CASE AUTH/3275/10/19

BRITANNIA v EVER PHARMA

Promotion of Dacepton

Britannia Pharmaceuticals complained about the promotion of Dacepton (apomorphine for injection) by Ever Pharma.

Dacepton was indicated for the treatment of motor fluctuations ('on-off' phenomena) in patients with Parkinson's disease which were not sufficiently controlled by oral anti-Parkinson medication. Dacepton was available in two forms – a 10mg/ml cartridge for injection and a 5mg/ml solution for infusion.

There were a number of allegations.

The detailed response from Ever Pharma is given below.

A Email to a health professional from an Ever Pharma nurse advisor

Britannia alleged that an email appeared to be unsolicited and thus was promotional both in content and intent. Moreover, as it had been sent from a non-promotional member of Ever Pharma staff, it was disguised promotion. The linking of an offer of nursing support with organising a sales call with a promotional member of staff to discuss cost within the email, clearly offered a benefit to health professionals in breach of the Code. Britannia alleged that the offer went beyond the scope of a *bona fide* package deal.

Britannia also alleged that prescribing information was not provided nor was the non-proprietary name nor a list of active ingredients given. Britannia stated that the promotional email was not certified, was sent without prior consent and the sender was a medical representative who had not sat or passed an appropriate examination. This clearly demonstrated poor standards and brought discredit upon, and reduced confidence in, the pharmaceutical industry.

The Panel noted that neither it nor Ever Pharma had seen the original unredacted email trail. In the Panel's view, the content of the email in question, as provided by Britannia, was not clear that it was a reactive response to a health professional as submitted by Ever Pharma. It could equally be viewed as an unsolicited general introduction to Ever Pharma's nurse service offerings. It introduced the nurses by reference to their role in the provision of nursing support to patients who might be considered and commenced on Dacepton (apomorphine) and then offered to show and demonstrate new devices and to send support materials.

The Panel noted that, on the evidence provided, it was not possible to determine whether any information had been specifically requested by the health professional. The complainant had not established, on the balance of probabilities, that the email was

unsolicited and thereby promotional as alleged. The Panel therefore ruled no breaches of the Code including that as the complainant had not established that the nurse was acting as a representative in sending the email, the requirement to take an appropriate examination was not relevant.

In relation to the allegation that the reference in the email to patients 'who may be considered or commenced on Dacepton' meant that the package deal was not *bona fide*, the Panel noted Ever Pharma's submission that it offered a package deal for Dacepton which included nurse support. It was not available to providers who did not purchase or intend to purchase a Dacepton product. The package deal offered benefits associated with Dacepton products including bespoke training for providers, patients and carers on how to use the D-mine Pump and D-mine Pen, one of the services referred to in the email in question.

In relation to the narrow allegation that the package deal was not *bona fide*, the Panel considered that the reference to patients who may be considered for, or commenced on, Dacepton was not necessarily inappropriate in relation to the overall commercial arrangements for a package deal. Such arrangements were promotional and health professionals might consider such arrangements in relation to patients who may be considered for, or commenced on, Dacepton. The Panel therefore ruled no breach of the Code including Clause 2.

B Leavepiece for Dacepton Pump 5mg/ml in 20ml vials for infusion

Britannia alleged that the image of a male patient with what appeared to be the D-mine 8 pump attached to his belt with an infusion line sited on his stomach had been distorted to make the D-mine pump appear smaller than it really was; it was a misleading representation of the true dimensions. Britannia stated that although the revised material (ref EVP-091) had a footnote giving the dimensions this did not rectify, or negate, the misleading visual representation of the true dimensions of the D-mine pump.

In the Panel's view, noting Ever Pharma's submission, the size of the pump in relation to the belt size within the image did not appear to be misleading. The Panel further noted that the actual size of the pump was given below the image and, although it would have been helpful if the text was more prominent, the information was given in a standalone paragraph and 'pump size' was written in uppercase font which, in the Panel's view, meant that it was reasonably noticeable. The Panel therefore ruled no breach of the Code.

Britannia alleged that the claim '7 days in-use stability data supports entire content use' was inconsistent with the summary of product characteristics (SPC) for Dacepton 5mg/ml solution for infusion which included:

> **'After opening and filling the drug product in syringes attached with infusion sets: chemical and physical in-use stability has been demonstrated for 7 days at 25°C. From a microbiological point of view, unless the method of opening and further handling precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.'**

Britannia submitted that as the Dacepton D-mine pump was designed to be used at home by the patient and would be sited next to the patient, where temperatures could exceed 25 degrees, then it failed to see how the risk of microbial contamination could be prevented in such conditions. The item failed to recognise, or draw the prescriber's attention to, the risk of microbial contamination and therefore that the product should be used immediately, as stated in the SPC. Such microbial contamination would also be far more likely if the patient was using the reservoir for up to 7 days with a new infusion line every day being required. Britannia alleged that the claim failed to encourage rational use of Dacepton 5mg/ml solution for infusion and thus represented a serious risk to patient safety.

The Panel noted that the headline on page 3 of the Dacepton 5mg/ml leavepiece stated 'EVER Pharma D-mine Pump advantages:'. This was followed by two columns comparing the D-mine pump with the 20ml syringe driver used with APO-go. A feature of the D-mine pump included '7 days in-use stability data supports entire content use' whilst for the 20ml syringe driver used with APO-go it was stated that '24 hour in-use stability data was less supportive of using entire content'.

The Panel considered that the failure to include a reference to the risk of microbiological contamination either within, or within the visual field of the table, was misleading. The Panel considered that the claim '7 days in-use stability data supports entire content use' in the absence of such qualification implied that there was no need to consider microbiological contamination and that was not so. The claim was misleading and the failure to qualify the claim in question meant that it was inconsistent with the particulars listed in the SPC and did not encourage the rational use of the medicine. Breaches of the Code were ruled.

Britannia noted that the claim '20ml Syringe Driver used with APO-go'appeared as a heading to an APO-go column. The SPCs for APO-go PFS 5mg/ml Solution for Infusion in Pre-filled syringe and also Dacepton 5mg/ml solution for infusion under Section 4.2 clearly referred to the option for the medicine 'to be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver. In deliberately choosing to describe the administration of APO-go via a 20ml syringe driver and not doing so for Dacepton, the promotional piece misleadingly implied that Dacepton was the only medicine that was delivered by a branded bespoke pump device, which was not so.

Moreover, a syringe driver had connotations of administering palliative medicine. Britannia provided patients with the Crono APO-go Mark 3 Pump, a portable infusion pump designed to be used with the APO-go PFS 5mg/ml Solution for Infusion in Pre-filled syringe. Britannia alleged that this deliberate choice of words was an attempt to directly and deliberately disparage the Crono APO-go Mark 3 Pump.

Britannia also considered that the description of the D-Mine Pump and use of apomorphine were misleading as it was not a medicine/device combination, and this insinuated that only EVER Pharma had a specifically designed pump for the subcutaneous infusion of apomorphine.

Britannia was of the opinion that a health professional would perceive the infusion pump as a pump and not a syringe driver.

The Panel noted that the SPCs for both the Dacepton 5mg/ml and APO-go PFS 5mg/ml Solution for Infusion in Pre-filled syringe referred to the option for the medicine 'to be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver' in Section 4.2. The Panel noted Britannia's submission that, typically, a syringe driver required an attached plastic plunger, and this was removed from the CRONO reservoir; thus, it was not a syringe. The Panel noted Ever Pharma's submission that the leavepiece described the attributions of the D-mine pump which did not function through a syringe driver mechanism whereas a letter from Britannia provided by Ever Pharma described the APO-go infusion, used in conjunction with APO-go solution as a small battery-operated syringe-driver. The Panel further noted that a four-page loan contract provided by Ever Pharma which it stated was used by Britannia referred to APO-go 'syringe driver'.

The Panel did not consider that Britannia had established that there was evidence that Ever Pharma, in referring to a syringe driver in relation to APO-go, was misleading or disparaged APO-go as alleged and no breaches of the Code were ruled.

In relation to the allegation that the description of the D-Mine Pump and use of apomorphine were misleading as it was not a medicine/device combination, and this insinuated that only Ever Pharma had a specifically designed pump for the subcutaneous infusion of apomorphine, the Panel did not consider that the features outlined in the D-Mine Pump column, although generally favourable to the D-mine Pump, implied that only Ever Pharma had a specifically designed pump for subcutaneous infusion as alleged. No breach of the Code was ruled.

Britannia noted that a claim 'Dacepton pump delivers annual cost savings vs APO-go Pump' appeared as the title to a cost comparison wheel featured on page 5 of the Dacepton leavepiece. This was supported by the second claim 'Most cost savings are generated by a reduction in waste' which appeared as the fifth bullet point under the title and cost comparison wheel. Britannia failed to understand, in the absence of a clear breakdown, on what criteria these calculations had been generated. Although Ever Pharma had presented different numbers to that shown in the previous Dacepton leavepiece, the concerns remained that these cost savings might have been made by ignoring the full wording in Section 6.3 of the Dacepton 5mg/ml solution for infusion SPC and suggested that the in-use shelf life of Dacepton was 7 days in all cases.

Britannia reiterated that the full wording of Section 6.3 of the Dacepton 5mg/ml solution for infusion.

As the Dacepton D-mine pump was designed to be used at home by the patient, Britannia failed to see how the risk of microbial contamination could be prevented in such conditions. By cherry-picking the wording from Section 6.3, as Ever Pharma appeared to have done, the promotional item failed to recognise or draw the prescriber's attention to the risk of microbial contamination and that the product should therefore be used immediately. Britannia alleged that the claim did not encourage rational use of Dacepton 5mg/ml solution for infusion, and thus represented a serious risk to patient safety. In addition, the claim deliberately disparaged the APO-go Pump which was the direct comparator.

The Panel noted its comments above about microbiological contamination and considered that they were relevant here. The Panel noted Ever Pharma's submission that the major difference between the products was in-use shelf life and noted its submission about the Toledo study. The Panel noted that, according to the Dacepton 5mg/ml SPC whilst chemical and physical in-use stability had been demonstrated for 7 days at 25 degrees Celsius, it did go on to state that from a microbiological point of view, unless the method of opening and further handling precluded the risk of microbial contamination, the product should be used immediately which was not stated or referred to on the page in question. The Panel noted the text beneath the cost wheel stated that most cost saving was generated due to a reduction in waste. The text also referred to the 7 day stability of Dacepton and the single use of Apo-go. On balance, the Panel considered that, given the cost saving was due primarily to the 7 day stability the failure to include relevant information about the risk of microbiological contamination, meant that the page in question was not sufficiently complete to enable the reader to form their own opinion in relation to the claims in question 'Dacepton pump delivers annual cost savings vs APO-go Pump' and 'Most cost savings are generated by a reduction in waste' which were thus misleading and within the context of the page were incapable of substantiation. Breaches of the Code were ruled.

C Leavepiece for Dacepton Cartridge 10mg/ml solution for injection

Britannia noted that the claim 'Has a safety stop' introduced a table which drew direct comparisons between the characteristics of the D-mine Pen and the APO-go Pen. Britannia alleged that the overall impression created by the table and the wording used to describe the characteristics of the two devices resulted in an unbalanced, unfair and ambiguous comparison. The table disparaged the APO-go Pen and also represented a risk to patient safety.

The Panel noted that the APO-go pen SPC stated 'Preparing for the next injection (q) Remove the outer sleeve of the Pen and check there is enough apomorphine left in the cartridge for your next injection. If there is, put a new needle in place in the same way as before'. The Panel noted Britannia's submission that the APO-go Pen could not be primed if there was insufficient medicine remaining in the pen. The Panel noted, however, that according to the APO-go pen PIL accessed on the emc, 'it was only if your dose was 1 mg, that a patient had to start by emptying a 1 mg dose onto a paper tissue and discarding it which was called "priming" and was important because it ensured they got a full dose the first time using the Pen. Then the dose could be set to that required for injection and could be injected in the usual way. If the first dose required was more than 1 mg, you did not need to prime the Pen'.

The Panel noted Ever Pharma's submission that, as presented in the leavepiece, both the D-mine pen and the APO-go pen had a safety stop. The Ever Pharma D-mine pen device primed the spring as it dialled up the dose. The device had a safety stop that would not allow users to dial up a dose of more than was left in the cartridge. The APO-go pen would allow the dose selector wheel to dial to doses of up to the maximum of 10mg. The user then manually primed the pen using the integral plunger by pulling the plunger out. Using the APO-go pen, regardless of the amount left in the pen, the user could dial up to the maximum dose. The safety stop in this device would not allow the user to pull the priming plunger out higher than the dose of apomorphine in the pen. Thus, there was a distinction between the safety mechanisms of the D-mine pen and the APO-go pen.

The Panel noted that it appeared that the APO-go Pen in contrast to the D-mine Pen would allow a user to dial up a dose higher than the remaining medicine in the cartridge, however, according to Ever Pharma, the safety stop in this device would not allow the user to pull the priming plunger out higher than the dose of apomorphine in the pen. The Panel noted that whilst it might have been helpful to provide further details in the table with regard to the safety stop mechanism in relation to the APO-go PEN, it was clear that it had a safety stop. On balance, the Panel considered that the failure to provide the equivalent details for the APO-go Pen implied that the D-mine Pen had a material benefit in this regard and was misleading. Breaches of the Code were ruled. The Panel did not consider that the failure to provide such equivalent details disparaged APO-go Pen as alleged, it was made clear that the Pen had a safety stop and the Panel ruled no breach in this regard.

The Panel noted Ever Pharma's submission with regard to dose correction that Britannia had highlighted the fact that dose correction when using the D-mine pen could be performed by dialling up and down, whereas dose modification with the APO-go pen could only be made by turning the dosage dial in one direction dialling to the original start point (zero), ie the user had to restart the process. The Panel noted that the APO-go pen SPC stated 'If you pass your prescribed dose while turning the dial, just continue pressing and turning in the same direction until the arrow points to the dose your doctor chose for you'. In the Panel's view, having to dial back to the dose required by turning the dosage dial in one direction and starting again at zero was, in essence, restarting the dosing process. However, the way it was worded in the detail aid might imply that the user had to restart the whole process of preparing the pen rather than merely continuing to press and turn the dial in the same direction until the arrow pointed to the required dose. The Panel considered that the comparison was misleading in this regard and breaches of the Code were ruled.

In relation to the claim 'In use stability 15 days', the Panel considered that its comments above were relevant here. The Panel noted that according to the Dacepton 10mg/ml pen SPC whilst chemical and physical in-use stability had been demonstrated for 15 days at 25 degrees Celsius, it went on to state that, from a microbiological point of view, unless the method of opening and further handling precluded the risk of microbial contamination, the product should be used immediately. The Panel considered that failure to include information about the risk of contamination as part of, or within the visual field of, the claim was misleading, the omission meant that the claim 'in use stability 15 days' was inconsistent with the particulars within the SPC and did not encourage the rational use of the medicine. Breaches of the Code were ruled.

In relation to a cost comparison Britannia stated that patients used apomorphine as an intermittent subcutaneous injection 'as needed' and so did not have a fixed dose per day, but instead a fixed dose per injection. The cost comparison model presented in the leavepiece, which was based purely on 'dose per day/mg', was therefore an unrealistic and misleading representation of how much medicine a patient would require, given the nature of Parkinson's disease and individual patient needs.

The Panel noted the text beneath the cost wheel stated that 'cost savings are mostly generated through reduction in wastage due to the prolonged in use life of Dacepton Cartridge'. The Panel noted its comments above and considered that they were relevant

here. The Panel noted that, according to Section 6.3, Shelf life of the Dacepton 10mg/ml SPC whilst chemical and physical in-use stability had been demonstrated for 15 days at 25 degrees Celsius, it went on to state that from a microbiological point of view, unless the method of opening and further handling precluded the risk of microbial contamination, the product should be used immediately. The Panel considered that failure to include this relevant information meant that the page in question was not sufficiently complete to enable the reader to form their own opinion in relation to the claims regarding cost savings and was thus misleading and breaches of the Code were ruled. The failure to include this relevant information about the risk of microbiological contamination meant that the impression given by the page, including the heading in relation to the magnitude of cost savings, was incapable of substantiation and a breach was ruled.

The Panel further noted Britannia's concern that patients used apomorphine as an intermittent subcutaneous injection 'as needed' and so did not have a fixed dose per day, but instead a fixed dose per injection and the cost comparison model presented in the leavepiece was based purely on 'dose per day/mg' which was therefore an unrealistic and misleading representation of how much medicine a patient would require, given the nature of Parkinson's disease and individual patient needs. The Panel noted that Ever Pharma had not responded in this regard.

The Panel considered that failure to include relevant information about the 'as needed' dosage of the APO-go Pen meant that the page in question was not sufficiently complete to enable the reader to form their own opinion in relation to the claims regarding cost savings based on a daily dose as alleged and was thus misleading and breaches of the Code were ruled.

Britannia Pharmaceuticals Limited complained about the promotion of Dacepton (apomorphine for injection) by Ever Pharma. Dacepton was indicated for the treatment of motor fluctuations ('on-off' phenomena) in patients with Parkinson's disease which were not sufficiently controlled by oral anti-Parkinson medication. Dacepton was available in two forms – a 10mg/ml cartridge for injection and a 5mg/ml solution for infusion.

Britannia raised a number of matters, some of which had either not been the subject of inter-company dialogue or had been resolved through inter-company dialogue. These matters were not taken up as a complaint. Both companies made detailed submissions in relation to inter-company dialogue. With regard to promotional material for Dacepton, Britannia noted that Ever Pharma had agreed to withdraw two leavepieces – one for the 5mg/ml presentation (ref EVP-016) and one for 10mg/ml presentation (ref EVP-005) – as of 30 August 2019. Britannia considered, however, at the time that Ever Pharma's undertaking in that regard had been poorly executed with only minor amendments being made to the new leavepieces which were prepared in September 2019 (ref EVP-091 for the 5mg/ml presentation and ref EVP-090 for the 10mg/ml presentation). Britannia considered that its original concerns remained, and that inter-company dialogue had not been successful. Britannia alleged that the revised materials continued to breach Clauses 3.2, 7.2, 7.3, 7.4, 7.8, 7.10 and 8.1.

In response to a request for further information, Britannia submitted that since the submission of this complaint, there had been significant internal developments within Britannia, namely a change of leadership within both the Medical and Compliance departments. Britannia stated

that its medical and compliance staff were actively working to create a strong compliance culture within the business and to encourage effective engagement with its competitors.

Britannia considered that Ever Pharma withdrew and redacted the materials of concern during the 2019 inter-company dialogue, as such Britannia saw no need to continue with this complaint.

Britannia was notified that Paragraph 15.1 of the Constitution and Procedure stated that a complaint may be withdrawn by a complainant with the consent of the respondent company up until such time as the respondent company's comments on the complaint have been received by the Authority, but not thereafter. As such, the complaint could not be withdrawn at this time and Britannia was asked to respond to the Panel's request for further information. The Case Preparation Manager had considered that inter-company dialogue had not resolved matters as at the relevant time Britannia had stated that whilst the two items that were the subject of the 2019 inter-company dialogue had been withdrawn, Ever Pharma's new campaign contained some similar concerns.

An appeal from Ever was subsequently withdrawn.

A Email sent to an independent health professional from an Ever Pharma Nurse Advisor

COMPLAINT

Britannia provided a copy of an email sent to a health professional working in a named region of England by a nurse advisor working for Ever Pharma who then forwarded it to a Britannia employee on 9 May 2019.

The email appeared to be unsolicited, and so, in Britannia's view, it was promotional both in content and intent. Moreover, as it had been sent from a non-promotional member of Ever Pharma staff, it was disguised promotion.

The email briefly described the support service that the Ever Pharma D-mine nurse advisors were offering health professionals. Clause 18.1 did not allow any benefit to be offered to members of the health professions in connection with the promotion of a medicine. The supplementary information to Clause 18.1, Package Deals, described the services of a nurse to administer a medicine as an example of a benefit that could be offered to health professionals as part of a commercial arrangement. Given that the author linked his/her offer of nursing support, with organising a sales call with a promotional member of staff to discuss cost, it clearly made this link.

Britannia noted that the email offered nursing support to patients who 'may be considered and commenced on Dacepton (apomorphine)'. The supplementary information for Clause 18.1, Package Deals, referred only to services of a nurse to administer a medicine and not to influence prescribing decisions for those Parkinson's patients under treatment consideration. Britannia alleged that the offer went beyond the scope of a *bona fide* package deal.

Britannia stated that the email did not contain, nor provide a link to, prescribing information for either presentation of Dacepton (10mg/ml solution for injection in a cartridge or 5mg/ml solution for infusion) which was mandatory for all promotional material. Britannia also noted that neither

the non-proprietary name nor a list of active ingredients, (apomorphine hydrochloride hemihydrate) was included.

On the balance of probabilities, Britannia alleged that the promotional email:

- did not go through any internal approval system and was therefore not certified in its final form by a nominated medical signatory
- was sent without prior consent from the recipient to receive promotional material from Ever Pharma via email
- was sent from a member of staff acting under the role of a medical representative who had not commenced, sat or passed an appropriate examination.

Britannia alleged that the activities which Ever Pharma had instructed the nurse in question to undertake clearly demonstrated poor standards. As an independent health professional had felt compelled to alert Britannia of this activity, led the company to consider that such activity had brought discredit upon, and reduced confidence in, the pharmaceutical industry.

In summary, Britannia alleged that the email was in breach of Clauses 2, 4.3, 9.1, 9.9, 12.1, 14.1, 16.3 and 18.1.

RESPONSE

Ever Pharma stated that the company recognised the content of this email as a response to questions from a health professional and thus considered it to be reactive and not unsolicited.

This was a standard format that Ever Pharma nurses had used on multiple occasions for solicited requests.

They referred to the local representatives to emphasise the separation of the clinical matters they could discuss and offered contact details for commercial matters they could not answer due to their promotional nature.

Ever Pharma provided briefing documents dated September and October 2019 dealing with how to demonstrate its devices and set out what nurses could and could not respond to.

Ever Pharma stated that if the physician reached out to the representative regarding a commercial or promotional matter, the representative would have followed the briefing document for gaining consent to email and used the template email (ref EVP-037 and EVP-034).

Ever Pharma stated that it was not being obstructive; it genuinely could not identify the specific email from the redacted information provided, despite investigating fully, as it did not contain the recipient, the date of sending, headers and footers, the total email trail or confirmation of which email account the Ever Pharma nurse had used. The nurse in question had an Ever Pharma email address and an NHS email address, Ever Pharma had no right to search the NHS email address.

Ever Pharma stated that it was confident that on every occasion this format was used, that it was a reactive response.

Ever Pharma stated that it was willing to contact the health professional if Britannia disclosed his/her name and obviously it would investigate with an open mind and, if necessary, it would be prepared to change its response if, following that contact, it came to a different conclusion.

Ever Pharma stated that if it became clear in this interaction that an email sent to a clinical team, including a Britannia nurse in his/her NHS role, was then forwarded to the Britannia commercial organisation by that Britannia nurse, this would, of course, be a significant breach of confidentiality.

In response to a request for further information, Ever Pharma submitted that the Ever Pharma nurse support team provided a service for patients who were prescribed Dacepton. All were experienced Parkinson's or Neurology nurses with specific training and significant experience in the use of Apomorphine as a treatment for Parkinson's disease. They had honorary NHS contracts which enabled them to liaise directly with the patients, NHS Parkinson's disease team and the prescribing physician. They were available to answer questions for patients and they might provide feedback to the prescribing team on optimising an individualised dose of apomorphine. The Nurse team trained individual patients or their carers in the use of the D-mine Pen and the D-mine pump. They would also offer support and training to supplementary care teams such as community nursing, ward staff (if patients were admitted) and for neurology, care of the elderly and pharmacy departments as requested. In this role, they operated in an essentially similar fashion to the Britannia apomorphine nurse team and many other Pharma disease or therapy supported nurse teams, a further example of another named pharmaceutical company was given. Ever Pharma noted that such practices were widespread across the UK Pharma industry and provided invaluable support to patients. In this regard, the Ever Pharma D-mine nurse team was no different. Ever Pharma offered a package deal for Dacepton which included nurse support in compliance with Clause 18.1 of the Code; details were provided.

Ever Pharma submitted that the legitimacy of an apomorphine nurse support team had been reviewed previously by the PMCPA (Case AUTH/2443/10/11 when Britannia was part of Genus Pharmaceuticals) and was found to be compliant with the Code guidance on package deals. Details of the nurse support service were provided.

The primary remit of the nurse team was to provide support for patients whose health professional had decided to prescribe Dacepton and, as a result, was non-promotional in nature. However, when Ever Pharma entered the UK market, a number of health professionals who had seen or heard of the new medical devices, which were specifically designed for the administration of Dacepton, requested a demonstration. The nurse team who had been specifically trained on the devices were asked to respond to demonstration requests from the health professionals as Ever Pharma felt that an expert-to-expert interaction was most appropriate. Ever Pharma noted that, as detailed in the accompanying briefing, the nurse team were tasked to focus solely on the form and functionality of the devices and not to discuss the medicine during such conversations.

Ever Pharma agreed that it was difficult to fully understand the nature of the email. It had been redacted and Ever Pharma had never seen the full communication, nor could it confirm its source or legitimacy. Ever Pharma stated that it was difficult to draw conclusions about the nature of the alleged communication without full access to the message and with it the remainder of the email trail which might place the message in a different light. If the representation provided by Britannia was accurate, Ever Pharma would expect that the email was written following a request for an introduction to D-mine devices. The wording indicated

that the Ever Pharma nurse recognised her non-promotional role by stating that she could not comment on the commercial nature of the product and if the health professional required this information, he/she would need to discuss this with a commercial colleague, this approach would be consistent with the nurse's job description and briefing. Ever Pharma noted that it struggled to interpret the email further without access to the full email trail. The current record was incomplete and could only be interpreted with a more comprehensive understanding of the setting in which it has been written.

PANEL RULING

The Panel noted that the complainant bore the burden of proof on the balance of probabilities. A judgement had to be made based on the evidence provided by both parties.

The Panel noted that neither it nor Ever Pharma had seen the original unredacted email trail. The Panel noted Ever Pharma's submission that it was thus difficult to fully understand the nature of the email. The Panel noted Ever Pharma's submission that it could not identify the email in question from the redacted information provided by Britannia nor could it confirm its source or legitimacy. Ever Pharma submitted that if the representation provided by Britannia was accurate, Ever Pharma would expect that the email was written following a request for an introduction to D-mine devices.

The Panel noted Ever Pharma's submission that it was a standard format that Ever Pharma nurses had used on multiple occasions for solicited requests and it was confident that on every occasion it was used, that it was a reactive response to a question from a health professional.

In the Panel's view, the content of the email in question, as provided by Britannia, was not clear that it was a reactive response to a health professional as submitted by Ever Pharma. It could equally be viewed as an unsolicited general introduction to Ever Pharma's nurse service offerings. It introduced the nurses by reference to their role in the provision of nursing support to patients who might be considered and commenced on Dacepton (apomorphine) and then offered to show and demonstrate new devices and to send support materials.

The Panel noted that the briefing document for the D-mine Care Nurse Advisor team (ref EVP-033 dated September 2018) provided by Ever Pharma stated that, in response to a request from a health professional for demonstration, the nurses were able to facilitate a short educational session. The briefing also stated that the session was non-promotional and that the nurses must not discuss the pricing of any active medicine, devices or associated ancillary consumables. The updated version (ref EVP-033.01 dated April 2020) included the same information outlined above. The Panel noted that the briefing material only referred to the demonstration of devices, not the other matters referred to in the email at issue.

The Panel considered that, given its content if the email was indeed proactive, it was thereby promotional. Noting its comments above, including the impression given by the email, the Panel considered that it was not possible to determine where the truth lay in relation to the solicited or unsolicited status of the email in question.

The Panel noted that the email in question went beyond a reference to the demonstration of devices; it introduced the authors of the letter by reference to their role in the provision of nursing support to patients who might be considered and commenced on Dacepton (apomorphine), offered to send support materials and arrange for a representative to come and

see the reader to discuss costs. The Panel noted Ever Pharma's submission that the nurse providers referred to the local representatives to emphasise the separation of the clinical matters they could discuss and offered contact details for commercial matters they could not answer due to their promotional nature. The Panel noted that, on the evidence provided, it was not possible to determine whether any information had been specifically requested by the health professional. The complainant had not established, on the balance of probabilities, that the email was unsolicited and thereby promotional as alleged. The Panel therefore ruled no breach of Clauses 12.1, 4.3, 9.9 and 14.1. Given that the status of the email was unclear, the complainant had not established that the nurse was acting as a representative in sending the email and thus the requirement to take an appropriate examination was not relevant. The Panel therefore ruled no breach of Clause 16.3.

In relation to the allegation that the reference in the email to patients 'who may be considered or commenced on Dacepton' meant that the package deal was not *bona fide*, the Panel noted that Clause 18.1 stated that no gift, pecuniary advantage or benefit may be supplied, offered or promised to members of the health professions or to other relevant decision makers in connection with the promotion of medicines or as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine, subject to the provisions of Clauses 18.2 and 18.3. The Panel noted that it had previously been decided that Clause 18.1 applied to individuals rather than organisations etc.

The supplementary information to Clause 18.1 stated that Clause 18.1 does not prevent the offer of package deals which are commercial arrangements whereby the purchase of a particular medicine is linked to the provision of certain associated benefits as part of the purchase price, such as apparatus for administration, the provision of training on its use or the services of a nurse to administer it. The transaction as a whole must be fair and reasonable, and the associated benefits must be relevant to the medicine involved.

The Panel noted Ever Pharma's submission that it offered a package deal for Dacepton which included nurse support in compliance with Clause 18.1. According to the document provided by Ever Pharma (ref EVP-065, dated October 2019), Ever Pharma offered a package deal to all primary and secondary care providers in England and Scottish, Welsh and Northern Irish equivalents who purchased, or had committed to purchase, a Dacepton product. It was not available to providers who did not purchase or intend to purchase a Dacepton product. The package deal offered benefits associated with Dacepton products including bespoke training for providers, patients and carers on how to use the D-mine Pump and D-mine Pen, one of the services referred to in the email in question.

The Panel noted, in general terms, that a package deal was a commercial arrangement and thereby promotional. The Panel noted that the complainant had not raised concerns about the status of health professionals who ought to be contacted about such matters and this was not considered by the Panel. In relation to the narrow allegation that the package deal was not *bona fide*, the Panel considered that the reference to patients who may be considered for, or commenced on, Dacepton was not necessarily inappropriate in relation to the overall commercial arrangements for a package deal. Such arrangements were promotional and health professionals might consider such arrangements in relation to patients who may be considered for, or commenced on, Dacepton. The Panel therefore ruled no breach of Clause 18.1.

The Panel noted its comments and rulings above and consequently ruled no breach of Clauses 9.1 and 2.

B Leavepiece for Dacepton Pump 5mg/ml in 20ml vials for infusion (ref EVP-091, dated September 2019)

1 Imagery of the pump attached to the patient's belt

This image appeared on the front page of the leavepiece.

COMPLAINT

Britannia noted the image of a male patient with what appeared to be the D-mine 8 pump attached to his belt with an infusion line sited on his stomach. Britannia alleged that the image had been distorted to make the D-mine pump appear smaller than it really was; it was a misleading representation of the true dimensions. Britannia stated that its concerns were supported by clinical observations made by its nurse team.

Britannia stated that although in the revised material (ref EVP-091) a footnote 'Pump size (without reservoir) Length 114.3mm, Width 61.4mm, Depth 29.9mm' appeared at the bottom of page under the image, Britannia did not consider that this rectified, or negated, the misleading visual representation of the true dimensions of the D-mine pump. The image juxtaposed on a man's belt clearly did not reflect the dimensions of the pump accurately, especially not its width and depth.

RESPONSE

Ever Pharma stated that, firstly, it was concerned that the Britannia nurse team had made clinical observations on patients who were being treated with the D-mine pump. Ever Pharma had not trained any members of the Britannia nurse team on the use of the device thus it did not consider clinical involvement by the Britannia nurse team was appropriate. Ever Pharma was concerned how Britannia nurses would justify that a clinical observation was in the patient's best interest if it had no purpose except to forward information to the commercial team at Britannia. Ever Pharma noted that no suggestion was made that the clinical nurses had secured patient consent to share observations of the device relative to their partially disrobed bodies. Ever Pharma stated that it was familiar with honorary contracts issued by the NHS and did not feel that Britannia nurses acting for an NHS trust could, or should, share such information with the commercial team at Britannia.

Secondly, Ever Pharma stated that it would respond quoting wording from the complaint itself 'the footnote pump size without reservoir (Length 114.3mm Width 64.1mm and Depth 29.9mm) appeared on the bottom of page 1 in EVP-091 under the imagery'. Indeed, the accurate dimensions were clearly stated immediately below the image in question. EVP-091 made no attempt to hide the true dimensions of the D-mine pump.

Thirdly, online sales sites that stocked the type of canvas belts illustrated in the picture in question typically had a width of between 3.8 and 4cm.

The pump without the case was 6.4cm wide thus Ever Pharma believed that the image was an accurate representation of a patient wearing the D-mine pump including the patient's belt as a visual reference. Britannia's assertion that the image did not clearly reflect the width and depth of the pump was particularly difficult to comprehend as it was a 2D image.

Ever Pharma stated, as further commitment to its total transparency in this matter, it had worked hard to ensure that health professionals had seen or held a physical device so that they could fully evaluate it. Indeed, many Parkinson's nurse specialists now routinely borrowed demonstration devices so they could discuss with the patient which device he/she would prefer. Ever Pharma would, of course, in confidence, lend a physical pump to the committee for evaluation if required.

PANEL RULING

The Panel noted Ever Pharma's submission that online sales sites that stocked the type of canvas belts illustrated in the picture in question typically had a width of between 3.8 and 4cm and that the image was an accurate representation of a patient wearing the D-mine pump including the patient's belt as a visual reference. In the Panel's view, there was a difference between the literal representation of a device and a depiction of it as part of an advertising visual. Whether the latter was acceptable in relation to the requirements of the Code, would depend on context. In the Panel's view, noting Ever Pharma's submission, the size of the pump in relation to the belt size within the image did not appear to be misleading. The Panel further noted that the actual size of the pump was given below the image and, although it would have been helpful if the text was more prominent, the information was given in a standalone paragraph and 'pump size' was written in uppercase font which, in the Panel's view, meant that it was reasonably noticeable. The Panel therefore ruled no breach of Clauses 7.2, 7.4 and 7.8.

2 Claim '7 days in-use stability data supports entire content use'

This claim appeared on page 3 of the leavepiece on a page headed 'EVER Pharma D-Mine Pump advantages:'. Two columns compared features of the D-mine Pump with the 20ml Syringe Driver used with APO-go in relation to handling, features, enhanced technology and discreet design.

COMPLAINT

Britannia alleged that it considered this claim, listed as a characteristic in the features box in the D-Mine pump column, was inconsistent with the summary of product characteristics (SPC) for Dacepton 5mg/ml solution for infusion. The full wording under Section 6.3 of the SPC read:

> 'After opening and filling the drug product in syringes attached with infusion sets: chemical and physical in-use stability has been demonstrated for 7 days at 25°C. From a microbiological point of view, unless the method of opening and further handling precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.'

Britannia submitted that as the Dacepton D-mine pump was designed to be used at home by the patient and would be sited next to the patient, where temperatures could exceed 25 degrees, then it failed to see how the risk of microbial contamination could be prevented in such conditions. By cherry-picking the wording from Section 6.3, as Ever Pharma appeared to have done, the promotional item failed to recognise, or draw the prescriber's attention to, the risk of microbial contamination and therefore that the product should be used immediately, as stated in the SPC. Such microbial contamination would also be far more likely if the patient was using the reservoir for up to 7 days with a new infusion line every day being required. Britannia

alleged that the claim failed to encourage rational use of Dacepton 5mg/ml solution for infusion and thus represented a serious risk to patient safety.

RESPONSE

Ever Pharma considered that UK prescribers, pharmacists and specialist nurses were aware of the possibility of microbial contamination of parenteral infusions, and that the medicine was always initiated in secondary care after an area prescribing committee meeting in which the medicine's SPC was fully evaluated.

Ever Pharma submitted that the wording of the complaint suggested confusion over Britannia's understanding of the significance of the 25 degrees Celsius criteria which was used as a measure of ambient temperature in assessing the stability of medicines in general for European licensing. There was no data on microbial contamination of Dacepton at different temperatures.

The phrase 'From a microbiological point of view unless the method of opening and further handling precludes the risk of further contamination the product should be used immediately. If not used immediately in use storage times and conditions were the responsibility of the user' was widely used on the SPCs of parenteral products and did not convey any particular additional risk associated with Dacepton 5mg/ml solution for infusion. The phrase was suggested by the European Medicines Agency (EMA) as a standard phrase and had been since 1999.

Ever Pharma submitted that patients and health professionals were trained in the use of the D-mine pump including daily infusion line changes by the Ever Pharma nurse team prior to its use by individual patients. Part of this training included an emphasis on reducing microbiological contamination through aseptic technique. Ever Pharma provided a blank nurse initial response test form showing the nurses education on the pump use. Ever Pharma also provided an uncontrolled copy of the standard operating procedure (SOP) for patient and health professionals training on the D-mine pump. There were local guidelines in place regarding the use of sterile and alcohol wipes etc, in all cases these took precedence over the company's standard procedures.

Patients who were considered unable to maintain this standard of use, either through the severity of the patient's existing movement disorder or cognitive impairment, were not accepted for D-mine pump use. The relevant patient and staff training materials were provided. The D-mine pump was a European Conformity (CE) marked device which was labelled as being suitable for use by patients and their carers.

With regard to the licensing of Dacepton, Ever Pharma noted that it had been asked by the MHRA to provide information on the in-use life of the product.

Ever Pharma provided confidential information from the product dossier for Dacepton regarding in-use stability testing.

Ever Pharma noted that in the UK all patients using Dacepton and D-mine devices were fully trained, including techniques to avoid contamination, when they started to use the system. Patients were observed and retrained if required as part of the follow-up.

Dacepton 5mg/ml solution for infusion included sodium metabisulphite and sodium hydroxide as an additional protection against microbial contamination. Ever Pharma noted that it had not received any safety reports of local or systemic infections in patients receiving treatment with the D-mine devices.

In response to a request for further information, Ever Pharma submitted that it had not received a reply from the MHRA regarding the regulatory interpretation of Dacepton stability data. Ever Pharma noted that it sent follow-up emails to the original requester asking if they required further information but, to date, had had no further communications.

Ever Pharma submitted that the Dacepton 5mg/ml solution for infusion – Summary of Product Characteristics stated in Section 6.3 Shelf life:

> 'Unopened: 30 months
> After opening and filling the drug product in syringes attached with infusion sets: chemical and physical in-use stability has been demonstrated for 7 days at 25 °C.'

PANEL RULING

The Panel noted that the headline on page 3 of the Dacepton 5mg/ml leavepiece stated 'EVER Pharma D-mine Pump advantages:'. This was followed by two columns comparing the D-mine pump with the 20ml syringe driver used with APO-go. A feature of the D-mine pump included '7 days in-use stability data supports entire content use' whilst for the 20ml syringe driver used with APO-go it was stated that '24 hour in-use stability data was less supportive of using entire content'.

The Panel noted that according to the Dacepton 5mg/ml SPC, whilst chemical and physical in-use stability had been demonstrated for 7 days at 25 degrees Celsius, it did go on to state that, from a microbiological point of view, unless the method of opening and further handling precluded the risk of microbial contamination, the product should be used immediately. The Panel noted Ever Pharma's submission that the wording of the complaint suggested confusion over Britannia's understanding of the significance of the 25 degrees Celsius criteria which was used as a measure of ambient temperature in assessing the stability of medicines in general for European licensing. There was no data on microbial contamination of Dacepton at different temperatures. In relation to the risk of contamination, Ever Pharma submitted that the phrase was widely used on the SPCs of parenteral products and did not convey any particular additional risk associated with Dacepton 5mg/ml solution for infusion. The phrase was suggested by the EMA as a standard phrase and had been since 1999. The Panel also noted Ever Pharma's detailed submission about training to reduce microbiological contamination, including that patients who were considered unable to maintain this standard of use, either through the severity of the patients existing movement disorder or cognitive impairment, were not accepted for D-mine pump use.

The Panel noted that the SOP for patient and health professionals training on the D-mine pump stated that, although D-mine nurses could provide training to fellow nurses, carers patients and their family members, it was not recommended that they provided a competency statement or signed anyone off as being competent in the procedure as this would need to be done while observing practice and would also mean the D-Mine Nurse would have ongoing responsibility for their practice. The SOP stated that nurses should advise the patient that they might keep using the pump for up to 7 days if there was remaining liquid in the reservoir. If the patient was

using the same reservoir the following day, they would be required to remove the infusion line at the end of the day and place a combi stopper in the reservoir to ensure the medication was kept clean. When the patient started the infusion the next day (using the same reservoir) they were required to use a new infusion line and insert as usual to start the infusion up again.

The Panel considered that the failure to include a reference to the risk of microbiological contamination either within, or within the visual field of the table, was misleading. The Panel considered that the claim '7 days in-use stability data supports entire content use' in the absence of such qualification implied that there was no need to consider microbiological contamination and that was not so. A breach of Clause 7.2 was ruled. In the Panel's view, the failure to qualify the claim in question meant that it was inconsistent with the particulars listed in the SPC and did not encourage the rational use of the medicine and breaches of Clauses 3.2 and 7.10 were ruled.

3 Claim '20ml Syringe Driver used with APO-go'

This claim appeared on page 3. Two columns compared features of the D-mine Pump with the 20ml Syringe Driver used with APO-go in relation to handling, features, enhanced technology and discreet design. The claim in question was the heading to the APO-go column.

COMPLAINT

Britannia noted that the claim appeared as a column heading. The SPCs for APO-go PFS 5mg/ml Solution for Infusion in Pre-filled syringe and also Dacepton 5mg/ml solution for infusion under Section 4.2 clearly referred to the option for the medicine 'to be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver. In deliberately choosing to describe the administration of APO-go via a 20ml syringe driver and not doing so for Dacepton, the promotional piece misleadingly implied that Dacepton was the only medicine that was delivered by a branded bespoke pump device, which was not so. Moreover, a syringe driver had connotations of administering palliative medicine. Britannia provided patients with the Crono APO-go Mark 3 Pump, a portable infusion pump designed to be used with the APO-go PFS 5mg/ml Solution for Infusion in Pre-filled syringe. Britannia alleged that this deliberate choice of words was an attempt to directly and deliberately disparage the Crono APO-go Mark 3 Pump.

In response to a request for further information, Britannia submitted that the manufacturer of the pump in question, stated that the CRONO PAR ambulatory infusion pump (CRONO APO Pump III was a specific version of CRONO PAR developed for Britannia) was designed for the subcutaneous infusion of apomorphine in the treatment of Parkinson's disease. The CRONO APO Pump III used specific 20ml CRONO syringes (copy provided) called reservoirs, the use of any other type of syringe was not advised with the CRONO infusion pump. APO-go was supplied in pre-filled glass syringes as apomorphine was not stable in plastic syringes long term. The pre-filled syringe was then transferred to a CRONO reservoir syringe to enable the solution to be delivered via the portable infusion. The reservoir was modified by the removal of the piston rod to enable its attachment to the CRONO APO Pump III (copy provided).

Typically, a syringe driver required an attached plastic plunger, and this was removed from the CRONO reservoir; thus, it was not a syringe. Britannia considered that it was misleading for EVER Pharma to describe the administration of APO-go as via a 20ml syringe driver as the SPC for both APO-go PFS and Dacepton Solution stated 'the choice, of which mini pump and/or

syringe driver to use, and the dosage setting required, will be determined by the physician in accordance with the particular needs of the patient'.

Britannia also alleged that the description of the D-Mine Pump and use of apomorphine were misleading as it was not a medicine/device combination, and this insinuated that only EVER Pharma had a specifically designed pump for the subcutaneous infusion of apomorphine.

Britannia was of the opinion that a health professional would perceive the infusion pump as a pump and not a syringe driver.

RESPONSE

Ever Pharma submitted that this was a vexatious and frivolous complaint which it believed could be answered in a succinct fashion.

Ever Pharma stated that it struggled slightly in replying to this due to the confusion around the Britannia pump's name, as all Britannia materials referred to it as the APO-go pump not the Crono APO-go Mark 3 Pump except when the company referred to it as a syringe driver.

Ever Pharma stated that it assumed that Britannia was complaining that the APO-go Pump was being described as a syringe driver device. Ever Pharma was surprised at this for reasons set out below.

Ever Pharma provided a copy of Britannia's Patient Holiday Letter which stated that it was a syringe driver and copies of a four-page loan contract used by Britannia which referred to 'syringe driver' 20 times. Thus, Ever Pharma stated that its description of the APO-go pump as a syringe driver was consistent with Britannia's own description of the Crono APO-go Mark 3 pump.

Ever Pharma noted that the phrase 'The choice, of which minipump and/or syringe-driver to use, and the dosage settings required, would be determined by the physician in accordance with the particular needs of the patient' was included in the Dacepton SPC.

Ever Pharma stated that the leavepiece, however, clearly described the attributions of the D-mine pump which indeed did not function through a syringe driver mechanism.

Ever Pharma noted that its SPC envisaged that a syringe driver could be used as an alternative to the D-Mine Pump which demonstrated that the company had no negative belief structures associated with syringe drivers.

Further, Ever Pharma did not agree that the term syringe driver was strongly linked to palliative care and believed that prolonged subcutaneous infusions of medicines administered in a variety of clinical settings were often delivered by syringe driver. Ever Pharma believed that syringe drivers continued to play an important role in the delivery of medicines across a wide range of therapeutic areas. Ever Pharma did not share Britannia's negative view of syringe drivers.

PANEL RULING

The Panel noted that the SPCs for both the Dacepton 5mg/ml and APO-go PFS 5mg/ml Solution for Infusion in Pre-filled syringe referred to the option for the medicine 'to be

administered as a continuous subcutaneous infusion by minipump and/or syringe-driver' in Section 4.2. The Panel noted Britannia's submission that, typically, a syringe driver required an attached plastic plunger, and this was removed from the CRONO reservoir; thus, it was not a syringe. The Panel noted Ever Pharma's submission that the leavepiece described the attributions of the D-mine pump which did not function through a syringe driver mechanism whereas a letter from Britannia provided by Ever Pharma described the APO-go infusion, used in conjunction with APO-go solution as a small battery-operated syringe-driver. The Panel further noted that a four-page loan contract provided by Ever Pharma which it stated was used by Britannia referred to APO-go 'syringe driver'.

The Panel did not consider that Britannia had established that there was evidence that Ever Pharma, in referring to a syringe driver in relation to APO-go, was misleading or disparaged APO-go as alleged and no breach of Clauses 7.2 and 8.1 were ruled.

In relation to the allegation that the description of the D-Mine Pump and use of apomorphine were misleading as it was not a medicine/device combination, and this insinuated that only Ever Pharma had a specifically designed pump for the subcutaneous infusion of apomorphine, the Panel did not consider that the features outlined in the D-Mine Pump column, although generally favourable to the D-mine Pump, implied that only Ever Pharma had a specifically designed pump for subcutaneous infusion as alleged. No breach of Clause 7.2 was ruled.

4 Claims 'Dacepton pump delivers annual cost savings vs APO-go Pump' and 'Most cost savings are generated by a reduction in waste'

Page 5 was headed 'Dacepton pump delivers annual cost savings vs APO-go Pump' and featured a cost saving visual which showed the annual savings to be achieved when comparing the annual cost of Dacepton Pump with that of the APO-go Pump at a dose of 75mg per day. Different doses could be input to calculate relevant savings. Text beneath included 'Most cost savings are generated by a reduction in waste'.

COMPLAINT

Britannia noted that the first claim 'Dacepton pump delivers annual cost savings vs APO-go Pump' appeared as the title to a cost comparison wheel featured on page 5 of the Dacepton leavepiece (ref EVP-091). This was further supported by the second claim 'Most cost savings are generated by a reduction in waste' which appeared as the fifth bullet point under the title and cost comparison wheel. Britannia failed to understand, in the absence of a clear breakdown, on what criteria these calculations had been generated. Although Ever Pharma had presented different numbers to that shown in leavepiece EVP-016, the concerns remained that these cost savings might have been made by ignoring the full wording in Section 6.3 of the Dacepton 5mg/ml solution for infusion SPC and suggested that the in-use shelf life of Dacepton was 7 days in all cases.

Britannia, reiterated that the full wording of Section 6.3 of the Dacepton 5mg/ml solution for infusion SPC read:

> 'After opening and filling the drug product in syringes attached with infusion sets: chemical and physical in-use stability has been demonstrated for 7 days at 25°C. From a microbiological point of view, unless the method of opening and further handling precludes

the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.'

As the Dacepton D-mine pump was designed to be used at home by the patient, Britannia failed to see how the risk of microbial contamination could be prevented in such conditions. By cherry-picking the wording from Section 6.3, as Ever Pharma appeared to have done, the promotional item failed to recognise or draw the prescriber's attention to the risk of microbial contamination and that the product should therefore be used immediately. Britannia alleged that the claim did not encourage rational use of Dacepton 5mg/ml solution for infusion, and thus represented a serious risk to patient safety. In addition, the claim deliberately disparaged the APO-go Pump which was the direct comparator.

RESPONSE

Ever Pharma provided a copy of the data on file from EVP-091 to support its position.

Ever Pharma submitted that the D-mine pump device used an interchangeable mechanical volumetric pump (known as the pump reservoir) that was housed in a battery and display unit. Both parts together became the D-Mine pump.

The reservoir was filled via an automatic system from a 20ml (5mg/ml, 100mg) vial of Dacepton. The reservoir was listed in Part IX of the drug tariff.

Ever Pharma noted that it charged for this item. To offset the cost and reduce cost burden, the company supplied infusion lines free of charge with the medicine and the pump battery and display unit was supplied free of charge as a loan by Ever Pharma. APO-go (apomorphine) was supplied by Britannia Pharmaceuticals. Britannia supplied 10ml (5mg/ml, 50mg) prefilled syringes of APO-go and also supplied a syringe driver free and dedicated plastic syringes for the driver free of charge. Britannia did not supply infusion lines; they were supplied as an extra prescription item.

Ever Pharma submitted that the major difference between the two products was the in-use shelf life.

Ever Pharma stated that, according to the most recent study, the Toledo Study (Lancet 2017), the average patient used 4.65mg/hour for 16 hours a day. A total daily dose of approximately 75mg. Every patient used 1 infusion line per day.

In that case, a patient would use two APO-go pre-filled syringes each day, ie 100mg, but, as according to the SPC, APO-go must be used within 24 hours or discarded, the patient would use 75mg and discard the remaining 25mg. This process would repeat daily.

Alternatively, with Dacepton, the patient would use 1 vial (100mg) but only use 75mg on the first day. On the next day the patient would use the remaining 25mg and then refill a new reservoir. The patient would repeat the process every 1.333 days, thus saving 175mg of medicine over the course of the week.

Item	Dacepton	APO-go	Daily Cost at 75mg/day Dacepton/D-mine reservoir*	Daily Cost at 75mg/day APO-go	Annual Cost at 75mg/day Dacepton*	Annual Cost at 75mg/day APO-go
Pump	Free	Free	0	0		
Reservoir/Syringe	£70/10	Free	5.38	0	1,916.25	
Infusion line	Free	£47.62/10	0	4.76		1,738.86
Medicine for 100mg	29	29.24	21.75	29.244	7938.75	10674.06
		Total daily cost	**27.13**	**34.004**	**£ 9,855.00**	**£ 12,412.92**

* D-mine reservoir cost calculated by cost/no. of day used

Ever Pharma noted that Britannia's core assertion was that it either disputed the in-use life of Dacepton, in which case Ever Pharma asserted that it was entitled to base claims on its current licence, or perhaps additionally Britannia was asserting that Ever Pharma was making promotional claims that were not a fair representation of Ever Pharma's licence or as Britannia described it 'cherry picking'. Ever Pharma referred to the documentation (provided), the information above and the guidance note from the EMA on biological stability and wording of SPCs.

PANEL RULING

The Panel noted its comments at Point 2 above about microbiological contamination and considered that they were relevant here. The Panel noted Ever Pharma's submission that the major difference between the products was in-use shelf life and noted its submission about the Toledo study. The Panel noted that, according to the Dacepton 5mg/ml SPC whilst chemical and physical in-use stability had been demonstrated for 7 days at 25 degrees Celsius, it did go on to state that from a microbiological point of view, unless the method of opening and further handling precluded the risk of microbial contamination, the product should be used immediately which was not stated or referred to on the page in question. The Panel noted the text beneath the cost wheel stated that most cost saving was generated due to a reduction in waste. The text also referred to the 7 day stability of Dacepton and the single use of Apo-go. On balance, the Panel considered that, given the cost saving was due primarily to the 7 day stability the failure to include relevant information about the risk of microbiological contamination, meant that the page in question was not sufficiently complete to enable the reader to form their own opinion in relation to the claims in question 'Dacepton pump delivers annual cost savings vs APO-go Pump' and 'Most cost savings are generated by a reduction in waste' which were thus misleading and a breach of Clauses 7.2 and 7.3 were ruled. The claims within the context of the page were incapable of substantiation and a breach of Clause 7.4 was ruled.

C Leavepiece for Dacepton Cartridge 10mg/ml solution for injection (ref EVP-090)

1 Claim 'Has a safety stop' and statements in relation to dose correction

The claims in question appeared on page 2 which featured 2 columns comparing features of the D-mine Pen with APO -go Pen in relation to design, handling and usability, in use stability and precision.

COMPLAINT

Britannia noted that this claim introduced the table on page 2 which drew direct comparisons between the characteristics of the D-mine Pen with the APO-go Pen.

Britannia stated that the overall impression created by the table and the wording used to describe the characteristics of the two devices resulted in an unbalanced, unfair and ambiguous comparison. The table disparaged the APO-go Pen and also represented a risk to patient safety for the reasons given below:

- 'Has a safety stop' was listed as a characteristic in the handling and usability box under the APO-go Pen column and was directly compared to 'Safety stop: Will not allow dialling up of doses higher than remaining drug in the cartridge' as a characteristic in the handling and usability box under the D-mine pen column.

The APO-go Pen could not be primed if there was insufficient medicine remaining in the pen. Britannia considered that by not providing supplementary information in the APO-go Pen column, as had been done in the D-mine Pen column, a deliberate attempt had been made to suggest that the APO-go pen had an inferior safety stop feature compared with the D-mine pen, which was not so.

- 'Dose Correction: Dose correction as pen can dial up and down' was listed as a characteristic in the handling and usability box under the D-mine pen column and was directly compared to 'Can only dial up doses, corrections require a restart of the process' as a characteristic in the handling and usability box under the APO-go Pen column.

Britannia submitted that the APO-go Pen allowed a patient to select his/her dose by turning the dosage dial in one direction. If a dose correction was required, the patient just needed to continue turning the dosage dial until the correct dose was selected. Britannia considered that the wording used in the comparison was a deliberate attempt to suggest the APO-go Pen was inferior to the D-mine pen.

- 'In-use stability: 15 days' is listed as a characteristic under the D-mine pen column.

Britannia alleged that the claim was inconsistent with the SPC for Dacepton 10mg/ml solution for injection in cartridge. The full wording under Section 6.3 read:

> 'After first opening: Chemical and physical in-use stability has been demonstrated for 15 days at 25°C. From a microbiological point of view, unless the method of opening and further handling precluded the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions were the responsibility of the user.'

Britannia stated that as the Dacepton D-mine Pen was designed to be used at home by the patient, it failed to see how the risk of microbial contamination could be prevented in such conditions, especially if the patient continued to handle and use the pen over a 15 day period. By cherry-picking the wording from Section 6.3, as Ever Pharma appeared to have done, the promotional item failed to recognize or draw to the prescriber's attention the risk of microbial contamination and therefore that the product should be used immediately. Britannia alleged that the claim did not encourage rational use of Dacepton 10mg/ml solution for injection in cartridge and therefore represented a serious risk to patient safety.

RESPONSE

Ever Pharma stated that, as presented in the leavepiece, both the D-mine pen and the APO-go pen had a safety stop. The Ever Pharma D-mine pen device primed the spring as it dialled up the dose. The device had a safety stop that would not allow users to dial up a dose of more than was left in the cartridge. The APO-go pen would allow the dose selector wheel to dial to doses of up to the maximum of 10mg. The user then manually primed the pen using the integral plunger by pulling the plunger out. Using the APO-go pen, regardless of the amount left in the pen, the user could dial up to the maximum dose. The safety stop in this device would not allow the user to pull the priming plunger out higher than the dose of apomorphine in the pen. Thus, there was a distinction in the safety mechanisms offered between the D-mine pen and the APO-go pen. This difference was the basis of the claims in the leavepiece.

With regard to dose correction, Ever Pharma submitted that the claim was supported by the wording in the complaint itself. Brittania highlighted the fact that dose correction when using the D-mine pen could be performed by dialling up and down whereas dose modification with the APO-go pen could only be made by turning the dosage dial in one direction . This was clearly consistent with the claim. By dialling to the original start point (zero), Ever Pharma suggested that the user had restarted the process.

With regard to in-use stability, Ever Pharma submitted that UK prescribers, pharmacists and specialist nurses were aware of the possibility of microbial contamination of parenteral medicines, and as part of the process of being approved by Area Prescribing Committees, this matter would have been reviewed.

Ever Pharma considered that the complaint suggested that Britannia was confused over its understanding of the significance of 25 degrees Celsius which was used as a measure of ambient temperature in assessing the stability of medicines in general.

Ever Pharma stated that there was no data on microbial contamination of Dacepton at different temperatures.

Ever Pharma stated that the phrase ‘From a microbiological point of view unless the method of opening and further handling precludes the risk of further contamination the product should be used immediately. If not used immediately in use storage times and conditions were the responsibility of the user’ was widely used on the SPC of parenteral products and did not infer any particular additional risk associated with Dacepton.

Ever Pharma submitted that all patients and health professionals were trained to use the D-mine pen by the Ever Pharma nurse team before it was used by individual patients. Part of this training included an emphasis on reducing microbiological contamination through aseptic technique a feature which was also a focus of the accompanying patient support materials. Patients who were considered unable to maintain this standard of use, either through existing movement disorder or cognitive impairment, were not accepted for D-mine pen use.

Ever Pharma noted that Dacepton included sodium metabisulphite and sodium hydroxide as an additional protection against microbial contamination. The company had not received any safety reports of local or systemic infections in patients receiving treatment with D-mine devices.

In response to a request for further information, Ever Pharma stated that it had not received a reply from the MHRA with regard to the regulatory interpretation of Dacepton stability data. It sent the full response it had provided to the MHRA to the PMCPA. Ever Pharma stated that it sent follow-up emails to the original requester asking if they required further information, but to date, it had had no further communications. The current SPCs clearly stated:

> 'Ever Pharma noted that 6.3 Shelf life of the Dacepton 10 mg/ml solution for injection in cartridge SPC stated:
>
> > Unopened: 2 years
> > After first opening: Chemical and physical in-use stability has been demonstrated for 15 days at 25°C.'

PANEL RULING

The Panel noted that the APO-go pen SPC stated 'Preparing for the next injection (q) Remove the outer sleeve of the Pen and check there is enough apomorphine left in the cartridge for your next injection. If there is, put a new needle in place in the same way as before'. The Panel noted Britannia's submission that the APO-go Pen could not be primed if there was insufficient medicine remaining in the pen. The Panel noted, however, that according to the APO-go pen PIL accessed on the emc, 'it was only if your dose was 1 mg, that a patient had to start by emptying a 1 mg dose onto a paper tissue and discarding it which was called "priming" and was important because it ensured they got a full dose the first time using the Pen. Then the dose could be set to that required for injection and could be injected in the usual way. If the first dose required was more than 1 mg, you did not need to prime the Pen'.

The Panel noted Ever Pharma's submission that, as presented in the leavepiece, both the D-mine pen and the APO-go pen had a safety stop. The Ever Pharma D-mine pen device primed the spring as it dialled up the dose. The device had a safety stop that would not allow users to dial up a dose of more than was left in the cartridge. The APO-go pen would allow the dose selector wheel to dial to doses of up to the maximum of 10mg. The user then manually primed the pen using the integral plunger by pulling the plunger out. Using the APO-go pen, regardless of the amount left in the pen, the user could dial up to the maximum dose. The safety stop in this device would not allow the user to pull the priming plunger out higher than the dose of apomorphine in the pen. Thus, there was a distinction between the safety mechanisms of the D-mine pen and the APO-go pen.

The Panel noted that it appeared that the APO-go Pen in contrast to the D-mine Pen would allow a user to dial up a dose higher than remaining medicine in the cartridge, however, according to Ever Pharma, the safety stop in this device would not allow the user to pull the priming plunger out higher than the dose of apomorphine in the pen. The Panel noted that whilst it might have been helpful to provide further details in the table with regard to the safety stop mechanism in relation to the APO-go PEN, it was clear that it had a safety stop. On balance, the Panel considered that the failure to provide the equivalent details for the APO-go Pen implied that the D-mine Pen had a material benefit in this regard and was misleading. A breach of Clauses 7.2 and 7.3 was ruled. The Panel did not consider that the failure to provide such equivalent details disparaged APO-go Pen as alleged, it was made clear that the Pen had a safety stop. No breach of Clause 8.1 was ruled.

The Panel noted Ever Pharma's submission with regard to dose correction that Britannia had highlighted the fact that dose correction when using the D-mine pen could be performed by dialling up and down, whereas dose modification with the APO-go pen could only be made by turning the dosage dial in one direction dialling to the original start point (zero), ie the user had to restart the process. The Panel noted that the APO-go pen SPC stated 'If you pass your prescribed dose while turning the dial, just continue pressing and turning in the same direction until the arrow points to the dose your doctor chose for you'. In the Panel's view, having to dial back to the dose required by turning the dosage dial in one direction and starting again at zero was, in essence, restarting the dosing process. However, the way it was worded in the detail aid might imply that the user had to restart the whole process of preparing the pen rather than merely continuing to press and turn the dial in the same direction until the arrow pointed to the required dose. The Panel considered that the comparison was misleading in this regard and a breach of Clauses 7.2 and 7.3 were ruled.

In relation to the claim 'In use stability 15 days', the Panel considered that its comments at Point 2 above were relevant here. The Panel noted that according to the Dacepton 10mg/ml pen SPC whilst chemical and physical in-use stability had been demonstrated for 15 days at 25 degrees Celsius, it went on to state that, from a microbiological point of view, unless the method of opening and further handling precluded the risk of microbial contamination, the product should be used immediately. The Panel considered that failure to include information about the risk of contamination as part of, or within the visual field of, the claim was misleading and a breach of Clauses 7.2 and 7.3 were ruled. In the Panel's view, the omission meant that the claim 'in use stability 15 days' was inconsistent with the particulars within the SPC and did not encourage the rational use of the medicine and breaches of Clauses 3.2 and 7.10 were ruled.

2 Page 3 Cost comparison

Page 3 was headed 'Dacepton pump delivers annual cost savings vs APO-go Pump' and featured a cost saving visual which showed the annual savings to be achieved when comparing the annual cost of Dacepton Cartridge with that of the APO-go Pump at a dose of 7mg per day. Different doses could be input to calculate relevant savings. Text beneath included 'Cost savings are mostly generated through reduction in wastage due to the prolonged in use life of Dacepton Cart[r]idge'.

COMPLAINT

Britannia stated that as Ever Pharma had not provided, via inter-company dialogue, a clear cost breakdown and on what criteria these calculations had been generated, the overall impression created by the cost comparison wheel resulted in an unbalanced, unfair and ambiguous comparison. Britannia alleged that the claim 'Dacepton pump delivers annual cost savings vs APO-go Pump' represented a false and misleading cost saving to any budget holder who had received this material, was inconsistent with the SPC and thus represented a risk to patient safety. In addition, the cost comparison wheel disparaged the APO-go Pen for the reasons given below:

> Britannia was concerned that the cost savings had been made by ignoring the full wording in section 6.3 of the Dacepton 10mg/ml solution for injection in cartridge SPC, suggesting that the in-use shelf life of Dacepton was 15 days in all cases.

The full wording under Section 6.3 of the Dacepton 10mg/ml solution for injection in cartridge SPC read:

> 'After first opening: Chemical and physical in-use stability has been demonstrated for 15 days at 25°C. From a microbiological point of view, unless the method of opening and further handling precluded the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions were the responsibility of the user.'

As the Dacepton D-mine Pen was designed to be used at home by the patient, Britannia failed to see how the risk of microbial contamination could be prevented in such conditions. By cherry-picking the wording from Section 6.3, as Ever Pharma appeared to have done, the promotional item failed to recognize or draw to the prescriber's attention the risk of microbial contamination and therefore that the product should be used immediately.

Britannia stated that patients used apomorphine as an intermittent subcutaneous injection 'as needed' and so did not have a fixed dose per day, but instead a fixed dose per injection. The cost comparison model presented in the leavepiece, which was based purely on 'dose per day/mg', was therefore an unrealistic and misleading representation of how much medicine a patient would require, given the nature of Parkinson's disease and individual patient needs.

RESPONSE

Ever Pharma submitted that UK prescribers, pharmacists and specialist nurses were aware of the possibility of microbial contamination of parenteral medicines and as part of the process of being approved by area prescribing committees, this matter would have been reviewed.

Ever Pharma stated that the wording of the complaint suggested confusion over Britannia's understanding of the significance of 25 degrees Celsius which was used as a measure of ambient temperature in assessing the stability of medicines in general. There was no data on microbial contamination of Dacepton at different temperatures.

The phrase 'From a microbiological point of view unless the method of opening and further handling precludes the risk of further contamination the product should be used immediately. If not used immediately in use storage times and conditions are the responsibility of the user' was widely used on the SPCs of parenteral products and did not infer any particular additional risk associated with Dacepton. Ever Pharma noted that the pens had no aseptic transfer step.

All patients and health professionals were trained to use the D-mine pen by the Ever Pharma nurse team prior to its use by individual patients. Part of that training included an emphasis on reducing microbiological contamination through aseptic technique, a feature which was also a focus of the accompanying patient support materials. Patients who were considered unable to maintain this standard of use, either through existing movement disorder or cognitive impairment, were not accepted for D-mine pen use.

Finally, Ever Pharma noted that the Dacepton formulation included sodium metabisulphite and sodium hydroxide as an additional protection against microbial contamination. The company had not received any safety reports of local or systemic infections in patients receiving treatment with the D-mine devices.

PANEL RULING

The Panel noted the text beneath the cost wheel stated that 'cost savings are mostly generated through reduction in wastage due to the prolonged in use life of Dacepton Cartridge'. The Panel noted its comments above at Point B4 and considered that they were relevant here. The Panel noted that, according to Section 6.3, Shelf life of the Dacepton 10mg/ml SPC whilst chemical and physical in-use stability had been demonstrated for 15 days at 25 degrees Celsius, it went on to state that from a microbiological point of view, unless the method of opening and further handling precluded the risk of microbial contamination, the product should be used immediately. The Panel considered that failure to include this relevant information meant that the page in question was not sufficiently complete to enable the reader to form their own opinion in relation to the claims regarding cost savings and was thus misleading and breaches of Clauses 7.2 and 7.3 were ruled. The failure to include this relevant information about the risk of microbiological contamination meant that the impression given by the page, including the heading in relation to the magnitude of cost savings, was incapable of substantiation and a breach of Clause 7.4 was ruled.

The Panel further noted Britannia's concern that patients used apomorphine as an intermittent subcutaneous injection 'as needed' and so did not have a fixed dose per day, but instead a fixed dose per injection and the cost comparison model presented in the leavepiece was based purely on 'dose per day/mg' which was therefore an unrealistic and misleading representation of how much medicine a patient would require, given the nature of Parkinson's disease and individual patient needs. The Panel noted that Ever Pharma had not responded in this regard.

The Panel noted that the cost calculation wheel stated 'Input your dose per day and find out what your annual saving could be using Dacepton Cartridge vs using APO-go PEN'. Below the cost calculation wheel it stated that daily dose was calculated as number of doses per day x mg per dose'.

According to the APO-GO pen and D-Mine SPCs, the optimal dosage of apomorphine hydrochloride varied between individuals, but once established, remained relatively constant for each patient.

The daily dose of Dacepton varied widely between patients, typically within the range of 3-30mg, given as 1-10 injections and sometimes as many as 12 separate injections per day. It was recommended that the total daily dose of apomorphine hydrochloride hemihydrate should not exceed 100mg and that individual bolus injections should not exceed 10mg.

The Panel noted that according to the APO-GO pen and D-Mine SPCs, patients selected for treatment should be able to recognise the onset of their 'off' symptoms and be capable of injecting themselves with the appropriate dose once it was determined or else have a responsible carer able to inject for them when required as a single subcutaneous injection into the lower abdomen or outer thigh at the first signs of an 'off' episode. It could not be excluded that absorption may differ with different injection sites within a single individual. Accordingly, the patient should then be observed for the next hour to assess the quality of their response to treatment and alterations in dosage might be made according to the patient's response.

The Panel considered that failure to include relevant information about the 'as needed' dosage of the APO-go Pen meant that the page in question was not sufficiently complete to enable the

reader to form their own opinion in relation to the claims regarding cost savings based on a daily dose as alleged and was thus misleading and breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **24 October 2019**

Case completed **31 August 2021**