CASE AUTH/2834/4/16

TAKEDA v AMDIPHARM MERCURY

Promotion of Lutrate

Takeda UK complained about a Lutrate (leuprorelin acetate depot injection) promotional email (ref AMCo/LUT/1115/0027) sent by Amdipharm Mercury Company (AMCo) to health professionals and budget holders in the NHS about the availability of a new formulation of leuprorelin with the potential for cost savings to the NHS.

The detailed response from AMCo is given below.

Takeda alleged that AMCo had falsely implied that Lutrate and Prostap DCS were interchangeable and could be used for the same indications in prostate cancer. Lutrate had a much narrower licensed indication which Takeda alleged could lead to patients being prescribed Lutrate inappropriately. This was promotion outside the marketing authorization and only a limited number of Prostap DCS patients would be eligible for Lutrate. The email was likely to lead GP practices to overestimate the cost savings they could achieve by using Lutrate in place of Prostap DCS which was alleged to be misleading and did not encourage rational use.

The Panel noted that Prostap and Lutrate were both leuprorelin depot injections and in the Panel's view, the email implied that the two medicines were interchangeable. The Panel noted however that the indications for Prostap were broader than those for Lutrate. The Panel did not accept that the differences in indication were made clear. The impression was that the only difference between the medicines was the cost. No detail had been provided regarding the cost comparison but it again implied the products were interchangeable, ie Lutrate could be used whenever Prostap was used. This was not so. The Panel considered that the impression from the cost comparison and a poll was that Lutrate and Prostap were interchangeable. This was inconsistent with the Lutrate SPC and the Panel ruled a breach of the Code. This impression was not negated by the use of the term 'for eligible patients'.

Neither Takeda nor AMCo provided details about the basis of the cost comparison, the number of patients and what proportion of patients could be changed from Prostap to Lutrate. The impression was that all Prostap patients could be changed to Lutrate which was not so. The Panel considered that the claims for cost savings were misleading and did not promote the rational use of Lutrate as alleged and breaches of the Code were ruled.

Further only efficacy data regarding Lutrate's testosterone suppression was included with no balance of safety information regarding common adverse events or withdrawals due to adverse events which was alleged to be an unbalanced view of the evidence.

The Panel noted that there was no mention of adverse events in the body of the email. The only information about common adverse events or withdrawals due to adverse events was in the prescribing information. The Panel did not consider that this necessarily meant that the email was an unbalanced view of the evidence as alleged. It noted that the material at issue was not lengthy and that leuprorelin was not a new medicine, the formulation was new. The SPC stated that most of the treatment related adverse events reported were mainly subject to the specific pharmacological action of leuprorelin and associated with testosterone suppressing therapy. Local adverse reactions reported after injection were similar to those with similar products administered via intra-muscular [injection]. The email did not state nor imply that there were no adverse events etc. The Panel did not consider that the email was unbalanced as alleged and ruled no breach of the Code.

Takeda further alleged that the claim 'A novel leuprorelin formulation to maintain effective testosterone suppression' was misleading and disparaging since it implied that Lutrate offered some advantage over other leuprorelin formulations in terms of testosterone suppression. This had never been established.

The Panel considered that the claim 'Novel formulation to maintain effective testosterone suppression' implied that the novel formulation maintained testosterone suppression rather than the leuprorelin. Although there was no mention of Prostap in this section as the active ingredients of both medicines was leuprorelin, there was an implication that Lutrate was an improvement over Prostap in relation to maintenance of effective testosterone suppression. The Panel considered that the claim implied a special merit which had not been established and that the claim disparaged other formulations of leuprorelin. Breaches of the Code were ruled.

Takeda alleged that the claim 'Lutrate is simple and easy to administer' had not been substantiated and was a hanging comparison. Takeda stated that since Prostap DCS was the obvious alternative treatment for patients eligible for Lutrate, the claim would likely be interpreted by prescribers as indicating that Lutrate was at least as simple and easy to administer as Prostap DCS. No evidence to support this assertion was referenced in the email, or by AMCo during inter-company dialogue. Takeda alleged that administration of Lutrate was, in fact, a more complex process than administration of Prostap DCS.

The Panel noted that the claim 'Lutrate: simple and easy to administer' was followed by 8 illustrations

of the steps needed to prepare the medicine and the injection area for administration. There was no mention of Prostap in this section. The first mention of Prostap in the email was in the following section. The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The Panel did not accept that the claim was a comparison; it was therefore not a hanging comparison as alleged. Readers would not necessarily interpret the claim as being that Lutrate was at least as simple and easy to administer as Prostap. The Panel ruled no breaches of the Code.

Takeda alleged that given its continued concerns and the range of clauses alleged to have been breached, AMCo's conduct in relation to this material suggested a failure to maintain high standards and brought discredit to and reduced confidence in the industry.

The Panel noted its rulings above. It considered that the lack of clarity regarding the comparison of Lutrate's indications and how these compared to Prostap and the general claim for cost savings ruled in breach meant that high standards had not been maintained and a breach of the Code was ruled.

The Panel noted that Clause 2 was a sign of particular censure. It did not consider that the material brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

Takeda UK Limited complained about a Lutrate (leuprorelin acetate depot injection) promotional email (ref AMCo/LUT/1115/0027) which was sent by Amdipharm Mercury Company Limited (AMCo) to health professionals and budget holders in the NHS. The email was to alert them about the availability of a new formulation of leuprorelin with the potential for cost savings to the NHS.

When printed the email consisted of three pages. Page 1 was headed 'Lutrate' 'new leuprorelin formulation' and Lutrate: A novel leuprorelin formulation' followed by details of the sustained delivery system with a 'click here to view email and prescribing information' link. Page 2 included details of how to prepare the injection and also referred to the link to the email and prescribing information. Page 3 referred to cost savings and included a brief survey. There were a number of links including to request a representative visit, view an administration guide and order a video.

Lutrate 1 month depot injection was indicated for palliative treatment of locally advanced or metastatic prostate cancer. Lutrate 3 month depot injection was indicated for palliative treatment of hormone dependent advanced prostate cancer.

Takeda's product Prostap DCS (leuprorelin depot injection) was indicated for: metastatic prostate cancer; locally advanced prostate cancer, as an alternative to surgical castration; as an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer at high risk of disease progression and as an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer; as neo-adjuvant treatment prior to radiotherapy in patient with high-risk localised or locally advanced prostate cancer. Prostap could also be used for a number of gynaecological indications.

A Alleged lack of clarity on licence differences between Prostap DCS and Lutrate

Page 3 of the email included a section headed 'A new leuprorelin formulation with significant cost savings compared to Prostap'. This was followed by 'Annual cost saving with Lutrate: £135 per patient' followed by 'NHS list price comparisons for available leuprorelin acetate formulations for Prostap SR DCS 3.75mg (monthly) and Prostap 3 DCS 11.25mg (3 monthly)'. Further down the email on the same page was a poll 'Based on the significant savings that can be made, which type of patients would you consider prescribing Lutrate for?'. The choices were 'New eligible prostate cancer patients who require treatment with a [luteinizing hormone releasing hormone] LHRH agonist' or 'Those eligible patients currently receiving Prostap'.

COMPLAINT

Takeda alleged that by including a direct comparison between the two medicines in terms of potential cost savings and a poll regarding the type of patients the prescriber would treat (ie new eligible prostate cancer patients who require LHRH agonist therapy or eligible patients currently receiving Prostap) AMCo had falsely implied that the two products were interchangeable and could be used for the same indications in prostate cancer. Lutrate had a much narrower licensed indication in prostate cancer compared with Prostap DCS, which could lead to patients being prescribed Lutrate inappropriately. Takeda alleged that this represented promotion outside the marketing authorization in breach of Clause 3.2.

Furthermore, because in reality only a limited number of Prostap DCS patients would be eligible for Lutrate, the email in question was likely to lead GP practices to overestimate the cost savings they could achieve by switching patients from Prostap DCS to Lutrate or using Lutrate in place of Prostap DCS. Takeda alleged breaches of Clauses 7.2, 7.3 and 7.10.

RESPONSE

AMCo stated that Takeda was concerned that a direct comparison between the two medicines with regards to cost saving implied that the products were interchangeable. AMCo did not understand how a *bona fide* and legitimate promotional activity targeted at health professionals and NHS decision makers whom would reasonably be entitled to know information regarding availability of Lutrate, could imply that the products were interchangeable as alleged.

AMCo noted that it had not used words such as 'interchangeable' or 'switch', and had further clarified that only 'eligible' patients could help realise the cost

savings shown. The prescribing information with the full licensed indications for Lutrate was prominently displayed. AMCo submitted that the promotion of Lutrate was in accordance with the terms of its marketing authorization and was not inconsistent with the particulars listed in the summary of product characteristics (SPC).

AMCo noted that in inter-company dialogue, Takeda accepted that the Code did not formally require competitor licences to be stated every time they were mentioned, yet it continued to request that AMCo provided an undertaking that whenever a comparison was made between Prostap DCS and Lutrate in any materials, that the difference in licensed indication was clearly stated. AMCo had twice requested clarity from Takeda as to exactly what was requested but had not received a response.

In addition, all internal materials and training of AMCo staff in relation to this piece as well as related budget impact models stated:

> 'The selection of LHRH therapy based on efficacy is at the discretion of the prescribing physician following clinical assessment…..it would not be acceptable to state that all LHRHs are interchangeable based on efficacy.'
>
> 'Representatives should not discuss switching patients as it would be unacceptable if a patient's medication was changed without prior clinical assessment.'

PANEL RULING

The Panel noted that Prostap and Lutrate were both leuprorelin depot injections. In the Panel's view, the email in question implied that the two medicines were interchangeable. There appeared to be a heading to pages 3 and 4 'A cost-saving option in prostate cancer'. The Panel noted however that the indications for Prostap were broader than those for Lutrate. The Panel did not accept that the differences in indication were made clear either by the reference to 'eligible patients' or the inclusion of the prescribing information. It was not stated in the email which prostate cancer patients were eligible for Lutrate other than in the prescribing information. Nor did the email include the indications for Prostap or even imply that the two medicines had different indications. Pages 1 and 2 focussed on Lutrate's formulation and administration. The impression from page 3 was that the only difference between the medicines was the cost. No detail had been provided regarding the cost comparison but it again implied the products were interchangeable, ie Lutrate could be used whenever Prostap was used. This was not so. The Panel considered that the impression from the cost comparison and the poll was that Lutrate and Prostap were interchangeable. This was inconsistent with the Lutrate SPC and the Panel ruled a breach of Clause 3.2. This impression was not negated by the use of the term 'for eligible patients'.

Neither party provided details about the basis of the cost comparison, the number of patients and what proportion of patients could be changed from Prostap to Lutrate. The impression was that all Prostap patients could be changed to Lutrate which was not so. The Panel considered that the claims for cost savings were misleading and did not promote the rational use of Lutrate as alleged. The Panel ruled breaches of Clauses 7.2, 7.3 and 7.10.

B Alleged lack of fair balance between efficacy claims and safety information

COMPLAINT

Takeda alleged that the reader was only presented with efficacy data regarding Lutrate's testosterone suppression with no balance of safety information regarding common adverse events or withdrawals due to adverse events. Including prescribing information in this piece was not sufficient to address the requirement to provide a balance of efficacy and safety information in promotional materials. The result was an unbalanced view of the evidence in breach of Clause 7.2.

RESPONSE

AMCo submitted that the email was intended to provide short succinct information about the availability of a new formulation of leuprorelin and its efficacy regarding testosterone suppression in line with the licensed indication.

The entire email was only one page in length, and included the prescribing information in line with the Code requirements for digital communication. The material was all-inclusive and was programmed to display the prescribing information together with the promotional content on the same page. The prescribing information thus formed part of the promotional email and was presented in line with the Code requirements.

The information on withdrawals and common adverse events, which could be found within the prescribing information was placed in a position such that its relationship to the claims could be appreciated by the reader. Since this was a concise one page email with the prescribing information as an inherent part of that page. AMCo submitted that the safety information in the prescribing information sufficiently addressed the Code requirement regarding provision of fair and balanced information.

AMCo submitted that the information presented was sufficiently complete to enable the reader to form their own opinion of the value of the medicine. Therefore, AMCo denied that this breached Clause 7.2 as all safety requirements of the Code were met.

PANEL RULING

The Panel noted that there was no mention of adverse events in the body of the email. The only information about common adverse events or withdrawals due to adverse events was in the prescribing information. The Panel did not consider that this necessarily meant that the email was an unbalanced view of the evidence as alleged. It noted

that the material at issue was not lengthy and that leuprorelin was not a new medicine, the formulation was new. The SPC stated that most of the treatment related adverse events reported were mainly subject to the specific pharmacological action of leuprorelin and associated with testosterone suppressing therapy. Local adverse reactions reported after injection were similar to those with similar products administered via intra-muscular [injection]. The email did not state nor imply that there were no adverse events etc. The Panel did not consider that the email was unbalanced as alleged and ruled no breach of Clause 7.2.

C Linking 'Lutrate A novel leuprorelin formulation', 'Sustained release delivery system' to 'a novel formulation to maintain effective testosterone suppression

The email was headed 'Lutrate' followed by 'Lutrate: A novel leuprorelin formulation sustained release delivery system' which was followed by three bullet points the third of which was 'Novel formulation to maintain effective testosterone suppression'. It was stated elsewhere in the email that Lutrate achieved effective suppression and maintenance of testosterone to castration levels.

COMPLAINT

Takeda alleged that the claim that a novel leuprorelin formulation '... to maintain effective testosterone suppression' was misleading and disparaging since it implied that Lutrate offered some advantage over other leuprorelin formulations in terms of testosterone suppression. To its knowledge, this had never been established. A breach of Clauses 7.10 and 8.1 was alleged.

RESPONSE

AMCo submitted that the claim did not disparage Prostap DCS nor did 'novel' imply that Lutrate was any more efficacious than Prostap DCS in this or any other regard. Acceptability of words such as 'new' or 'novel' were well established in the Code and pharmaceutical medicine. This was a clear situation where AMCo was entirely justified and entitled to use this terminology. AMCo did not accept that this constituted a breach of the Code.

AMCo submitted that Lutrate was a novel formulation of leuprorelin and had been available since its launch in December 2015. This was a clear and factually accurate statement and did not imply that Lutrate had any special merit, quality or property vs Prostap DCS and did not disparage any medicine. AMCo denied a breach of Clauses 7.10 or 8.1.

PANEL RULING

The Panel considered that the claim 'Novel formulation to maintain effective testosterone suppression' implied that the novel formulation maintained testosterone suppression rather than the leuprorelin. Although there was no mention of Prostap in this section as the active ingredients of both medicines was leuprorelin, there was an implication that Lutrate was an improvement over Prostap in relation to maintenance of effective testosterone suppression.

The Panel considered that the claim implied a special merit and this had not been established. A breach of Clause 7.10 was ruled. The Panel considered that the claim disparaged other formulations of leuprorelin. A breach of Clause 8.1 was ruled.

D Lutrate administration guide

COMPLAINT

Takeda alleged that the claim 'Lutrate is simple and easy to administer' had not been substantiated and was a hanging comparison. Since Prostap DCS was the obvious alternative treatment for patients eligible for Lutrate, the claim would likely be interpreted by prescribers as indicating that Lutrate was at least as simple and easy to administer as Prostap DCS. No evidence to support this assertion was referenced in the email, or by AMCo during inter-company dialogue. Takeda alleged that administration of Lutrate was, in fact, a more complex process than administration of Prostap DCS. A breach of Clauses 7.2 and 7.4 was alleged.

RESPONSE

AMCo submitted that the claim 'Lutrate is simple and easy to administer' was not a hanging comparison, simply an accurate statement of fact that did not require further substantiation. Lutrate had been specifically designed to be reconstituted and administered by health professionals with relative ease. Takeda had stated that since 'Prostap DCS was the obvious alternative treatment for patients eligible for Lutrate' (thus contradicting its own earlier concerns) then the claim would likely be interpreted by prescribers as indicating that Lutrate was as 'easy' to administer as Prostap DCS.

Consequently AMCo denied a breach of either Clauses 7.2, or 7.3.

PANEL RULING

The Panel noted that the claim 'Lutrate: simple and easy to administer' was followed by 8 illustrations of the steps needed to prepare the medicine and the injection area for administration. There was no mention of Prostap in this section (page 2). The first mention of Prostap in the email was in the following section. Neither party had provided a copy of the Lutrate administration guide referred to in the email so the Panel considered the allegation only in relation to the content of the email.

The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The Panel did not accept that the claim was a comparison; it was therefore not a hanging comparison as alleged. Readers would not necessarily interpret the claim as being that Lutrate was at least as simple and easy to administer as Prostap. The Panel ruled no breach of Clauses 7.2 and 7.3.

E Alleged breach of Clauses 9.1 and 2

COMPLAINT

Takeda stated that given its continued concerns and the range of clauses alleged to have been breached, AMCo's conduct in relation to this material suggested a failure to maintain high standards and brought discredit to and reduced confidence in the industry. Takada alleged a breach of Clauses 9.1 and 2.

RESPONSE

AMCo submitted that it had maintained high standards throughout, in its conduct and the use of the materials. It remained disappointed by the actions and premature referral of these matters before the PMCPA and thus rejected by Takeda's allegation that there had been breach of Clauses 9.1 or 2.

PANEL RULING

The Panel noted its rulings at points 1- 4 above. It considered that the lack of clarity regarding the comparison of Lutrate's indications and how these compared to Prostap and the general claim for cost savings ruled in breach (point 2 above) meant that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that Clause 2 was a sign of particular censure. It did not consider that the material brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

Complaint received **11 April 2016**

Case completed **3 June 2016**