**CASE AUTH/2885/11/16**

# ANONYMOUS, NON-CONTACTABLE v GEDEON RICHTER

## Esmya patient support leaflet

**An anonymous, non-contactable complainant, who described him/herself as a senior grade doctor in obstetrics and gynaecology, complained about a patient support leaflet for Esmya (ulipristal acetate) produced by Gedeon Richter. Esmya was indicated for the pre-operative or intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.**

**The complainant noted that the leaflet advised patients to use an alternative contraceptive method to 'oral hormonal contraception' whilst taking Esmya due to an interaction that would influence the efficacy of both medicines. The leaflet did not refer to other widely used hormonal methods such contraceptive injections etc; the complainant noted that any type of hormonal contraceptive, regardless of delivery route, would interfere with the efficacy of Esmya and more worryingly, contraception. Patients could thus potentially conceive whilst taking Esmya; the patient support leaflet should be corrected as a matter of urgency in the interest of patient safety.**

**The detailed response from Gedeon Richter is given below.**

**The Panel noted that one of the contraindications listed in Section 4.3 of the Esmya summary of product characteristics (SPC) was 'pregnancy'. Section 4.5, Interaction with other medicinal products and other forms of interaction, stated that hormonal contraceptives and progestogens were likely to reduce the efficacy of Esmya and that Esmya might interfere with the action of hormonal contraceptives (progestogen only, progestogen-releasing devices or combined oral contraceptive pills). The patient support leaflet in question, however, only referred to the inadvisability of taking oral contraceptives whilst on Esmya treatment because the two medicines might interact.**

**The Panel noted Gedeon Richter's submission that as both Esmya and contraceptives had to be prescribed by a health professional, women would be unlikely to receive a prescription for both at the same time. Nonetheless, the Panel considered that given the extreme importance that such concomitant administration did not occur, the failure of the patient support leaflet to alert women to the fact that they should not use any form of hormonal contraception whilst taking Esmya was a serious matter. Although the Esmya package leaflet dealt with the matter, each piece of material should be capable of standing alone. In the Panel's view the statement in the patient support leaflet was inaccurate and misleading. High standards had not been maintained. Breaches of the Code were ruled. In the Panel's view that such a serious and fundamental error existed at all was such as to reduce confidence in the industry being able to produce even simple material to the required quality standards. A breach of Clause 2 was ruled.**

**Gedeon Richter provided the requisite undertaking and assurance and as the case completed at Panel level the Appeal Board received the case report as set out in Paragraph 13.4 of the Constitution and Procedure.**

**The Appeal Board noted the Panel's comments and rulings above. The Appeal Board considered that this case raised serious issues regarding patient safety and was of the view that further sanctions should be imposed under Paragraph 11.1 of the Constitution and Procedure such as the issuing of a corrective statement and recovery of the material from health professionals.**

**The detailed response from Gedeon Richter to the possibility of further sanctions being imposed is given below.**

**The Appeal Board noted its previous comments and that Esmya was likely to be initiated in secondary care when the misleading patient support leaflet would be available for health professionals to give to patients. The Appeal Board considered that when Esmya was initiated it was unlikely that contraception methods would be discussed in any great detail. The Appeal Board noted that there was also the potential that repeat prescriptions for Esmya would be referred to general practitioners. Reading the leaflet, patients might not think to raise that they were using non-oral hormonal contraception and GPs would not necessarily be aware of the incomplete information that their patients might have been given via the patient support leaflet about the use of contraception and Esmya. The Appeal Board noted that whilst the onus was on the GPs to ensure that they prescribed appropriately, women might not necessarily source their contraception from their GP.**

**In accordance with Paragraph 11.3 of the Constitution and Procedure, the Appeal Board decided to require Gedeon Richter to issue a corrective statement to health professionals who had received the leaflets in question. [The corrective statement, which was agreed by the Appeal Board prior to use, appears at the end of this report].**

An anonymous, non-contactable complainant, who described him/herself as a senior grade doctor in obstetrics and gynaecology, complained about a patient support leaflet for Esmya (ulipristal acetate) (ref UK/ESM5/0416/0033) produced by Gedeon Richter (UK) Ltd. Esmya was indicated for the pre-operative or intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

**COMPLAINT**

The complainant explained that the leaflet advised patients to use an alternative contraceptive method to 'oral hormonal contraception' whilst taking Esmya due to an interaction that would influence the efficacy of both medicines. The complainant noted that the leaflet did not refer to other widely used hormonal methods such as the Mirena coil, contraceptive injections etc. The complainant

submitted that any type of hormonal contraceptive, regardless of delivery route, would interfere with the efficacy of Esmya and more worryingly, contraception. This could potentially result in patients becoming pregnant whilst taking Esmya.

The complainant submitted that the mistake was brought to his/her attention by a colleague who assured him/her that Gedeon Richter knew about the error and would take appropriate action. However, the complainant noted that the leaflet was still in circulation.

The complainant strongly recommended that the patient support leaflet was corrected as a matter of urgency in the interest of patient safety.

When writing to Gedeon Richter, the Authority asked it to consider the requirements of Clauses 7.2, 9.1 and 2 of the Code.

**RESPONSE**

Gedeon Richter stated that it took compliance with the Code very seriously. The company regularly trained staff on the Code including most recently a two day meeting in October 2016 for the UK head office staff and senior managers. Further commitment to compliance and high standards was evidenced by the fact that the company still required two signatories (medical signatory and non-medical) to approve all materials before they were used or disseminated.

Gedeon Richter noted that the complainant had taken issue with reference to the need to avoid reliance on 'oral hormonal contraception' rather than referring to all forms of hormonal contraception in that regard in a patient support leaflet. The patient support leaflet which was provided as 50 identical tear off sheets stated: 'You should not take oral contraceptives whilst you are on ESMYA treatment because the two drugs might interact. Ask your healthcare professional if you are not sure'.

Gedeon Richter submitted that the leaflet was electronically certified in May 2016 and the printed version was approved in June; it was first disseminated in July, the associated briefing document having been certified two days previously. A copy of the leaflet was provided, along with the associated briefing document and related certificates. The tear off leaflet was certified for use by health professionals to hand to patients prescribed Esmya so the 'audience' was patients prescribed Esmya but delivery to the patients would be via their health professional. Gedeon Richter submitted that the text on the leaflet itself was very clear as to the audience.

Gedeon Richter stated that when it received the complaint, the leaflet was already in the late stages of revision/certification following customer feedback received via the sales team. The revised version, which addressed the matter now at issue ie reference to 'oral [hormonal] contraception' rather than the broader term 'hormonal contraception', was certified on 4 November 2016. Copies of this revised and certified version and associated briefing document, together with the corresponding certificates, were provided.

Gedeon Richter noted that Clause 7.2 required, *inter alia*, that 'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis'.

Gedeon Richter further noted that the complaint was that 'oral [hormonal] contraception' was inappropriately specific as other forms of hormonal contraception could interact with Esmya to reduce the efficacy of medicines.

Gedeon Richter submitted that it now realised that the wording on the patient support leaflet could potentially cause confusion but emphasised that this was certainly not intended; on the contrary, the company had hoped to simplify language for the patient in order to clearly convey the relevant information. In laymen's terms it was not unusual to use the term oral contraception to cover hormonal contraception in general. Gedeon Richter acknowledged that the outcome had inadvertently caused a misunderstanding which was unfortunate and regrettable. Gedeon Richter submitted that it had already revised the wording in the leaflet and the updated version was now in use following the withdrawal of the previous version which was the subject of this complaint.

Gedeon Richter submitted that the leaflet was the only piece of Esmya patient material it had produced and so the wording in question only appeared in that leaflet.

Gedeon Richter noted that the package leaflet for Esmya, which under the heading 'What you need to know before you take Esmya', clearly stated 'Warnings and precautions: - If you are currently taking hormonal contraception (for example birth control pills) (see "Other medicines and Esmya") you should use an alternative reliable barrier contraceptive method (such as a condom) while taking Esmya'. Gedeon Richter submitted that it was clear that the statement in the patient support leaflet was factually correct but inadvertently did not extend to other forms of hormonal contraception. However the leaflet text did include the clear and prominent statements 'You should not take oral contraceptives whilst you are on ESMYA treatment because the two drugs might interact. Ask your healthcare professional if you are not sure' and 'Further information on Esmya is available in the leaflet inside the product pack'.

Gedeon Richter denied a breach of Clause 7.2 on the basis that the combined information provided by the patient support leaflet, its reference to the package leaflet and that the package leaflet itself provided the information needed for the patient to understand the need for non-hormonal contraception while taking Esmya.

Gedeon Richter noted that in addition to the specific wording cited, the complaint related to the continued use of the patient support leaflet; the complaint was dated 1 November 2016 and referred to the material being in use 'last week'.

Gedeon Richter submitted that it was first made aware of the wording at issue by a health professional on 20 October and steps were then taken to draft a revised version which had now been certified for subsequent distribution. The previous version was withdrawn from use on 4 November.

Gedeon Richter submitted that all of its health professional materials and the prescribing information covered that concomitant hormonal contraceptives were not recommended with Esmya. As all hormonal contraception (oral or other routes) was available by prescription only, no patient would receive hormonal contraception without an interaction with her health professional who would follow due process with regards to checking medicine interactions before prescribing any hormonal contraceptive. Additionally, the patient support leaflet directed the patient to her health professional and/or the package leaflet for further information.

On that basis, Gedeon Richter did not accept that the continued use of the leaflet while its replacement was in preparation, represented an actual risk to patient safety as (a) patients could only obtain hormonal contraception on prescription from a health professional as described above, and (b) all other materials, including those for health professionals, referred to the need to avoid 'hormonal contraception' and not specifically 'oral hormonal contraception'. Gedeon Richter therefore refuted a breach of Clause 9.1.

Gedeon Richter submitted that it acted reasonably and not in a manner which would bring discredit upon, or reduce confidence in, the pharmaceutical industry. It had taken steps to ensure appropriate withdrawal and turnaround of revised materials following external feedback, which was nearing completion on receipt of this complaint.

Gedeon Richter submitted that once the wording was brought to its attention, it was subsequently revised; the previous version of the leaflet was withdrawn as soon as the revised version was certified. All other materials relating to Esmya were checked and no other instance identified where the same wording was used. As access to hormonal contraception was solely via consultation with a health professional, it obviated the possibility that a woman could take hormonal contraception concomitantly with Esmya. Taking this into account, Gedeon Richter submitted that the complainant had not demonstrated that, on the balance of probabilities, patient safety would be compromised by the wording in question.

Based on the company's actions and lack of impact on patient safety as described above, Gedeon Richter denied a breach of Clause 2.

**PANEL RULING**

The Panel noted that one of the contraindications listed in Section 4.3 of the Esmya SPC was 'pregnancy'. Section 4.4, Special warnings and precautions for use, stated that with regard to contraception, concomitant use of progestogen-only pills, a progestogen-releasing intra-uterine device or combined oral contraceptive pills was not recommended. Section 4.5 of the SPC, Interaction with other medicinal products and other forms of interaction, stated that hormonal contraceptives and progestogens were likely to reduce the efficacy of Esmya and that Esmya might interfere with the action of hormonal contraceptives (progestogen only, progestogen-releasing devices or combined oral contraceptive pills). The patient support leaflet in question, however, only referred to the inadvisability of taking oral contraceptives whilst on Esmya treatment because the two medicines might interact.

The Panel noted that the quality standards set out in Clause 7 of the Code for promotional information also applied to information for the public. Clause 7.2 required information, claims and comparisons to be, *inter alia*, accurate and not misleading. The Panel noted Gedeon Richter's submission that as both Esmya and contraceptives had to be prescribed by a health professional, women would be unlikely to receive a prescription for both at the same time. Nonetheless, the Panel considered that given the extreme importance that such concomitant administration did not occur, the failure of the patient support leaflet to alert women to the fact that they should not use any form of hormonal contraception whilst taking Esmya was a serious matter. Although the Esmya package leaflet dealt with the matter, each piece of material should be capable of standing alone. In the Panel's view the statement at issue in the patient support leaflet was inaccurate and misleading. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. In the Panel's view that such a serious and fundamental error existed at all was such as to reduce confidence in the industry being able to produce even simple material to the required quality standards. A breach of Clause 2 was ruled.

**APPEAL BOARD CONSIDERATION OF CASE REPORT**

Gedeon Richter provided the requisite undertaking and assurance and as the case completed at Panel level the Appeal Board received the case report as set out in Paragraph 13.4 of the Constitution and Procedure.

The Appeal Board noted the Panel's comments and rulings above. The Appeal Board considered that this case raised serious issues regarding patient safety. It noted Gedeon Richter's submission that as both Esmya and contraceptives had to be prescribed by a health professional, women would be unlikely to receive a prescription for both at the same time. The Appeal Board was of the view that further sanctions should be imposed under Paragraph 11.1 of the Constitution and Procedure such as the issuing of a corrective statement and recovery of the material from health professionals.

[Post meeting note: Following the Appeal Board meeting the Chairman was asked by the Director to reconsider the process in Paragraph 11 of the Constitution and Procedure regarding the arrangements when the Appeal Board considered imposing additional sanctions in cases which completed at Panel level. The Chairman noted that in such cases the Appeal Board was not provided with all the papers, further the respondent company had no opportunity to put its view or appear before the Appeal Board as it would have done if there had been an appeal or a report from the Panel to the Appeal Board. The Chairman also noted this aspect of the process in Paragraph 11 had not been used previously. In the interests of fairness, the Chairman decided that the company should be advised that the Appeal Board was considering imposing additional sanctions and asked to respond in writing, as well as be given the opportunity to attend the next meeting of the Appeal Board when the matter of sanctions would be considered afresh.]

**COMMENTS FROM GEDEON RICHTER**

Gedeon Richter entirely accepted the Panel's ruling of breaches of Clauses 2, 9.1 and 7.2 of the Code.

The patient support leaflet in question had been withdrawn from use within the required timeline and all relevant staff and third parties briefed as detailed below. Gedeon Richter sincerely regretted the error and accepted the sanctions already placed upon it.

Gedeon Richter submitted that it was committed to abiding by the Code and took its responsibilities under the Code extremely seriously. Gedeon Richter's existing key focus on patient safety and the maintenance of high standards within the industry had sharpened following the Panel's ruling. Gedeon Richter was taking appropriate steps to ensure there was no repetition of this failure.

Gedeon Richter noted that the head office and senior management team had received compliance training in late October 2016 and further compliance training was undertaken in early January 2017 for the entire company including the field force. Training records were provided.

Gedeon Richter submitted that it was placing considerable additional emphasis on its compliance with the Code and was in the process of appointing a compliance and regulatory affairs officer to provide additional support and ensure increased rigour to its processes, training schedules and records maintenance.

Gedeon Richter fully recognised that when its field teams made it aware of the issue, it had not acted quickly enough. Gedeon Richter sincerely regretted that it had not immediately withdrawn the patient support leaflet at issue. A number of factors caused this delay. The increased resource within its compliance team would help to ensure such an unfortunate and regrettable incident, with its attendant consequences for patient safety, did not reoccur.

Gedeon Richter submitted that it had audited and checked all of its current materials to ensure similar wording was not present in any other material and all standard operating procedures (SOPs) had been reviewed and updated. Additional SOP training was ongoing and would be completed by the end of February 2017.

On receipt of the complaint, Gedeon Richter submitted that it had withdrawn the patient support leaflet at issue; details of the actions taken and the number of leaflets destroyed were provided.

Gedeon Richter noted that it had previously provided details of the revised material.

Gedeon Richter submitted that the sales team were instructed verbally to brief customers on the revision to the patient support leaflet and to retrieve the superseded version from customers wherever possible. This direction to the sales team was repeated at a team meeting held in January 2017 with a follow-up email requesting confirmation of these actions. To summarise, the company had withdrawn, amended and replaced the patient support leaflet in question. All relevant staff had been briefed on the complaint, its outcome and ensuing actions including further Code training and roll-out of revised SOPs and policies relating to the Code.

Finally, Gedeon Richter reiterated its sincere regret that the patient support leaflet had been found in breach of the Code; this was entirely unintended and fell far short of the standards by which the company operated. Gedeon Richter recognised the serious nature of the error and had not appealed the ruling but had focussed its energies in upskilling the team and making its processes more robust.

**APPEAL BOARD CONSIDERATION**

The Appeal Board noted the Panel's rulings of breaches of Clauses 2, 7.2 and 9.1 regarding the patient support leaflet which only told women that they should not use oral contraception whilst taking Esmya when in fact they should not use any form of hormonal contraception. The Appeal Board noted that Esmya might interfere with the action of all hormonal contraceptives which were also likely to reduce the efficacy of Esmya. The Appeal Board considered that this case raised serious issues regarding patient safety.

The Appeal Board noted that Esmya was likely to be initiated in secondary care when the misleading patient support leaflet would be available for health professionals to give to patients. The Appeal Board considered that when Esmya was initiated it was unlikely that contraception methods would be discussed in any great detail. The Appeal Board noted that there was also the potential that repeat prescriptions for Esmya would be referred to general practitioners. Reading the leaflet, patients might not think to raise that they were using non-oral hormonal contraception and GPs would not necessarily be aware of the incomplete information that their patients might have been given via the patient support leaflet about the use of contraception and Esmya. The Appeal Board noted that whilst the onus was on the GPs to ensure that they prescribed appropriately, it noted that women might not necessarily source their contraception from their GP.

In accordance with Paragraph 11.3 of the Constitution and Procedure the Appeal Board decided to require Gedeon Richter to issue a corrective statement to health professionals who had received the leaflets in question. [The corrective statement, which was agreed by the Appeal board prior to use, appears at the end of this report].

**Complaint received** **2 November 2016**

**Undertaking received** **6 December 2016**

**Appeal Board consideration 11 January and 9 February 2017**

**On 30 March 2017, Gedeon Richter sent the following corrective statement to relevant hospital doctors**

**'Corrective statement**

Between July and November 2016, a patient support leaflet for Esmya (ulipristal acetate) (ref UK/ESM5/0416/0033) produced by Gedeon Richter (UK) Ltd was circulated. Esmya is indicated for the pre-operative or intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

You are being sent this corrective statement because you may have received the Esmya patient support leaflets to pass on to your patients when you prescribed them Esmya.

Following a complaint under the ABPI Code of Practice for the Pharmaceutical Industry, the Code of Practice Panel ruled that the patient support leaflet was inaccurate and misleading in that it only told the woman that she should not take oral contraceptives whilst on Esmya whereas she should have been told not to use hormonal contraceptives whilst taking Esmya. The Panel ruled that Gedeon Richter had failed to maintain high standards and had brought discredit upon and reduced confidence in the pharmaceutical industry. As a result of the above and concerns about patient safety, the Code of Practice Appeal Board has required Gedeon Richter to issue this corrective statement and to circulate a copy of the published report for the case which contains full details. This is enclosed.

If you have any remaining copies of the above patient support leaflet please dispose of them.

In addition, where relevant, please draw this issue to the attention of any GP to whom you might have referred patients for repeat prescriptions of Esmya.

Details of this case (Case AUTH/2885/11/16) are also available on the PMCPA website (www.pmcpa.org.uk).'