ANONYMOUS v MERCK SERONO

Promotion of Pergoveris

An anonymous, non-contactable complainant alleged that Merck Serono had encouraged its representatives to promote Pergoveris (follitropin alfa and lutropin alfa for injection) outwith its licence.

The complainant referred to two emails sent to the fertility team. The complainant stated that the first email asked the team to identify clinics that used Menopur [marketed by Ferring Pharmaceuticals Ltd] in *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles because the doctor believed in the need for luteinizing hormone (LH). The second email told the team members that they must target these IVF/ICSI cycles for use with Pergoveris. The complainant noted that Pergoveris was indicated to produce monofollicular development.

The detailed response from Merck Serono is given below.

The Panel noted that the first email referred to studies and the role of LH in improving pregnancy rates in some patients. The data suggested that LH addition was not beneficial for the unselected population but was beneficial in poor responders to FSH alone. The data for adding LH in patients over 35 was also not convincing. The email requested estimates regarding the proportion of hMG cycles that were being prescribed predominately due to belief in the positive effect of LH. This was to better target efforts with Pergoveris.

The second email referred to the need to target cycles where Menopur (hMG) was used primarily due to its LH activity leading to the use of Pergoveris in these cycles. It asked the team to focus activities on, *inter alia*, establishing Pergoveris as the recombinant alternative to u-hMG in patients who needed LH.

It appeared to the Panel from their respective summaries of product characteristics (SPCs) that there were differences between the products. Pergoveris was only indicated for use in 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 objective of Pergoveris therapy was to develop one follicle. Conversely there was no mention of the LH and FSH profiles for women being treated with Menopur and it could be used to induce multiple follicular development.

The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The complainant could not be contacted for further information. The complainant had not provided the emails which were the subject of the complaint. Merck Serono had found one and the other was of a different date to that cited by the complainant. It was not possible to ascertain whether this was indeed the email referred to by the complainant.

The Panel considered that the second email was not sufficiently clear about the differences between the products and the fact that not every patient prescribed Menopur would be suitable for Pergoveris. Pergoveris patients had to be severely LH and FSH deficient. Nonetheless, the Panel did not consider that there was sufficient evidence to show that Pergoveris had been promoted outside its marketing authorization as alleged nor had Merck Serono failed to maintain a high standard and thus no breach of the Code was ruled.

An anonymous, non-contactable complainant raised concerns about the promotion of Pergoveris (follitropin alfa and lutropin alfa for injection) by Merck Serono Limited.

COMPLAINT

The complainant asked the Authority to consider two emails sent to the fertility team on 23 May 2008 and 26 June 2008.

The complainant stated that the first email asked the team to identify clinics that used Menopur [marketed by Ferring Pharmaceuticals Ltd] in *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles because the doctor believed in the need for luteinizing hormone (LH). The second email told the team members that they must target these IVF/ICSI cycles for use with Pergoveris.

The complainant alleged that this was outside the licence for Pergoveris as it was indicated to produce monofollicular development.

When writing to Merck Serono the Authority asked it to respond in relation to Clauses 3.2 and 9.1 of the Code.

RESPONSE

Merck Serono submitted that the complainant was incorrect to state that Pergoveris was indicated for monofollicular development. The summary of product characteristics (SPC) stated 'Pergoveris is indicated for the stimulation of follicular development in women with severe LH and FSH

[follicule stimulating hormone] deficiency. In clinical trials, these patients were defined by an endogenous serum LH level <1.2IU/L'.

Prior to the launch of Pergoveris clinicians had two options to treat infertile patients with severe LH and FSH deficiency. They could use urinary derived hMG (u-hMG) or a combination of recombinant FSH and recombinant LH. The majority of these patients were treated with u-hMG as treatment could be given in a single daily injection. Pergoveris (fixed combination of 150 IU recombinant FSH and 75 IU LH) was also dosed in a single daily injection making it a logical alternative to u-hMG in patients with severe FSH and LH deficiency.

The email of 23 May 2008 asked the fertility sales team to identify fertility clinics where prescribers believed that LH supplementation was beneficial in follicular development in assisted reproduction. The team was asked to do this because prescribers that believed in the benefits of LH supplementation were likely to be interested in using Pergoveris in patients with FSH and LH deficiency. The team was also asked to quantify the number of cycles currently performed in each of these units where LH deficiency drove product choice. This was done to help them prioritise clinics where LH supplementation belief was strongest. Both these requests were consistent with the licensed indication for Pergoveris and the email did not ask the sales team to promote Pergoveris outside this indication. The email asked the team members to contact the sender if they were not clear about what they were being asked to do. All members of the team provided data in line with the request without asking for further clarification.

Merck Serono could not find an email of 26 June which matched the description outlined in the complaint but an email of 20 June might be the one referred to by the complainant although Merck Serono could not be certain.

The 20 June email aimed to clarify the sales team's objectives for the second half of 2008. One of these was to target prescribers at the clinics identified as a result of the email sent on 23 May 2008 so as to establish Pergoveris as the recombinant alternative to u-hMG in LH deficient patients. This request was consistent with the licensed indication for Pergoveris and the email did not ask the sales team to promote Pergoveris outside this indication.

In conclusion Merck Serono submitted that there had been no breach of Clauses 9.1, 3.2 or 2 of the Code.

In response to a request for further information Merck Serono referred to the licensed indication for Menopur and stated that severely LH deficient women might be candidates for either Menopur or Pergoveris.

The fertility sales team had received training from the launch of the product which emphasised the licensed indication. The initial launch presentation showed the indication on the front page and prominently in the conclusions; both reiterated that Pergoveris was limited to those women with 'severe LH and FSH deficiency'. The presentation was accompanied by two paper based materials. The product monograph gave a factual account of the trials used to support the product licence and included a copy of the SPC. The points at which the licence was emphasised were highlighted throughout the document. The sales aid supported the importance of LH and also contained the licensed indication. Both documents had been used since launch to support the key data around Pergoveris and remind the sales team of the appropriate indication.

At a meeting in July the sales team was updated on new scientific data in the morning, given an overview of sales results and shared best practice in the afternoon. The morning's discussion centred around a clinical study (Shoham *et al* 2008) on the use of recombinant LH in women with profound LH deficiency. This paper supported the use of a combination of 75 IU recombinant LH (Luveris) and 150 IU recombinant FSH (Gonal-f) in inducing follicular development in women with profound LH deficiency. The data from this study was within the licensed indication of Pergoveris and was accompanied by a briefing document which stated this fact.

In the afternoon, each member of the sales team was given the opportunity to update others on the uptake of Pergoveris at their fertility clinics. A discussion then followed on how best to increase its use by clinicians in women who were severely LH deficient. No new presentations on Pergoveris were given at this meeting. The meeting concluded with an opportunity for team members to air their views on issues they believed should be addressed in the 2009 marketing plan.

In summary, although the indications of Menopur and Pergoveris differed, the use of Menopur by a centre would indicate that it was more likely to recognise the benefits of LH as part of follicular stimulation. Therefore, identifying these centres would allow the sales team to target its efforts in the most appropriate way. This did not negate the guidance given to the sales team to promote Pergoveris within these centres only within the licensed indication which was reiterated in all materials.

PANEL RULING

The Panel noted that Pergoveris was indicated for women with severe LH and FSH deficiency. The SPC stated 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 chorionic gonadotrophin (hCG).

The Panel noted that the 23 May email referred to studies and the role of LH in improving pregnancy rates in some patients. The data suggested that LH addition was not beneficial for the unselected population but was beneficial in poor responders to FSH alone. The data for adding LH in patients over 35 was also not convincing.

The Panel noted that the 23 May email requested estimates regarding the proportion of hMG cycles that were being prescribed predominately due to belief in the positive effect of LH. This was to better target efforts with Pergoveris.

The 26 June email referred to the need to target cycles where Menopur (hMG) was used primarily due to its LH activity leading to the use of Pergoveris in these cycles. It asked the team to focus activities on, *inter alia*, establishing Pergoveris as the recombinant alternative to u-hMG in patients who needed LH.

The Panel noted that the SPC for Menopur gave a number of indications for the product which included use in women undergoing superovulation to induce multiple follicular development in patients undergoing an assisted conception technique. The SPC for Menopur also recommended that there should be at least 3 follicles greater than a defined size.

It appeared to the Panel from their respective SPCs that there were differences between the indications and uses of Pergoveris and Menopur. Pergoveris was only indicated for use in 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 objective of Pergoveris therapy was to develop one follicle. Conversely there was no mention of the LH and FSH profiles for women being treated with Menopur and it could be used to induce multiple follicular development.

The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The complainant was anonymous and non-contactable. It was thus not possible to go back for further information. The complainant had not provided the emails which were the subject of the complaint. Merck Serono had found one and the other was of a different date to that cited by the complainant. It was not possible to ascertain whether this was indeed the email referred to by the complainant.

The Panel considered that the email dated 26 June was not sufficiently clear about the differences between the products and the fact that not every patient prescribed Menopur would be suitable for Pergoveris. Pergoveris patients had to be severely LH and FSH deficient. Nonetheless, the Panel did not consider that there was sufficient evidence to show that Pergoveris had been promoted outside its marketing authorization as alleged. Thus no breach of Clause 3.2 was ruled. The Panel did not consider that Merck Serono had failed to maintain a high standard and thus no breach of Clause 9.1 was also ruled.

Complaint received **16 December 2008**

Case completed **27 January 2009**