CASE AUTH/3571/10/21 ***NO BREACH OF THE CODE***

COMPLAINANT v MERCK SERONO

Alleged promotion of Pergoveris (lutropin alfa, follitropin alfa)

A contactable complainant who described him/herself as a health professional complained about a promotional e-symposium organised by Merck Serono on Tuesday, 20 July.

1 Alleged off-label promotion

The complainant noted that a slide shown at the e-symposium referred to the use of Pergoveris in association with in-vitro fertilisation (IVF) and alleged that it was off-label promotion as Pergoveris was not licensed for multiple follicular development associated with IVF and IVF was not included in the Pergoveris summary of product characteristics (SPC).

The complainant further alleged that case studies that made reference to IVF had the potential to mislead the audience with regard to the correct indication for Pergoveris.

2 Alleged provision of information that was not sufficiently complete

The complainant alleged that a second slide headed 'Improved pregnancy rates in r-hFSH +r-hLH compared to hMG-HP in hypogonadotropic hypogonadism patients' shown during the session which compared rec follicle-stimulating hormone (FSH) and rec luteinizing hormone (LH) with human menopausal gonadotropin (HMG) in hypo-hypo patients from Carone *et al* 2012 did not provide enough information to allow health professionals to form an opinion about the methodological veracity of the study and subsequently the clinical relevance of its findings. The complainant drew attention to a number of aspects which were absent from the presentation: the 'sample size was not calculated according to a power analysis' as stated in Carone *et al*; the slide did not clarify that the result was a combined figure of three cycles and that there was no significant difference between the 2 groups for each individual cycle; the audience was not made aware that if the sample size for one series was limited, then combining the results with the other 2 series could potentially produce erroneous results; and the absence of a washout period in the study was not made clear.

The detailed response from Merck Serono is given below.

1 Alleged off-label promotion of Pergoveris (300 IU + 150 IU)/0.48 mL solution for injection in pre-filled pen)

The Panel noted that Pergoveris was indicated for the stimulation of follicular development in adult women with severe LH and FSH deficiency. In clinical trials, these patients were defined by an endogenous serum LH level < 1.2 IU/L. The Panel noted that

no reference to IVF was made anywhere in the SPC including that it was contraindicated or not advised.

The Panel noted Merck's submission that follicular development using exogenous gonadotrophins was the first step of a controlled ovarian stimulation process which was followed by fertilisation; oocyte fertilisation could then occur in many ways, such as natural methods (coitus) or methods that were part of a wider strategy of medically assisted reproduction technologies (MAR), which included techniques such as intrauterine insemination (IUI) and procedures using assisted reproductive technologies (ART), which included IVF. Merck further submitted that the preferred method of fertilisation was a decision independently discussed and agreed between a clinician and their patient based on several factors and outcomes and was not directly related to the previous step of follicular development. Pergoveris was only indicated for the follicular development and the fertilisation process that followed was independent from this follicular development process.

The Panel noted that slide 3 of the symposium presentation included the indication for Pergoveris. In the Panel's view, the complainant had not established that reference to IVF within the presentation was inconsistent with the particulars listed in the Pergoveris SPC and no breach of the Code was ruled.

The Panel noted Merck's submission that the patient in the case study referred to by the complainant had had a previous cycle of IVF but did not get the expected treatment response, showing possible ovarian hyposensitivity related to polymorphisms in the gonadotrophin receptors. Further details were then discussed about the patient case study to explore what the potential root causes of the problem could be and what treatment options could be available for the following cycle(s) that could result in a different response. When the case study was reviewed in full over slides 12 to 16, the case identified that the patient was severely LH & FSH deficient and therefore could be a potential candidate for future treatment with Pergoveris, to optimise follicular stimulation. The Panel noted its comments above and did not consider that the complainant had established that inclusion of the case study that made reference to IVF would mislead the audience with regard to the correct indication for Pergoveris as alleged; Pergoveris' indication was included on slide 3. The Panel therefore ruled no breach of the 2021 Code.

The Panel noted its comments and rulings above and did not consider that Merck had failed to maintain high standards and no breach of the 2021 Code was ruled, including no breach of Clause 2.

2 Alleged provision of information that was not sufficiently complete

Whilst the Panel noted that the slide at issue did not state that the sample size was not calculated according to a power analysis, it noted the small numbers of patients in each treatment arm were clearly stated in the first bullet point of the slide. The Panel further noted Merck's submission that the fact the patients in the study were patients with World Health Organisation (WHO) type 1 hypogonadotropic anovulation, which were known to the community to be a rare group of patients, meant that viewers would be aware that the sample size was a limitation of the study.

The Panel did not consider that the complainant had established that in not stating that the sample size was not calculated according to power analysis, meant that the audience had not been provided with sufficient information with regard to the sample size to enable them to form their own therapeutic value of this medicine and, based on those very narrow allegations, the Panel ruled no breaches of the Code in relation to each allegation.

The Panel noted that according to the Carone *et al* study protocol, patients were initially treated for one cycle (Series A). If consenting, patients who did not become pregnant during the first cycle were treated for a further optional one (Series B) or two series (Series C) of cycles, with the same criteria of randomisation, ie maintaining the same treatment as the previous cycle.

The Panel noted Merck's submission that the paper discussed subgroups and referred to Series A, B and C which included groups of patients that had different clinical features. The Panel further noted Merck's submission that given the primary endpoint was not met, drawing conclusions from smaller groups, as the complainant had, was not scientifically robust, which was why the speaker did not present such data; the data presented reflected those of the study and the reader therefore had enough information to be able to form an opinion of the statistical validity of the results.

The Panel noted that according to Carone *et al*, the primary efficacy analysis was done including all patients who received at least one dose of the study medicine.

Whilst the Panel considered that it would have been helpful to include further details of the study, it noted Merck's submission that the overall summary results were set out in the bullet points on the slide with the graphs below giving further details. The Panel further noted Merck's submission that in the Carone *et al*, 2012 study, analysis was conducted on all of the patients randomised, not by the groups that received different numbers of cycles and the slide therefore presented data that was fully in line with what was reported in the study. In the Panel's view, the complainant had not established that in failing to clarify that the results was a combined figure of three cycles and that there was no significant difference between the 2 groups for each individual cycle, meant that the slide was misleading as the audience had not been given sufficient information to enable them to form their own therapeutic value of the medicine as alleged and based on the narrow allegation, the Panel ruled no breaches of the Code.

Nor did the Panel consider that in failing to refer to the author's conclusion from Series C that the two groups were limited in terms of patients and that the results gained should be considered absolute rather than for any statistical significance, and for not making the audience aware that if the sample size for this Series was limited, then combining the results with the other 2 Series could potentially produce erroneous results meant that the slide was misleading as the audience had not been given sufficient information to enable them to form their own therapeutic value of the medicine as alleged. Based on the narrow allegation, the Panel ruled no breaches of the Code.

Further, the Panel noted that patients were initially treated for one cycle (Series A). If consenting, patients who did not become pregnant during the first cycle were treated for a further optional one (Series B) or two series (Series C) of cycles, with the same criteria of randomisation, ie maintaining the same treatment as the previous cycle. The Panel

noted its comments above and did not consider that the complainant had established that failing to refer to the absence of a washout period in the study was misleading as alleged and, based on the narrow allegation, the Panel ruled no breaches of the Code.

A contactable complainant who described him/herself as a health professional and wished to remain anonymous complained about a promotional e-symposium organised by Merck Serono on Tuesday, 20 July during which he/she believed the Code was seriously breached.

COMPLAINT

1 Alleged off-label promotion

The complainant provided a screenshot of a slide shown at the e-symposium headed 'Pregnancy rate significantly higher with rFSH+rLH 2:1 than u-hMG alone or in combination with r-hFSH in a case-control study, N=4,719 patients subjected to [in-vitro fertilisation] IVF'.

The complainant stated that the product used in this study was Pergoveris (300 IU r FSH + 150 IU r LH) which was indicated for the stimulation of follicular development in adult women with severe LH and FSH deficiency. It was licensed to be used in association with coitus or IUI: 'When an optimal response was obtained, a single injection of 250 micrograms of r-hCG or 5,000 IU to 10,000 IU hCG should be administered 24-48 hours after the last Pergoveris injection. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination (IUI) might be performed'. Pergoveris was not licensed for multiple follicular development associated with IVF.

The complainant noted that the slide referred to the use of Pergoveris in association with IVF and alleged that this was off-label promotion in breach of the Code as IVF was not included in the Pergoveris summary of product characteristics (SPC).

The complainant further alleged that the inclusion of case studies that made reference to IVF had the potential to mislead the audience with regard to the correct indication for Pergoveris. An example of such a case study referred to in the symposium was provided.

The complainant stated that in order to comply with the Code, all promotional materials which referred to the use of Pergoveris in association with IVF should be withdrawn and all customer-facing promotional roles should be briefed to not link Pergoveris with use in IVF.

2 Alleged provision of information that was not sufficiently complete

The complainant provided a screenshot of a second slide headed 'Improved pregnancy rates in r-hFSH +r-hLH compared to hMG-HP in hypogonadotropic hypogonadism patients' which he/she stated was shown during the session and compared rec FSH and rec LH with HMG in hypo-hypo patients from Carone *et al* 2012. The complainant alleged that the slide did not provide the audience with enough information to allow health professionals to form an opinion about the methodological veracity of the study and subsequently the clinical relevance of its findings. The complainant drew attention to a number of aspects which were absent from the presentation:

- The slide did not mention that the 'sample size was not calculated according to a power analysis' as stated in Carone *et al*. Viewers of this presentation should have

been made aware that the sample size might not be sufficiently large to demonstrate difference between treatment groups.

- The slide did not clarify that the result was a combined figure of three cycles and that there was no significant difference between the 2 groups for each individual cycle.

- The slide did not state the author's conclusion from Series C that 'the two groups were limited in terms of patients and the results gained should be considered absolute rather than for any statistical significance'. The audience should have been made aware that if the sample size for this Series was limited, then combining the results with the other 2 Series could potentially produce erroneous results.

- The study did not appear to have had a washout period between cycles. This could mean that the results of Series 2 and 3 could be impacted by outcomes of Series 1 and this impact might differ depending upon the treatment. The absence of a washout period in this study should have been made clear.

The complainant stated that he/she would expect to see all references to Pergoveris and IVF withdrawn and content from the Carone study either removed or referred to in a balanced way and the specific shortcomings of the study, referred to above, included.

The complainant alleged a breach of the Code, as promotional material should be balanced and fair and not mislead and the slide did not provide sufficient information to allow health professionals to form a reasonable opinion about the value of this medicine.

When writing to Merck Serono, the Authority asked it to consider the requirements of Clauses 11.2, 6.1, 5.1 and 2 (Point 1) and Clauses 14.1, 6.2 and 6.1 (Point 2) of the 2021 Code.

RESPONSE

Merck stated that it took any allegation of non-compliance with the Code very seriously and refuted the allegations made by the complainant.

The complaint was about several slides presented by a named doctor at a Merck promotional symposium held on 20 July 2021. The complainant provided three screen shots which were of three of the slides that were presented. Merck provided a copy of the whole presentation (ref GB-PER-00021).

1 Alleged off-label promotion of Pergoveris (300 IU + 150 IU)/0.48 mL solution for injection in pre-filled pen)

Merck stated that section 4.1 of the SPC stated that Pergoveris was indicated for the stimulation of follicular development in adult women with severe LH and FSH deficiency, which was acknowledged by the complainant. Indeed, the licensed indication was made clear by the presenter on slide 3 of the presentation. However, the complainant then went on to claim that Pergoveris was licensed to be used in association with coitus or IUI but not IVF, and that Merck was promoting Pergoveris for use in IVF and referred to two slides in this regard.

Follicular development using exogenous gonadotrophins was the first step of a controlled ovarian stimulation process which then was followed by fertilisation. Fertilisation could be done

using different medically assisted reproduction (MAR) technologies or natural methods. As outlined in Section 4.2 of the SPC, in LH and FSH deficient women (hypogonadotrophic hypogonadism), the objective of treatment with Pergoveris therapy was to develop at least one single mature Graafian follicle from which the oocyte would be liberated after the administration of human chorionic gonadotrophin (hCG). This was the last step linked to controlled ovarian stimulation. Oocyte fertilisation could then occur in many ways, such as natural methods (coitus) or methods that were part of a wider strategy of MAR, which included techniques such as intrauterine insemination (IUI) and procedures using assisted reproductive technologies (ART), which included in-vitro fertilisation (IVF).

The preferred method of fertilisation was a decision independently discussed and agreed between a clinician and their patient. The chosen method of fertilisation therefore represented an agreement between a clinician and their patient, based on several factors tailored to the profile and outcomes of the patient in question and was not directly related to the previous step of follicular development. Pergoveris was only indicated for the follicular development and the fertilisation process that followed was independent from this follicular development process.

Merck noted that by the wording of the licensed indication there was no limitation on the number of follicles that were developed. Indeed, depending on the individual patient, there might be a need to develop more than one follicle. Section 4.2 of the SPC stated that 'treatment should be tailored to the individual patients' response' and went on to describe the possibility and need for the adjustment of the dose of Pergoveris based on patient characteristics and response and implied that the physiological response to stimulation could vary, resulting in the development of more than one Graafian follicle. Furthermore, Section 4.6 of the SPC acknowledged the use of Pergoveris for infertility, with again nothing to exclude treatment in IVF or other ART methodologies. This emphasised that Pergoveris played a role in the follicular stimulation and did not dictate use of any one fertilisation process that followed.

The first slide referred to by the complainant, referenced Buhler *et al*, 2012, a retrospective study of matched groups of women who had received previous cycles of ART but required further treatment. The patient population was matched in terms of number of previous failed ART cycles, age, body mass index and diagnosis, depending on the patient profile and needs, followed by an ART procedure, which could be either IVF or intracytoplasmic sperm injection (ICSI). Due to its observational nature and population size, the study gave important insights into options in real world practice. Nothing in the study was inconsistent with the licensed indication of Pergoveris, as the exogenous gonadotrophins were used only in the follicular development phase, in a defined patient population. In fact, the study showed that, following the use of Pergoveris in the follicular development phase (as per the licensed indication of the product), several MAR methods could be used, including IVF.

Merck strongly disagreed with the allegation that the case study that was discussed in the meeting referred to off label promotion. The patient in the case study had had a previous cycle of IVF but did not get the expected treatment response (sub-optimal response), showing possibly ovarian hyposensitivity related to polymorphisms in the gonadotrophin receptors. Further details were then discussed about the patient case study to explore what the potential root causes of the problem could be, and what treatment options could be available for the following cycle(s), that could result in a different response. When this case study was reviewed in full over slides 12 to 16, the case identified that the patient was severely LH & FSH deficient (Poseidon Group 1, slide 16) and therefore could be a potential candidate for future treatment with Pergoveris, to optimise follicular stimulation.

Based on these facts Merck believed that the promotion of Pergoveris at this meeting was in line with the SPC and there had been no breach of Clause 11.2. The information shared in the presentation fully complied with Clause 6.1 and high standards had been maintained in accordance with Clause 5.1. Therefore, Merck did not believe that it had acted in breach of the Code, particularly Merck had not breached Clause 2.

2 Alleged provision of information that was not sufficiently complete

Merck responded to each of the four points raised by the complainant in relation to the slide from the Carone *et al* 2012 study.

a) The complainant stated that the slide did not mention that the 'sample size was not calculated according to a power analysis'. Viewers should have been made aware that the sample size might not be sufficiently large to demonstrate difference between treatment groups.

Merck stated that the patients in this study were patients with World Health Organisation (WHO) type 1 hypogonadotropic anovulation. Such patients represented a rare group of patients with a congenital disorder that resulted in absent or decreased function of the gonads. The numbers of patients enrolled in this study were clearly outlined in bullet point 1 of the slide in question, with 18 and 17 patients in each treatment group. With such small numbers of patients in the study clearly stated and the fact that these were known to the community to be a rare group of patients, Merck submitted that viewers would be aware that this was a limitation of this study.

b) The complainant then stated that the slide did not clarify that the result was a combined figure of three cycles and that there was no significant difference between the 2 groups for each individual cycle.

Merck submitted that the study population was clearly and prominently set out in the first bullet point on the slide. The overall summary results were also set out there, with the graphs below giving further details. The Carone study 2012 (page 997) clearly showed the enrolment diagram, which showed that analysis was conducted on all of the patients randomised, not by the groups that received different numbers of cycles. The slide therefore presented data that was fully in line with what was reported in the study. Therefore, Merck disagreed that the point made by the complainant was of relevance.

c) The complainant further stated that the slide did not state the author's conclusion from Series C: 'the two groups were limited in terms of patients and the results gained should be considered absolute rather than for any statistical significance'. The audience should have been made aware that if the sample size for this Series was limited, then combining the results with the other 2 Series could potentially produce erroneous results.

Merck submitted that the patient numbers had been clearly shown on the slide in bullet point 1, together with the fact that this study did not meet its primary endpoint (in large clear text) – bottom right-hand side of the slide. When results data were presented in Carone 2012 paper (page 998), the primary endpoint clearly referred to all patients, which was as the data were presented. The paper discussed subgroups and text in the paper referred to Series A, B & C referring to groups of patients that had different clinical

features, however, given the primary endpoint was not met, drawing conclusions from smaller groups, as the complainant had, was not scientifically robust, which was why the speaker did not present such data. Therefore, Merck believed that the data presented reflected those of the study and that the viewer had enough information to be able to form an opinion of the statistical validity of the study results.

d) The complainant finally stated that the study did not appear to have had a washout period between cycles. This could mean that the results of Series 2 and 3 could be impacted by outcomes of Series 1 and this impact might differ depending upon the treatment. The absence of a washout period in this study should have been made clear to viewers.

Merck submitted that the complainant seemed to have formed an opinion here that was not borne out of the clinical paper. The slide did not present information regarding the specific nature of washout periods, because there was no reference to washout periods in the publication. Furthermore, the complainant was again trying to break down the small study population into even smaller groups which made any further meaningful interpretation difficult. The data and text presented by the speaker communicated the key challenges of the study – namely the rare population, small patient population enrolled into the study and the fact the study did not meet the primary objective. Merck submitted that the viewer would be able to draw their own conclusions about how representative it was to be informing clinical practice.

In addition, the slide did not try to make any statistical comparisons between the treatment groups, other than those made by the author on the graph within the slide. The data was faithfully adapted and represented from Carone *et al* 2012 and the text represented the authors testimony.

Merck submitted that there was no breach of Clause 6.1 as the data was sufficiently complete to enable the recipient to be able to form their own opinion of the therapeutic value of the medicine, and no breach of Clause 6.2 as the information presented was faithfully reproduced and capable of substantiation and was not misleading, therefore Clause 14.1 was not breached.

Merck stated that the slide presentation (GB-PER-00021) was certified in accordance with the requirements of the Code; the certificate and the approval route-map were provided. The route map showed that the presentation was certified for use by a qualified medical signatory, in line with the requirements of the Code at 15.53 on 20 July 2021. Despite some last-minute changes that were made by the speaker, the presentation was approved just before it was scheduled to commence at 15.55. The final certificate for the job was generated by Merck's system two days later, on the 22 July. This was because Merck's standard operating procedure (SOP) required a second signatory to also certify the job. Therefore, although company process could not be fully adhered to on this occasion, the presentation was approved in compliance with the requirements set out in the Code.

PANEL RULING

1 Alleged off-label promotion of Pergoveris (300 IU + 150 IU)/0.48 mL solution for injection in pre-filled pen)

The Panel noted the complainant's allegation that a slide presented during a Merck promotional e-symposium referred to the use of Pergoveris in association with IVF which was off-label

promotion, as IVF was not included in the Pergoveris SPC. The complainant also provided a slide with a case study and alleged that its reference to IVF had the potential to mislead the audience with regard to Pergoveris' indication.

The Panel noted that, according to its SPC (section 4.1), Pergoveris was indicated for the stimulation of follicular development in adult women with severe LH and FSH deficiency. In clinical trials, these patients were defined by an endogenous serum LH level < 1.2 IU/L. Section 4.6 stated Pergoveris was indicated for use in infertility and referred readers to Section 4.1.

Section 4.2 (Posology) of the Pergoveris SPC stated, *inter alia*, that in LH and FSH deficient women (hypogonadotrophic hypogonadism), the objective of Pergoveris therapy was to develop a single mature Graafian follicle from which the oocyte would be liberated after the administration of human chorionicgonadotrophin (hCG). It further stated that Pergoveris should be given as a course of daily injection and when an optimal response was obtained, a single injection of 250 micrograms of r-hCG or 5,000 IU to 10,000 IU hCG should be administered 24-48 hours after the last Pergoveris injection. The patient was recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination (IUI) might be performed. Section 4.2 further stated that if an excessive response was obtained, treatment should be stopped and hCG withheld and treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle. Further, Section 4.4 stated that if signs of ovarian hyperstimulation syndrome (OHSS) occurred such as serum oestradiol level > 5,500pg/mL or > 20,200 pmol/L and/or ≥ 40 follicles in total, it was recommended that hCG be withheld and the patient be advised to refrain from coitus or to use barrier contraceptive methods for at least 4 days and in patients undergoing induction of ovulation, the incidence of multiple pregnancies and births was increased compared with natural conception. To minimise the risk of multiple pregnancy, careful monitoring of ovarian response was recommended. The patients should be advised of the potential risk of multiple births before starting treatment. When risk of multiple pregnancies was assumed, treatment discontinuation should be considered. The Panel noted that the SPC made no reference to IVF in this regard nor anywhere in the SPC including that it was contraindicated or not advised.

The Panel noted Merck's submission that follicular development using exogenous gonadotrophins was the first step of a controlled ovarian stimulation process which was followed by fertilisation. According to Merck, oocyte fertilisation could then occur in many ways, such as natural methods (coitus) or methods that were part of a wider strategy of medically assisted reproduction technologies (MAR), which included techniques such as intrauterine insemination (IUI) and procedures using assisted reproductive technologies (ART), which included in-vitro fertilisation (IVF). The Panel further noted Merck's submission that the preferred method of fertilisation was a decision independently discussed and agreed between a clinician and their patient based on several factors tailored to the profile and outcomes of the patient in question and was not directly related to the previous step of follicular development. Pergoveris was only indicated for the follicular development and the fertilisation process that followed was independent from this follicular development process.

The Panel noted that Clause 11.2 stated that the promotion of a medicine must be in accordance with the terms of its marketing authorisation and must not be inconsistent with the particulars listed in its SPC. In the Panel's view, it was not necessarily unacceptable to promote a medicine using data that were not listed in its SPC as long as such data was not inconsistent with the particulars listed in the SPC.

The Panel noted that slide 3 of the symposium presentation included the indication for Pergoveris. In the Panel's view, the complainant had not established that reference to IVF within the presentation was inconsistent with the particulars listed in the Pergoveris SPC and no breach of Clause 11.2 of the 2021 Code was ruled.

The Panel noted Merck's submission that the patient in the case study referred to by the complainant had had a previous cycle of IVF but did not get the expected treatment response, showing possible ovarian hyposensitivity related to polymorphisms in the gonadotrophin receptors. Further details were then discussed about the patient case study to explore what the potential root causes of the problem could be, and what treatment options could be available for the following cycle(s), that could result in a different response. When the case study was reviewed in full over slides 12 to 16, the case identified that the patient was severely LH & FSH deficient and therefore could be a potential candidate for future treatment with Pergoveris, to optimise follicular stimulation. The Panel noted its comments above and did not consider that the complainant had established that inclusion of the case study that made reference to IVF would mislead the audience with regard to the correct indication for Pergoveris as alleged. The Panel further noted that Pergoveris' indication was included on slide 3 of the presentation. The Panel therefore ruled no breach of Clause 6.1 of the 2021 Code.

The Panel noted its comments and rulings above and did not consider that Merck had failed to maintain high standards and no breach of Clause 5.1 of the 2021 Code was ruled. The Panel consequently ruled no breach of Clause 2.

2 Alleged provision of information that was not sufficiently complete

The Panel noted that the slide at issue referenced to Carone *et al* 2012 was headed 'Improved pregnancy rates in r-hFSH+ r-hLH compared to hMG-HP in hypogonadotropic hypogonadism patients'. Below this were four bullet points namely: 18 patients received 150 IU hMG-HP and 17 patients received 150 IU r-hFSH/75 IU r-hLH; Ovulation was induced when the leading follicle was >17mm; In the r-hLH group, 15/17 (88%) patients became pregnant after 27 stimulation cycles; and In the hMG-HP group, a total of 43 cycles were needed to achieve 10 pregnancies in 18 women (56%). Below this was a prominent bar chart showing the number of pregnancies and number of total cycles for each of the two treatment groups along with an image showing the % pregnancy rate/number of cycles ($p<0.05$), LH IU required ($p<0.01$) and number of follicles >17mm for each group. In the bottom right-hand corner of the slide, in the same size and colour font as the bullet points described above, it stated 'Please note the primary end point (ovulation induction) was not met in this study'.

The Panel noted that Carone *et al* detailed a 2-arm randomised, open-label study which enrolled 35 hypogonadotropic hypogonadism women (aged 25-36 year: 30.4±3.78) attending the Center of Reproduction and Andrology (CREA) in Italy between July 2008 and November 2011 and fulfilled certain criteria to compare the efficacy of human recombinant FSH (r-hFSH) plus human recombinant LH (r-hLH) in a 2:1 ratio with highly purified human menopausal gonadotropin (hMG-HP) urinary extract, containing LH-like activity, in women with hypogonadotropic hypogonadism. Considering that WHO type I hypogonadotropic anovulation was a rare alteration of the reproductive system, it was decided to include in the study all patients affected by this condition who approached the center during the enrolment period. The sample size was not calculated according to power analysis. Patients received gonadotropin treatment for a maximum of 16 days and ovulation was induced by a single administration of hCG on the day after the last hMG-HP or r-hFSH/r-hLH. The study's primary efficacy endpoint

was the induction of ovulation, measured as follicular development, and defined by the following three parameters (all of which were to be fulfilled): 1) at least one follicle with a mean diameter of ≥17 mm; 2) pre-ovulatory serum E2 level of ≥400 pmol/l; and 3) mid-luteal phase serum P4 level of ≥25 nmol/l. Secondary efficacy end-points included E2 levels/follicle at mid-cycle, number of follicles at mid-cycle and pregnancy rate (PR). Following a total of 70 cycles, 70% of r-hFSH/r-hLH treated patients met the primary endpoint vs 88% in hMG-HP group (p=0.11). However, pregnancy rates in r-hFSH/r-hLH group was 55.6% compared to 23.3% in hMG-HP group (p=0.01). The primary endpoint achievement did not correlate with pregnancy rate. The study showed the superiority of LH compared to hCG in supporting FSH-induced follicular development in hypogonadotropic hypogonadism (HH)] women.

Whilst the Panel noted that the slide at issue did not state that the sample size was not calculated according to a power analysis, it noted the small numbers of patients in each treatment arm were clearly stated in the first bullet point of the slide; the Panel further noted Merck's submission that the fact the patients in the study were patients with World Health Organisation (WHO) type 1 hypogonadotropic anovulation which were known to the community to be a rare group of patients, viewers would be aware that the sample size was a limitation of the study.

The Panel did not consider that the complainant had established that in not stating that the sample size was not calculated according to power analysis, meant that the audience had not been provided with sufficient information with regard to the sample size to enable them to form their own therapeutic value of this medicine and based on those very narrow allegations, the Panel ruled no breach of Clauses 6.1, 6.2 and 14.1 in relation to each allegation.

The Panel noted that according to the Carone *et al* study protocol, patients were initially treated for one cycle (Series A). If consenting, patients who did not become pregnant during the first cycle were treated for a further optional one (Series B) or two series (Series C) of cycles, with the same criteria of randomisation, ie maintaining the same treatment as the previous cycle.

The Panel noted Merck's submission that the paper discussed subgroups and referred to Series A, B and C which included groups of patients that had different clinical features. The Panel further noted Merck's submission that given the primary endpoint was not met, drawing conclusions from smaller groups, as the complainant had, was not scientifically robust, which was why the speaker did not present such data; the data presented reflected those of the study and the reader therefore had enough information to be able to form an opinion of the statistical validity of the results.

The Panel noted that according to Carone *et al*, the primary efficacy analysis was done including all patients who received at least one dose of the study medicine.

Efficacy assessment of the secondary endpoints included that during the first cycle of treatment on 35 patients (Series A), 4/18 pregnancies occurred in the hMG-HP group and 10/17 in the r-hFSH/r-hLH set (hMG-HP 22%; r-hFSH/r-hLH 58%; p=0.06). Pregnancy rate was not statistically different between hMG-HP and r-hFSH/r-hLH although a clear trend was observed. All four clinical pregnancies in the hMG-HP group and nine of the ten in the r-hFSH/r-hLH group resulted in live birth, following one spontaneous abortion before 12 weeks. There was one multiple pregnancy in the hMG-HP group and two in the r-hFSH/r-hLH group (bigeminal). The patient that suffered a spontaneous abortion in Series A did not accept to have a further cycle of

treatment. No statistical difference between the two groups was observed for total follicles number, E2/follicle and P4 level and endometrial thickness at mid-luteal phase.

In Series B, the fourteen patients from the hMG-HP group who did not become pregnant during Series A were treated for a second cycle and similarly the seven patients from the r-hFSH/r-hLH group. No significant difference in terms of pregnancy rate was observed although a trend in favour of the recombinant preparation was maintained (hMG-HP 28.6%; r-hFSH/r-hLH 57.1%; p=0.42). Both treatments produced four pregnancies, but the hMG-HP group showed one spontaneous abortion and one multiple pregnancy. The patient who suffered an abortion in the hMG-HP group chose to continue her participation in the last series.

Finally, ten patients who did not become pregnant in Series B and the one who suffered an abortion were treated with hMG-HP and three with r-hFSH/r-hLH in the third series of cycles (Series C). Carone *et al* stated that the two groups were limited in terms of patients and the results gained should be considered in absolute value rather than for any statistical significance, nevertheless, the statistical analysis was performed. Pregnancy rate was 18.2% in the hMG-HP group and 33.3% in the r-hFSH/r-hLH group. In this third series, hMG-HP group presented one multiple pregnancy.

The Panel further noted that Carone *et al* included the overall evaluation of Series A, B and C which showed that pregnancy rate in the r-hFSH/r-hLH group was 55.6% (15/27) compared to 23.3% (10/43) in the hMG-HP group ($p<0.05$) showing a significant difference in favour of the recombinant gonadotropin preparation. Considering the study design, with each patient having access to three treatment cycles to achieve pregnancy, a pregnancy rate of 23.3% in the hMG-HP group appeared low as it reflected a total of 43 cycles on 18 patients. In the r-hFSH/r-hLH group, there was clearly more success in terms of pregnancy rate as 17 patients needed only 27 stimulation cycles to get a pregnancy rate of 55.6%. On evaluating the pregnancy rate for each patient included in the study, the difference was even further increased, 15 out of 17 patients became pregnant in the r-hFSH/r-hLH group (88%) whereas only 10 out of 18 (55%) did in the hMG-HP. This difference, although just outside statistical significance, due to the sample size (p=0.07), showed an evident trend. hMG-HP group produced significantly more follicles (p=0.007) but resulted in fewer pregnancies. Carone *et al* noted that the amount of LH used in the hMG-HP group was significantly higher than in the r-hFSH/r-hLH set ($p<0.001$). Considering that the LH activity present in the hMG-HP was generated by u-hCG, it seemed that r-hLH was effectively more efficient than u-hCG when the same amount of LH labelled IU was used. The results in Series A showed that only two patients in the hMG-HP group (11%) met both the primary and secondary (PR) endpoints and eight in the r-hFSH/r-hLH group (47%) (p=0.04). A similar ratio between the two sets was also achieved in Series B (hMG-HP 28%; r-hFSH/r-hLH 42%; p=0.87). Considering the overall analysis on 70 cycles, only 18% (n=8/43) in hMG-HP group and 40% (no.=11/27) in the r-hF-SH/r-hLH one fulfilled both criteria (p=0.07).

Whilst the Panel considered that it would have been helpful to include further details of the study, it noted Merck's submission that the overall summary results were set out in the bullet points on the slide with the graphs below giving further details. The Panel further noted Merck's submission that in the Carone *et al*, 2012 study, analysis was conducted on all of the patients randomised, not by the groups that received different numbers of cycles and the slide therefore presented data that was fully in line with what was reported in the study. In the Panel's view, the complainant had not established that in failing to clarify that the results was a combined figure of three cycles and that there was no significant difference between the 2 groups for each individual cycle, meant that the slide was misleading as the audience had not been given

sufficient information to enable them to form their own therapeutic value of the medicine as alleged and based on the narrow allegation, the Panel ruled no breach of Clauses 6.1, 6.2 and 14.1.

Nor did the Panel consider that in failing to refer to the author's conclusion from Series C that the two groups were limited in terms of patients and that the results gained should be considered absolute rather than for any statistical significance, and for not making the audience aware that if the sample size for this Series was limited, then combining the results with the other 2 Series could potentially produce erroneous results meant that the slide was misleading as the audience had not been given sufficient information to enable them to form their own therapeutic value of the medicine as alleged. Based on the narrow allegation, the Panel ruled no breach of Clauses 6.1, 6.2 and 14.1.

Further, the Panel noted that patients were initially treated for one cycle (Series A). If consenting, patients who did not become pregnant during the first cycle were treated for a further optional one (Series B) or two series (Series C) of cycles, with the same criteria of randomisation, ie maintaining the same treatment as the previous cycle. The Panel noted its comments above and did not consider that the complainant had established that failing to refer to the absence of a washout period in the study was misleading as alleged and, based on the narrow allegation, the Panel ruled no breach of Clauses 6.1, 6.2 and 14.1.

Complaint received **22 October 2021**

Case completed **27 July 2022**