CASE AUTH/2875/9/16

HEALTH PROFESSIONAL v RECORDATI

Promotion of Cleen and CitraFleet

A health professional complained about an advertisement for Cleen (sodium dihydrogen phosphate dihydrate and disodium phosphate dodecahydrate) and CitraFleet (sodium picosulphate and magnesium citrate (SPMC)) issued by Recordati Pharmaceuticals. The advertisement appeared in Gastrointestinal Nursing, September 2016.

The advertisement at issue was two pages with the first page split with one half covering Cleen and the other half CitraFleet. The advertisement for Cleen referred to its re-branding; its previous name (Fleet) was replaced by Cleen. The advertisement for CitraFleet highlighted the new approved split dose regime.

Cleen ready to use enema was indicated for use in the relief of occasional constipation and for use where bowel cleansing was required and surgery, delivery and post-partum, and before proctoscopy, sigmoidoscopy or colonoscopy and before radiological examinations of the lower bowel. CitraFleet was indicated for bowel cleansing prior to any diagnostic procedures requiring a clean bowel. The dose was usually administered as one sachet on the evening prior to the procedure and the second in the morning on the day of the procedure. Alternatively, both sachets were administered on the afternoon and evening prior to the procedure. This was more suitable when the procedure was early in the morning.

The complainant stated that the advertisement described the following as 'remarkable events' which seemed inappropriate given the subject matter:

Cleen was claimed to have a 'quick action' but included no comparison. The claim was referenced to the summary of product characteristics (SPC) which did not refer to 'quick'. The complainant alleged that it was an unfair comparison if the reference was supposed to be reference 1 which was a comparison with glycerine suppositories.

The CitraFleet part of the advertisement included the statement 'the approval of the split dosage regime in accordance to the European Guidelines' which the complainant understood to mean that the guidelines supported CitraFleet however, it was not mentioned in the guidelines. The advertisement also stated that 'CitraFleet is the FIRST SPMC [sodium picosulphate with magnesium citrate] in Europe combining split dose regime according to the Guidelines, with the lowest volumen and an effective colon cleansing **'. The explanation for ** was 'than previous-day regimes. SPMC regimens. Split-dose regime approval date: December 2015'. According to the complainant the only SPMC mentioned in the guidelines was Prepopik.

The complainant stated that the guideline listed other products as also having a volume requirement of two litres a day.

The complainant alleged that the claims 'Effective bowel cleansing with low side effects and less impact on daily living' and 'Preferred by patients for its low volume, nice lemon flavour and the free choice of clear liquids' were not clear as to what they were in comparison to.

The complainant also struggled to read the prescribing information because there were more than 100 characters per line.

The detailed response from Recordati is given below.

The Panel noted that the reference to remarkable events appeared as part of a heading across the advertisement that Recordati was committed to improve patients' quality of life and was '… delighted to announce, two remarkable events' and thus, in the Panel's view, applied to the matters described in each part. The Panel noted Recordati's submission that the remarkable events related to developments in its product portfolio. The Panel did not consider that either rebranding a well-established medicine or delivering a split dose regimen in this therapeutic area would be seen as remarkable events. The Panel considered that this exaggerated the developments described in each advertisement and ruled a breach of the Code.

In relation to the claim that Cleen had a 'Quick Action' the Panel considered this could potentially be read as a comparison with other products. It was referenced to the SPC which stated 'Generally 2 to 5 minutes are sufficient to obtain the desired effect. If delayed discontinue further use and consult a physician'. In the Panel's view this might be seen as quick. The Panel did not consider that the complainant had proven on the balance of probabilities that the claim was misleading as alleged or a comparison with glycerine suppositories and that such a comparison would be unfair. The Panel ruled no breach of the Code.

With regard to the claim regarding CitraFleet and split dosing, the Panel noted Recordati's submission that the product was licensed for such use in December 2015 and the competitor was so licensed in June 2016. The Guideline mentioned Picolax and Picoprep in relation to SPMC. There was no mention of CitraFleet. The Panel considered the advertisement gave the impression that the split dose regimen of CitraFleet was mentioned and supported by the Guidelines which was not so. The advertising was misleading as alleged and a breach of the Code was ruled.

The Panel considered that the claim 'CitraFleet is the First SPMC in Europe combining split dose

regime according to the Guidelines, with the lowest volumen and an effective colon cleansing' was a comparative claim as it implied CitraFleet had the lowest volume. The Panel noted Recordati's submission that both CitraFleet and Picolax had the same volume when reconstituted ie 300ml. However, only one product could have the lowest volume and CitraFleet therefore did not have the lowest volume. This use of a superlative was therefore ruled in breach of the Code. Further the Panel considered that the volume related to the whole treatment ie reconstituted medicine plus required clear liquid rather than just the reconstituted medicine. Other products appeared to have lower volume requirements than CitraFleet. The comparator was not clear as alleged. The claim for lowest volume was also misleading and the Panel ruled breaches of the Code.**

The Panel considered that the claim 'Effective bowel cleansing with low side effects and less impact on daily living' implied a comparison with a product that had more impact on daily living. The Panel noted that the advertisement did not mention the comparator polyethylene glycol (PEG) and as this had not been made clear, the Panel considered that this omission rendered the claim misleading. Breaches of the Code were ruled.

The claim 'Preferred by patients for its low volumen, nice lemon flavour and the free choice of clear liquids' was the final bullet point. The Panel considered that the comparator in the claim was not clear and its omission rendered the claim misleading. Breaches of the Code were ruled.

The Panel considered that the line length and spacing between the lines meant that the prescribing information was not clear or legible. A breach of the Code was ruled.

A health professional who until recently worked in the pharmaceutical industry, albeit in a different therapeutic area, complained about an advertisement for Cleen (sodium dihydrogen phosphate dihydrate and disodium phosphate dodecahydrate) and CitraFleet (sodium picosulphate and magnesium citrate (SPMC)) issued by Recordati Pharmaceuticals Ltd. The advertisement appeared in Gastrointestinal Nursing, September 2016.

The advertisement at issue was two pages with the first page split with one half covering Cleen and the other half CitraFleet. The second page had the prescribing information. The advertisement for Cleen referred to its re-branding; its previous name (Fleet) was replaced by Cleen. The advertisement for CitraFleet highlighted the new approved split dose regime.

Cleen ready to use enema was indicated for use in the relief of occasional constipation and for use where bowel cleansing was required, such as before and after lower bowel surgery, delivery and post-partum, and before proctoscopy, sigmoidoscopy or colonoscopy and before radiological examinations of the lower bowel.

CitraFleet was indicated for bowel cleansing prior to any diagnostic procedures requiring a clean bowel eg colonoscopy or x-ray examination in adults (including the elderly) aged 18 years and over. The dose was usually administered as one sachet on the evening prior to the procedure and the second in the morning on the day of the procedure. Alternatively, both sachets were administered on the afternoon and evening prior to the procedure. This was more suitable when the procedure was early in the morning. The time between the sachets should be five hours.

COMPLAINT

The complainant stated that the advertisement described the following as 'remarkable events' which seemed inappropriate given the subject matter:

Cleen was claimed to have a 'quick action' but included no comparison. The claim was referenced to the summary of product characteristics (SPC) which did not refer to 'quick'. The complainant alleged that it was an unfair comparison if the reference was supposed to be reference 1 which was a comparison with glycerine suppositories.

The CitraFleet part of the advertisement included the statement 'the approval of the split dosage regime in accordance to the European Guidelines' which the complainant understood to mean that the guidelines supported CitraFleet but it was not mentioned in the guidelines. The advertisement also stated that 'CitraFleet is the FIRST SPMC [sodium picosulphate with magnesium citrate] in Europe combining split dose regime according to the Guidelines, with the lowest volumen and an effective colon cleansing **'.

The explanation for ** was 'than previous-day regimes. SPMC regimens. Split-dose regime approval date: December 2015'.

According to the complainant the only SPMC mentioned in the guidelines was Prepopik.

The complainant stated that the guideline listed other products as also having a volume requirement of two litres a day.

The complainant alleged that the claims 'Effective bowel cleansing with low side effects and less impact on daily living' and 'Preferred by patients for its low volumen, nice lemon flavour and the free choice of clear liquids' were not clear as to what they were in comparison to.

The complainant also struggled to read the prescribing information because there were more than 100 characters per line.

When writing to Recordati the Authority asked it to consider the requirements of Clauses 4.1, 7.2, 7.3 and 7.10 of the Code.

RESPONSE

Recordati submitted that it took its global corporate compliance responsibility very seriously and was particularly mindful of its overarching obligation

to ensure regulatory compliance of all external communications. Each external communication was subject to rigorous review according to its established process and procedures. Its established review policy took full account of the requirements in law and the Code.

Recordati submitted that the word 'remarkable' was not a superlative; the natural meaning of the expression 'remarkable events' was no more than 'noteworthy events'. In addition, the effect of the word in the context of the advertisement was not to claim anything particular about either product. It related to developments for Recordati as a company in relation to its product portfolio.

For Recordati, the announcement of a brand change to one of the company's oldest products, which had been marketed in the UK for over 20 years, could be characterised as a noteworthy development, and an important one that should be communicated to health professionals to avoid confusion.

In relation to CitraFleet, the approval of the product had taken the company a substantial amount of time and work; obtaining such an approval from the UK authorities for a split-dose mode of administration allowed Recordati to be the first company able to market a product which used a mode of administration that had been recommended by the European Society of Gastrointestinal Endoscopy (ESGE) Guideline ('Guideline') which was a noteworthy development.

Recordati submitted that taking into account the subject matter, use of the word 'remarkable' was not inappropriate in the context. It had no adverse public health consequences and was justified on a factual basis.

Recordati noted that the complainant stated that he/she struggled to read the prescribing information as there were more than 100 characters per line. Recordati submitted that the prescribing information for both products was positioned for ease of reference, and formed part of the advertisement. Supplementary information to Clause 4.1 set out 'recommendations' for the legibility of prescribing information. In line with the supplementary information, the type size used was no less than 1mm in height. There was sufficient space between the lines to facilitate reading, and a clear style of type was used. There was also adequate contrast between the colour of the text and the background (black and white), which, according to the Code, was preferable. In addition, emboldened headings were used at the start of each section of the prescribing information. The Code did not prohibit the use of greater than 100 characters per line; the recommendations, taken as a whole, were a guideline 'to help achieve clarity'. Deviations might occur depending on various factors such as whether a page were in portrait or landscape orientation. The prescribing information contained around 120-130 characters per line. Taking into account its compliance with every other recommendation, the company submitted that the prescribing information was readable, even though like all prescribing information, careful scrutiny was required and the information was not a substitute for consideration of the full SPC, where appropriate (such as where the SPC was relied upon to support a claim). For that reason Recordati considered that fulfilment of seven out of eight of the recommendations was sufficient, and that that part of the complaint was rather vexatious.

Recordati submitted that the reference for the claim for 'quick action' in the Cleen advertisement was the SPC. Section 4.2 (Posology and method of administration) stated that 'generally, 2-5 minutes are sufficient to obtain the desired effect'. Furthermore, Section 4.4 (Precautions for use) stated 'In general, evacuation occurs approximately 5 minutes after Clean Ready-to-Use Enema administration …'. Recordati submitted that in the context of a bowel cleanser, this would ordinarily be accepted to constitute 'quick action'.

Recordati submitted that Clause 7 allowed for comparisons with other products as long as the comparison was not misleading and the medicines were for the same needs or intended for the same purpose. The advertisement for Cleen did not constitute a comparative claim. The language did not suggest that the product was superior in some way to another; the phrase 'quicker action' might imply this, but the advertisement did not use that wording. Recordati had been using the claim that Cleen has 'quick action' for many years, across multiple countries, and without any objection being raised.

Recordati noted that the complainant stated that the inclusion of the phrase 'the approval of the SPLIT DOSE REGIME in accordance to the European Guidelines' in the advertisement for CitraFleet suggested that the Guideline referred to and endorsed the product CitraFleet by name. Recordati submitted that that was not the case and it would seem the health professional had misread the advertisement. The inclusion of the phrase was not misleading; it did not reference the product at all, but instead the type of regime. The recommendation in the Guideline concerned the split-dose regime. 'Split dose regime' was even capitalized in the advertisement, which left little doubt to the preference described in the Guideline for a split dose regime, and not for CitraFleet in particular. Recordati submitted that this part of the complaint was misconceived.

The Guideline recommended the use of this new split dose mode of administration (recently approved for CitraFleet) to ensure better cleansing results. This normally involved administering the dose partly in the evening and partly the following day before the procedure in question. The two products most used in this field were based on polyethylene glycol (PEG) and based on sodium picosulfate with magnesium citrate (SPMC). The Guideline cited a meta-analysis of five random controlled trials which found that, compared with the administration of the full dose of PEG on the day before colonoscopy, a split-dose regimen of PEG significantly improved the percentage of patients with satisfactory colon cleanliness, significantly increased patient compliance, and significantly decreased nausea. The Guideline recommended that regime

regardless of whether a patient was using SPMC or any other bowel evacuant. The Guideline recommended a split regimen of four litres of PEG solution (or a same-day regimen in the case of afternoon colonoscopy) for routine bowel preparation. A split regimen (or same-day regimen in the case of afternoon colonoscopy) of two litres PEG plus ascorbate or of SPMC were said to be valid alternatives.

Recordati submitted that the statement on CitraFleet being the first authorised product, containing SPMC to be administered in a split dose regimen, was a statement of fact. CitraFleet was approved for administration using a split dose regime in December 2015, and the SPC was updated accordingly. In June 2016, six months after CitraFleet obtained its authorisation for the split dose regimen, CitraFleet's competitor product, Picolax, also received approval for that new regimen.

Recordati stated that this part of the complaint was similar to that above but Recordati was not stating that the Guideline referred to CitraFleet as being the first SPMC in Europe combining the split dose regime. It was well known that Guidelines did not contain promotional statements in respect of particular products. The statement was that CitraFleet was the first SPMC in Europe which reflected the split dose regime that was recommended in the Guidelines. It was the regime that was being recommended by the Guideline, not a specific product. The fact that this statement followed the earlier prominent one referring to the concept of the split dose regime proposed by the Guidelines reinforced this overarching message.

Recordati submitted that the asterisk mentioned by the claimant was qualifying the text appearing in the boxed area mentioned above, stating that 'CitraFleet is the FIRST SPMC in Europe combining split dose regime according to the Guidelines with the lowest volumen and an effective colon cleansing'. The text under the asterisk added:

> '(**) than previous-day regimens. SPMC regimens. Split-dose regime approval date: December 2015.'

The reference to 'lowest volumen', in the advertisement did not amount to a comparative claim (ie lower than other products as the claimant argued). It was generally accepted and hardly surprisingly that clinicians looked for a product with the lowest volume compatible with effective cleansing. Therefore, Recordati was entitled to highlight that no other product in the market had a lower volume. CitraFleet had a volume intake of 300ml once reconstituted, which was the same volume intake as the competitor product Picolax. Both, CitraFleet and Picolax had the same low volume. This volume was the lowest compared with the volume intake of the rest of the bowel preparations on the market. Therefore both products had the 'lowest volume'. This fact was supported by CitraFleet's SPC which was referenced.

The volume intake for each bowel preparation on the market appeared in Section 4.2 (Posology and Method of Administration) of the SPCs. These volumes, taking into account the usual dose recommended for adults were: two litres for Moviprep, four litres for Klean Prep and 500ml for Eziclen.

Recordati submitted that the statement in the boxed area concerning effective colon cleansing from a split-dosing regimen was supported by scientific literature such as Prieto-Frias *et al*, 2013 cited as reference 9. This stated that the split-dosing regimen provided higher efficacy than the previous-day regimen as follows:

> 'Background and Aims: It is known that sodium picosulfate–magnesium citrate (SPMC) bowel preparations are effective, well tolerated and safe, and that split-dosing is more effective for colon cleansing than previous-day regimens. (…)'

This statement was further supported by Schulz *et al*, 2016 which concluded that:

> 'A split-dose regimen of SPMC is superior to the AM/PM regimen administered the day before colonoscopy. Split regimen of SPMC should be considered the standard of use.'

Recordati submitted that in relation to the claim of effective bowel cleansing, the advertisement did not claim that SPMC provided more effective bowel cleansing than any other product, and that part of the claim was not a comparative statement. But the statement of effective cleansing was supported by the literature references Choi *et al*, 2014 and Hawkins *et al*, 1996.

With respect to the claim that CitraFleet offered 'low side effects and less impact on daily living', the results of the same studies and also Hamilton *et al*, 1967 showed that SPMC (or MC-SP) provided significantly better cleansing in the right colon, and better acceptability and tolerability profile in patients, compared to that achieved with a two litre PEG + ascorbic acid solution. Both solutions showed a similar level of effectiveness with regard to the overall quality of bowel cleansing.

Recordati submitted that with regard to the preference of patients for CitraFleet's low volume, Mane *et al*, 2013 showed that the better acceptability and tolerability of SPMC was due, among other things, to the amount of volume the patient was required to drink. A comparison between sodium picosulphate PEG for large bowel lavage and sodium picosulphate solution found the latter was more acceptable to patients than PEG and resulted in significantly less nausea and vomiting ($p = 0.0025$) and far fewer consumption difficulties ($p < 0.0001$); the volume intake required for the PEG solution, Klean-Prep was a significant problem. Neither cleansing solution showed a distinct efficacy advantage on the other. However due to the fact that sodium picosulphate was more acceptable to patients, the article stated that sodium picosulphate was the preferred solution for bowel preparation. This acceptability encompassed the taste of the product.

Recordati concluded that it fully appreciated and respected its obligations under the Code and applicable legislation with respect to promotion of its products. However, the complaint was unfounded. The statements made could be justified within the meaning of the Code and applicable legislation.

For the reasons given above, Recordati denied breaches of Clause 4.1, 7.2, 7.3 and 7.10 and stated that the complaint lacked merit.

PANEL RULING

The Panel noted that the reference to remarkable events appeared as part of a heading across the advertisement that Recordati was committed to improve patients' quality of life and was '… delighted to announce, two remarkable events' and thus, in the Panel's view, applied to the matters described in each part. The Panel noted Recordati's submission that the remarkable events related to developments in its product portfolio. The Panel did not accept that 'remarkable' (defined as notably or conspicuously unusual, extraordinary, worthy of notice or attention) would necessarily be interpreted by most readers as closely similar to 'noteworthy' (defined as worthy of notice or attention; notable, remarkable). The word 'remarkable' implied an unusual, extraordinary development. The Panel did not consider that either rebranding a well-established medicine or delivering a split dose regimen in this therapeutic area would be seen as remarkable events. The Panel considered that this exaggerated the developments described in each advertisement and ruled a breach of Clause 7.10.

In relation to the claim that Cleen had a 'Quick Action' the Panel considered this could potentially be read as a comparison with other products. The SPC did not describe the product as having a quick action. The Cleen SPC stated 'Generally 2 to 5 minutes are sufficient to obtain the desired effect. If delayed discontinue further use and consult a physician'. In the Panel's view this might be seen as quick. The Panel noted that the complainant referred to reference 1 which was a comparison of Fleet and glycerin suppositories (Underwood *et al* 2009). However, none of the claims in the advertisement cited reference 1. The study had not been provided by Recordati or by the complainant. The claim in question 'Quick Action' was referenced to the SPC. The Panel did not consider that the complainant had proven on the balance of probabilities that the claim was misleading as alleged or a comparison with glycerine suppositories and that such a comparison would be unfair. The Panel ruled no breach of Clauses 7.2 and 7.3 in this regard.

With regard to the claim regarding CitraFleet and split dosing, the Panel noted Recordati's submission that the product was licensed for such use in December 2015 and the competitor was so licensed in June 2016. The Panel noted that there were three recommendations in the ESGE Guideline, firstly a low fibre diet on the day preceding colonoscopy. Secondly, a split regimen of 4 litres of polyethylene glycol (PEG) solution (or same day regimen in the case of afternoon colonoscopy), a split regimen of 2 litres PEG plus ascorbate or of SPMC might be valid alternatives. Thirdly, advising against the routine use of sodium phosphate. The ESGE Guideline was based on a targeted literature search. The Guideline mentioned Picolax and Picoprep in relation to SPMC. There was no mention of CitraFleet. The Panel noted the claims that 'The Approval of the SPLIT DOSE REGIME in accordance to the European Guidelines' appeared immediately below the brand name and 'CitraFleet is the FIRST SPMC in Europe combining split dose regime according to the Guidelines …'. The Panel considered the advertisement gave the impression that the split dose regimen of CitraFleet was mentioned and supported by the Guidelines which was not so. The advertising was misleading as alleged and a breach of Clause 7.2 was ruled.

The Panel considered that the claim 'CitraFleet is the First SPMC in Europe combining split dose regime according to the Guidelines, with the lowest volumen and an effective colon cleansing**' was a comparative claim as it implied CitraFleet had the lowest volume. The Guidelines referred to magnesium citrate as a low volume bowel preparation in combination with a variety of stimulants including sodium picosulphate (Picolax or Picoprep). The Guideline referred to its combination with 2 litres of PEG. There was no mention of CitraFleet in the Guideline. The Panel noted Recordati's submission that both CitraFleet and Picolax had the same volume when reconstituted ie 300ml. However, only one product could have the lowest volume and CitraFleet therefore did not have the lowest volume. This use of a superlative was therefore ruled in breach of Clause 7.10. Further the Panel considered that the volume related to the whole treatment ie reconstituted medicine plus required clear liquid rather than just the reconstituted medicine. The Panel noted that each CitraFleet sachet was reconstituted in a cup of water and a further 1.5 to 2 litres of clear fluid was to be taken 10 minutes after that. Picolax was reconstituted in a cup of water, approximately 150ml followed by at least five 250ml drinks of clear liquid, ie 1.25 litres. The second sachet was similarly reconstituted and to be followed by at least three 250ml drinks, ie 0.75 litres. Each bottle of Izinova was diluted in water to approximately 0.5 litres followed by one litre of water or clear fluid within 2 hours. Those appeared to be lower volume requirements than CitraFleet. The comparator was not clear as alleged. The claim for lowest volume was also misleading and the Panel ruled breaches of Clauses 7.2 and 7.3.

The Panel considered that the claim 'Effective bowel cleansing with low side effects and less impact on daily living' implied a comparison with a product that had more impact on daily living. Recordati's response referred to studies comparing SPMC with PEG. Choi *et al* compared Coolprep with Picolight (MS-SP). Hawkins *et al* compared Picolax with Klean-Prep, ie SPMC with PEG. Hamilton *et al* was dated 1996 and not 1967 as stated by Recordati in its response. This study compared Picolax with Klean Prep, ie SPMC and PEG. The Panel noted that the advertisement did not mention the comparator (PEG) and as this had not been made clear, the Panel considered that this omission rendered the claim 'Effective bowel cleansing

with low side effects and less impact on daily living' misleading. A breach of Clauses 7.2 and 7.3 was ruled.

The claim 'Preferred by patients for its low volumen, nice lemon flavour and the free choice of clear liquids' was the final bullet point. It was referenced to Manes *et al* 2013 which compared SPMC citrate with low volume PEG plus ascorbic acid. The Panel considered that the comparator in the claim was not clear and its omission rendered the claim 'Preferred by patients for its low volumen, nice lemon flavour and the free choice of clear liquids' misleading. A breach of Clauses 7.2 and 7.3 was ruled.

The supplementary information to Clause 4.1 gave recommendations to assist legibility including, *inter alia*, that lines should be no more than 100 characters in length, including spaces and that sufficient space should be allowed between the lines to facilitate easy reading. The Panel noted the line length used in the prescribing information in the advertisement at issue was longer than 100 characters.

The Panel considered that the line length and spacing between the lines meant that the prescribing information was not clear or legible. A breach of Clause 4.1 was ruled.

Complaint received **21 September 2016**

Case completed **23 November 2016**