmasure denied a breach of Clause 7.2.

Pharmasure noted that not only was the source of hCG different, but the tertiary structure of placental and pituitary hCG was also different. This difference had an impact on the half-life and activity of the molecules. All these statements were backed up by Birken *et al*. Regarding the headline and the graphic, no clinical benefit was claimed and Pharmasure denied a breach of Clause 7.8.

Pharmasure stated that there was no claim of a clinical benefit linked to an amount of placental hCG. The LH activity in Meriofert was mainly from pregnancy urine which contained placental hCG; Pharmasure referred to comments above in response to Point 2. The relationship between pregnancy urine and placental hCG was clear; placental hCG was excreted in pregnancy urine and the hCG found in the urine of postmenopausal women was of pituitary origin (Birken *et al*).

The relevance of these data was to show that the products were different.

PANEL RULING

The Panel noted that the graphical representation of the source of LH activity for Meriofert and Menopur appeared below the claim **'**LH activity in Meriofert is predominantly from placental hCG which is mainly comprised of glycosylated hCG'. Below the graphic it stated 'Menopur is derived from menopausal urine which contains mainly pituitary hCG' which was referred to by the complainant at Point 2 above followed by a table which compared the sulphate content of pituitary and placental hCG subunits referenced to Birken *et al*. Below this were three bullet points beneath the heading 'Placental hCG vs pituitary hCG': *in vivo* clearance is lower (longer half-life: placental hCG 36h, pituitary hCG 20h, LH 26 minutes); *in vitro* biological activity is higher and receptor binding affinity is higher. The first bullet point was referenced to Birken *et al* and Cole *et al*, whereas the second and third bullet points were only referenced to Birken *et al*.

The Panel noted that whilst the table and bullet points were referenced to the second Birken *et al* study, 'Metabolism of hCG and hLH to multiple urinary forms, there was no direct reference to their content within that study. The Panel noted that the original Birken *et al* study, 'Isolation and Characterization of Human Pituitary Chorionic Gonadotrophin' stated that the presence of sulphate on pituitary hCG might play a role in its reduced *in vitro* biological activity but that this was not clear with regard to earlier studies of Baenziger. The sulphate content of pituitary hCG would be expected to lead to a rapid clearance *in vivo* by a liver receptor specific for the sulphate-4-GalNAc-GlcNAc-M structure.

The Panel noted that Clause 7.8 required that all artwork including illustrations, graphs and tables must conform to the letter and spirit of the Code and, when taken from published studies, a reference must be given. Graphs and tables must be presented in such a way as to give a clear, fair, balanced view of the matters with which they dealt, and must not be included unless they were relevant to the claims or comparisons made.

The Panel noted that the graphic in question showed the pregnancy urine for Meriofert LH activity in red. All other components for FSH and LH activity including Meriofert menopausal urine for LH activity were coloured blue. In the Panel's view, the reader's eye was likely to link the red graphic for pregnancy urine with the three red bullet points at the bottom of the page the claims adjacent to which favourably compared placental hCG with pituitary hCG. This point had not been raised by Ferring. The Panel noted that the allegation in relation to the graphic appeared to be that it, as a stand alone matter, was in breach of Clause 7.8 as the amount and clinically relevant amount of pregnancy urine was unclear, the relevance of this was not clear; nor was the relationship between pregnancy urine and placental hCG. In the context of the text 'LH activity in Meriofert is predominantly from placental hCG', the reader was not given information to understand any relevance to the data. The Panel did not consider that the reader would consider the graphic in isolation from the rest of the page, nonetheless that was the allegation before it. The Panel did not consider that the graphical representation of the source of LH activity for Meriofert and Menopur, when considered in isolation, misleadingly implied that Menopur was inferior to Meriofert as alleged. Whilst pregnancy urine was highlighted in red, the graphic in isolation made no claim based on this difference. In the Panel's view, Ferring had not established, on the balance of probabilities, that the graphic in isolation, including the amount of placental hCG present in Meriofert depicted, was misleading. No breach of Clause 7.8 was ruled based on the very narrow allegation.

The Panel noted that Ferring also referred to the three bullet points at the bottom of the page described above and alleged that page 4 implied that the source of hCG to provide LH bioactivity in Meriofert and Menopur somehow conferred a clinical relevance and an advantage for Meriofert. The Panel noted that the three bullets were in the same red colour as the pregnancy urine depicted in the graphical representation of the source of LH activity for Meriofert and Menopur and thereby implied that the lower *in vivo* clearance (longer half-life: placental hCG 36h, pituitary hCG 20h, LH 26min) the higher *in vitro* biological activity, and the higher receptor binding affinity of placental hCG vs pituitary hCG referred to in the bullet points was due to the source of hCG and the tertiary structure of placental vs pituitary hCG . The Panel noted Ferring's submission that the tertiary structure of hCG isoforms (how glycosylated they were) had a direct bearing on the half-life of the molecule and activity at the receptor. Each active was not a single molecule but a family of differently glycosylated or sulphated molecules, each variant having differences in biological activity and clearance rate.

The Panel further noted that the first Birken *et al* study isolated and characterised human pituitary hCG by analysing hCG content from pituitary glands and compared it with hCG purified from the urine of pregnant woman. The study undertook a series of analyses for sulphate and included the original table in question. The second Birken *et al* study stated that since many of the molecular forms of the two hormones (hCG and hLH) in urine differed from their forms in blood, it might be necessary to produce new immunoassays as well as novel urinary reference preparations to accurately measure these molecules within their urinary matrix.

The Panel noted that according to the first Birken study there were some differences between placental hCG vs pituitary hCG. The Panel noted its comments above and considered that in its view the overall implication of page 4 was that Menopur was inferior to Meriofert based on its LH activity being predominantly from placental hCG which was mainly comprised of glycosylated hCG and its low sulphate content. The Panel noted that it appeared that the bullet points on page 4 had been referenced to the incorrect Birken *et al* study and, in the Panel's view, the reader should have been provided with details of the original Birken *et al* study. The Panel

noted its comments at point 1 above about Lockwood *et al* and non-inferiority. Further information should have been provided to enable the reader to properly assess the information on page 4 including in relation to the claim 'Menopur is derived from menopausal urine which contains mainly pituitary hCG' and form his/her own opinion of the relative clinical value of Meriofert compared with Menopur. The Panel noted its comments above and ruled a breach of Clause 7.2.

5 Table: Comparative sulphate content of pituitary and placental hCG subunits

This table appeared on page 4 and was referenced to Birken *et al* (1996).

COMPLAINT

Ferring alleged that the table of data was misleading, in breach of Clause 7.2. Ferring noted that Birken *et al* analysed hCG content from pituitary glands and not from urine. As Meriofert contained hCG derived from the urine of postmenopausal and pregnant women, the data for sulphate content from Birken *et al* could not be extrapolated to Meriofert. Even Birken *et al* explained that many of the molecular forms of hCG in urine differed from their forms in blood. As far as Ferring knew, there was no evidence to show that data from pituitary extract could be extrapolated to products containing urinary human menopausal gonadotropins (hMG).

Ferring also noted that the table was incorrectly referenced to Birken *et al,* 'Metabolism of hCG and hLH to multiple urinary forms', however, this was only a secondary reference and the original data and table was from another Birken *et al* paper entitled 'Isolation and Characterization of Human Pituitary Chorionic Gonadotrophin', also published in 1996. Ferring also noted that the descriptions beneath the heading 'protein' had been altered and were not the same as in the original article.

RESPONSE

Pharmasure stated that it had not extrapolated the Birken *et al* data to apply to Meriofert. The company had presented the comparative sulphate content of pituitary and placental hCG to demonstrate how structurally the two types of hCG differed. Pharmasure had used Birken *et al* to illustrate the difference between placental and pituitary hCG, which was one way in which Meriofert and Menopur were different.

It was clear from Birken *et al* that a pituitary form of hCG, which was sulphated, was in postmenopausal women's urine.

Pharmasure stated that the table in the detail aid appeared in the reference cited but the company accepted that its first publication was in another 1996 paper by Birken *et al*.

It was clearly stated in the Menopur SPC that 'Menotrophin is a gonadotrophin extracted from the urine of postmenopausal women …'. Menopausal urine contained elevated pituitary sulphated hCG. HCG produced by non-pregnant women, such as postmenopausal women was of pituitary origin (Birken *et al*).

PANEL RULING

The Panel did not consider that it was necessarily unacceptable to use data from the second Birken *et al* publication and reference it to that publication rather than the original provided the way in which it was used complied with the Code.

The first Birken study, 'Isolation and Characterization of Human Pituitary Chorionic Gonadotrophin' isolated and characterised human pituitary hCG by analysing hCG content from pituitary glands and compared it with hCG purified from the urine of pregnant woman.

The second Birken study was titled 'Metabolism of hCG and hLH to multiple urinary forms'. The table as reproduced in the detail aid was present in both studies. The second Birken study stated that the table in question was reproduced from the first Birken study.

The Panel noted that the table in both Birken studies referred to pituitary $hCG_{\tilde{\alpha}}$ and hCG_{β} and urinary $hCG_{\tilde{\alpha}}$ and $hCG_{\beta,}$ whereas the detail aid referred to pituitary $hCG_{\tilde{\alpha}}$ and hCG_{β} and placental $hCG_{\tilde{\alpha}}$ and $hCG_{\beta.}$ The Panel noted Pharmasure's submission that purified hCG from pregnant women's urine was also called placental hCG. The first Birken *et al* study stated that the hCG excreted by pregnant woman into urine was designated urinary hCG in the report, and thus it appeared to the Panel that the urinary $hCG_{\tilde{\alpha}}$ and hCG_{β} referred to in the table was from the urine of pregnant women.

In the Panel's view, in the circumstances of this case, whilst the table appeared in both Birken studies, the reader would need to look at the original Birken study 'Isolation and Characterization of Human Pituitary Chorionic Gonadotrophin' in order to fully understand the implication of the table at issue. The Panel considered that it was therefore misleading not to reference the first Birken study in this regard and a breach of Clause 7.2 was ruled.

The Panel did not accept Pharmasure's submission that it had 'not extrapolated the Birken *et al* data to apply to Meriofert'. The table appeared prominently on a page headed 'Meriofert LH Activity from Placental hCG' which referred to Meriofert and placental hCG, illustrating the proportion of LH activity derived from pregnancy urine. The table then presented data for placental hCG. It was difficult to understand how the table including placental hCG could be viewed in isolation from the claims for Meriofert on the page. In the Panel's view, a reader would relate the data to Meriofert.

The Panel noted Ferring's submission that Birken *et al* analysed hCG content from pituitary glands and not from urine and as Meriofert contained hCG derived from the urine of postmenopausal and pregnant women, the data for sulphate content from Birken *et al* could not be extrapolated to Meriofert as had been done in the detail aid. Pharmasure stated that it had used Birken *et al* to illustrate the difference between placental and pituitary hCG, which was one way in which Meriofert and Menopur were different, and that it was clear from Birken *et al* that a pituitary form of hCG, which was sulphated, was in postmenopausal women's urine.

The Panel further noted that the second Birken *et al* study stated that since many of the molecular forms of the two hormones (hCG and hLH) in urine differed from their forms in blood, it might be necessary to produce new immunoassays as well as novel urinary reference preparations to accurately measure these molecules within their urinary matrix.

The Panel noted that it was not clear that the data within the table on page 4 of the leavepiece was from the second Birken *et al* study rather than the original Birken study and referred to hCG content isolated from pituitary glands rather than from urine. In the Panel's view, the reader did

not have sufficient information to form his/her own opinion of the relevance of the data which was misleading and a breach of Clause 7.2 was ruled.

6 Claim 'On average for each patient TWO more mature oocytes were retrieved and ONE more cleaved embryo on day 2 was observed during a shorter period of stimulation in the Meriofert group'

This was the main claim on page 5 which was headed 'Meriofert High Ovarian Yield'.

COMPLAINT

Ferring alleged that the claim, referenced to Lockwood *et al*, was misleading, in breach of Clause 7.2.

Ferring noted that Lockwood *et al* was a non-inferiority study with a primary endpoint of total number of oocytes retrieved. Differences in oocyte maturity, embryo cleavage or duration of stimulation were not primary endpoints of the study. To imply a clinically meaningful difference was therefore misleading, especially in the context of the capitalised 'TWO' and 'ONE'. The statistical analysis was not planned to proceed hierarchically or adjusted for multiplicity, therefore it was misleading to refer to secondary endpoints and attempt to imply clinical differences.

To imply clinical differences between Meriofert and a dose of Menopur which was less than that licensed in the UK was misleading. Lockwood *et al* prematurely discontinued the administration of Menopur compared with the licensed Menopur dose – thus patients were triggered earlier than recommended in the Menopur SPC which stated 'It is recommended there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500pmol/L (920picograms/ml; Human chorionic gonadotrophin should not be administered if these criteria have not been met)'.

Ferring noted that the Menopur SPC was mentioned in the small print at the foot of the page, however, case precedent had clearly established that misleading claims could not be corrected by a footnote.

The use of capital letters to highlight the differences ('TWO' and 'ONE') further emphasised these misleading claims.

RESPONSE

Pharmasure submitted that the claim was based on the significant outcome in Lockwood *et al* that it had commented on above and in that regard, it referred to its response at Point 1.

The primary endpoint was presented, which also showed a significant difference. The footnote was added to accommodate Ferring's comments from inter-company dialogue. Pharmasure denied that the claim was misleading and did not accept that it was a beach of Clause 7.2.

With regard to the dose and trigger criteria for the Menopur arm, Pharmasure referred to its response at Point 1 above.

Pharmasure noted that recommendations on the number, size of follicles and oestradiol levels was not part of the posology for Meriofert, which was approved many years after Ferring's Menopur licence was granted, yet they were the same class of product. This reflected recognition of the need for flexibility in the therapy area, as it did in the choice of criteria for Lockwood *et al* and Alviggi *et al*. Pharmasure contended that, in practice the sub-specialists that undertook this type of treatment used their own clinical judgement for stimulation, monitoring and triggering rather than sticking rigidly to the recommendations for one particular product SPC in the therapy area.

Pharmasure contended that, since the products were in the same class and the protocols were approved by the Danish authority and accepted by the UK authority, the comparison was valid and Ferring's allegation that it was an unfair comparison was not justified. Pharmasure noted that the Menopur SPC recommended the approach, but did not mandate it, so Lockwood *et al* did use Menopur 'on-licence' in line with the SPC.

PANEL RULING

The Panel considered that its comments at Point 1 above were relevant. Page 5 of the leavepiece implied that Meriofert was more efficacious than Menopur based on the higher mature oocytes retrieved and the number of cleaved embryos on day 2 as well as the total oocytes retrieved and inseminated injected oocytes and the duration of stimulation. The page did not refer to the fact that Lockwood *et al* concluded that Meriofert was non-inferior to Menopur in terms of clinical efficacy or the author's views that IVF efficacy corelated with the number of fertilized oocytes obtained and no statistically significant differences between Meriofert and Menopur were reported for most of the clinically significant end-points including embryo quality, fertilization rate, implementation rate, ongoing pregnancy rate and live birth rate.

The Panel further noted that, according to both companies, Lockwood *et al* was designed in such a way that Menopur was stopped earlier than recommended in its SPC.

According to both companies, the Menopur SPC recommended that there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500pmol/L (920 picograms/ml); Human chorionic gonadotrophin should not be administered if these criteria have not been met', whereas Lockwood *et al* was designed in a way that daily gonadotrophin administration was continued until at least two follicles had a mean diameter greater than 16mm, serum oestradiol levels greater than 400pg/ml (or 1500pmol/l), or both.

The Panel noted that neither company had provided a copy of the Menopur SPC and the Panel was unable to find reference to the specific recommendation referred to by both companies in the Menopur SPCs available on the eMC when the case was being considered. The Panel noted that the different strength Menopur SPCs available on eMC stated that 'when a suitable number of follicles have reached an appropriate size a single injection of 5,000 IU up to 10,000 IU hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval'.

The Panel queried whether the number of oocytes or MII (mature) oocytes retrieved for Menopur would have been different had the recommendation as referred to by both companies had been followed.

The Panel noted that the trial design of Lockwood *et al* did appear at the top of the page and it was stated in small font in a footnote at the bottom of the page the recommendation in the Menopur SPC as referred to by both companies. The Panel noted, however that unlike the footnote on page 2, the footnote on page 5 did not specifically state that the study had been designed in such a way that the Menopur SPC recommendation as referred to by both companies was not followed.

The Panel considered that the reader was not provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Meriofert vs Menopur. The Panel noted its comments above and considered that the claim in question was misleading and a breach of Clause 7.2 was ruled.

7 Claim 'Efficiency of (Meriofert) appears to be higher due to reduced quantity of drug used and the higher yield of mature oocytes retrieved'

This claim, referenced to Alviggi *et al*, appeared on page 6, beneath a figure which compared results of the primary endpoint (mean number of total collected oocytes) and secondary endpoints (ratio of MII/total oocytes retrieved, COS duration, total HMG units) using Menopur and Meriofert. The page was entitled 'Meriofert High Efficiency' followed by a description of the study design and a claim in the largest blue font on the page that '7% more mature oocytes were obtained with 14% less gonadotrophin being administered during a shorter period of stimulation in the Meriofert group'.

COMPLAINT

Ferring alleged that the claim was misleading, in breach of Clause 7.2. Alviggi *et al* was a non-inferiority study for the primary endpoint of total number of oocytes retrieved, with no statistical adjustment for hierarchical analysis or multiplicity on the depicted secondary endpoints (ratio metaphase II (MII) oocytes retrieved, controlled ovarian stimulation (COS) duration, total HMG units). Ferring reiterated that it was thus misleading to imply statistically significant differences between the comparators.

Ferring added that Alviggi *et al* used an unlicensed dose of Menopur as the Menopur SPC clearly stated: 'It is recommended there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500pmol/L (920 picograms/ml); Human chorionic gonadotrophin should not be administered if these criteria have not been met'. Alviggi *et al* stopped Menopur earlier than recommended in the SPC – 'Daily gonadotrophin administration was continued only until at least two follicles had a mean diameter greater than 16mm'. This had clinical relevance because if the product was not used as per the SPC, the outcomes shown might not be those obtained in clinical practice and therefore they formed the basis of misleading claims.

Ferring also noted that Alviggi *et al* compared Merional HG with Menopur. Ferring had discussed the similarity between Meriofert and Merional HG in inter-company dialogue during which Pharmasure contended that Meriofert and Merional HG were the same product. Ferring stated, however, that it had established with the MHRA, that the two products were different, based on the source of hCG and purification processes.

RESPONSE

Pharmasure stated that the claim at issue was not misleading since the primary endpoint was presented while key secondary endpoints were also presented when there was a statistically significant difference between the two products.

Alviggi *et al* was a regulatory study, used for the submission of the dossier in the EU. The dosage was agreed with the Italian authority and accepted by the UK authority, which was also based on the standard practice in each site. Pharmasure noted that it had clearly stated in its materials that the study was designed slightly differently from the recommendation on the Menopur SPC and, importantly, the Menopur SPC recommended the approach, but did not mandate it, so Alviggi *et al* used Menopur 'on-licence' in line with the SPC. The statement 'A prospective, randomised, investigator-blind, controlled, clinical study which was designed in a way that daily gonadotrophin administration was continued until at least two follicles had a mean diameter greater than 16mm and serum oestradiol levels were appropriate for the total number of developing follicles. In Menopur's SPC, it is recommended there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500pmol/L (920 picograms/ml)' appeared wherever claims were made based on Alviggi *et al*.

Pharmasure stated that Ferring's interpretation of its communication with the MHRA was incorrect. Pharmasure did not contend that Merional and Meriofert were the same product but that Merional HG and Meriofert were the same. Meriofert and Merional-HG were the same product with different brand names in different European countries.

Alviggi *et al* referred to Merional HG which was the name given to Meriofert in Switzerland. Merional HG was different to Merional and it was clear that the names of Merional (now discontinued) and Merional HG had confused Ferring. The correspondence with the MHRA referred only to Merional (not Merional HG) and had no bearing on the fact that Merional HG was the name given to Meriofert in Switzerland. The name Merional HG had never been used in the UK. Consequently, the study claims used for Meriofert were supported by Alviggi *et al* which used Merional HG, which was Meriofert.

PANEL RULING

The Panel noted that Alviggi *et al* was a prospective, randomised, investigator-blind, controlled non-inferiority clinical trial to evaluate the clinical efficacy and tolerability of a highly purified human menopausal gonadotrophin preparation (Merional-HG) and Menopur when administered to patients undergoing controlled ovarian stimulation (COS) for IVF procedure. The results showed that both preparations were equivalent in terms of number of oocytes retrieved (primary endpoint: 8.8±3.9 vs 8.4±3.8, p=0.54). In patients treated with Merional-HG, a higher occurrence of mature oocytes (78.3% vs 71.4%, p=0.005) and a reduced quantity of gonadotrophins administered per cycle (2.556±636 IU vs 2.969±855IU, p<0.001). Fertilization, cleavage, implantation rates and the number of positive β-human chorionic gonadotrophin (hCG; pregnancy) tests and the clinical pregnancy rate were comparable in the two groups. The author stated that the clinical outcome in the two treatment groups was comparable with no significant differences in total and mature oocyte number and conversely, significantly lower duration of treatment and gonadotrophin consumption were associated with Merional-HG use. In summary, the study authors stated that Merional-HG and Menopur were proven to be equally effective to achieve proper outcome of ART. In this regard, the Panel noted its understanding of a non-inferiority trial as referred to at Point 1 above.

The Panel note that according to the authors, Merional-HG appeared to be more efficient than Menopur in this setting as it allowed reducing drug consumption and might provide additional practical advantages in the management of ART procedures; not the higher yield of mature oocytes as implied by the page at issue.

The Panel further noted that Alviggi *et al* was designed in such a way that Menopur was stopped earlier than recommended in its SPC. According to both companies, the Menopur SPC recommended that there should be at least 3 follicles greater than 17mm in diameter with 17 beta-oestradiol levels of at least 3500pmol/L (920 picograms/ml); Human chorionic gonadotrophin should not be administered if these criteria have not been met', whereas Lockwood *et al* was designed in a way that daily gonadotrophin administration was continued until at least two follicles had a mean diameter greater than 16mm, serum oestradiol levels greater than 400pg/ml (or 1500pmol/l), or both.

The Panel noted that neither company had provided a copy of the Menopur SPC and the Panel was unable to find reference to the specific recommendation referred to by both companies in the Menopur SPCs available on the eMC when the case was being considered. The Panel noted that the different strength Menopur SPCs available on eMC stated that 'when a suitable number of follicles have reached an appropriate size a single injection of 5,000 IU up to 10,000 IU hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval'.

The Panel queried whether the number of oocytes or MII (mature) oocytes retrieved for Menopur would have been different had the recommendation as referred to by both companies had been followed.

The Panel noted that although it was stated in small font in a footnote at the bottom of the page the recommendation in the Menopur SPC and the trial design of Alviggi *et al* appeared at the top of the page, unlike the footnote on page 2, it was unclear that the study had been designed in such a way that the Menopur SPC recommendation as referred to by both companies was not followed. The Panel considered that the reader was not provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Meriofert vs Menopur. The Panel noted its comments above and considered that the claim in question was misleading and a breach of Clause 7.2 was ruled.

8 Safety claim table on Page 7

COMPLAINT

Ferring noted that page 7 compared the safety of Meriofert and Menopur. The second table on page 7 depicted several adverse events including injection site pain, persistent redness, tenderness and itching. Ferring alleged that the table was misleading, in breach of Clauses 7.2, 7.8 and 7.9.

Neither table had explanatory text to accompany the numbers.

The table showed the total number and percentage of specified adverse events. The information could easily be read as though Menopur had higher numbers than Meriofert and therefore had a worse adverse event profile, which was not so. The lack of p values on the table could be read as implying no statistically significant difference between the two products in

terms of side-effects, however, this was also not the case as the table was selective in its presentation.

The cited publication (Lockwood *et al*) was a non-inferiority study for total number of oocytes retrieved; it was not powered to show differences in adverse events. It was stated in the paper that 'No difference was reported in the frequency of the adverse events with the exception of vascular disorders (hot flushes) that were reported more often in the Meriofert group (8.2% vs 1.5%, p=0.02)'. The paper therefore clearly showed no clinically relevant differences between the products except for hot flushes.

Ferring was particularly concerned that the important and clinically relevant adverse event of hot flushes, which was reported more frequently in the Meriofert group was omitted from the table completely, although a statement about hot flushes appeared beneath the table. However, it did not state the numerical differences, as was done for the other stated adverse events in the table. The statement also appeared at the end of a paragraph that began by promoting a positive virtue of Meriofert ('Meriofert has good tolerability'). Given that hot flushes were the only adverse event that was significantly different, this appeared to be a deliberate attempt to hide this information from the reader.

RESPONSE

Pharmasure stated that doctors would want to know about the most severe side-effects to evaluate the safety of the products, which in this case was ovarian hyperstimulation syndrome of which there was no significant difference in the frequency and severity detected between the two treatment groups.

Injection site pain, persistent redness, tenderness and itching all described the tolerability at the injection site; hence they were presented together.

Hot flushes were reported more frequently in the Meriofert group which was specifically mentioned separately to make the difference clear.

Pharmasure denied any breach of Clauses 7.2, 7.8 and 7.9 but conceded that it would present the data differently if Ferring had any specific recommendations to discuss.

PANEL RULING

The Panel noted that below the table at issue it was stated that Meriofert had good tolerability and that cases of injection site pain were mainly mild and did not last after the time of injection followed by hot flushes which were reported more frequently in the Meriofert group. The Panel noted that it was misleading to provide data showing the difference between Meriofert and Menopur with regards to injection site pain and persistent redness, tenderness and itching which implied that there was a difference without including the p number or stating that tolerability at the injection site was found to be very good in both groups as stated in Lockwood *et al*. The data in the table was not presented in a way as to give a clear, fair, balanced view and a breach of Clauses 7.2 and 7.8 were ruled.

The Panel noted that in stating that hot flushes were reported more frequently in the Meriofert group without stating that there was a significant difference in the reporting of hot flushes (8.2% vs 1.5%, p = 0.02) was misleading.

In the Panel's view, the safety data was not adequately reflected in the leavepiece and a breach of Clause 7.9 was ruled.

Complaint received **19 July 2019**

Case completed **18 June 2020**