**CASE AUTH/3320/3/20**

# COMPLAINANT v TAKEDA

## Promotion of Prostap

**A complainant, who described him/herself as a concerned UK health professional, complained about Prostap (leuprorelin acetate) material produced by Takeda UK hosted on the website of the journal 'Guidelines in Practice'. Prostap was available in two formulations, Prostap SR DCS (dual chamber syringe) and Prostap 3 DCS; both were indicated for use in certain patients with breast cancer. Additionally, Prostap SR DCS was indicated for the preservation of ovarian function in pre-menopausal women with neoplastic disease undergoing chemotherapy treatment that could cause premature ovarian insufficiency.**

**The complainant drew attention to a webpage on the Guidelines in Practice website which presented a Formulary Decision Guide on Prostap DCS and provided details of the link to the prescribing information. The complainant stated that neither the Formulary Decision Guide nor the prescribing information included the statement that was added to Section 5.1 of the summary of product characteristics (SPC) in August 2019 that Prostap 3 DCS should not be used for preservation of ovarian function. The complainant stated that, in that regard, the Formulary Decision Guide promoted an off-licence indication as it listed ovarian preservation as an indication for use. The complainant considered that patient safety was at issue.**

**The detailed response from Takeda is given below.**

**The Panel noted that the material at issue was primarily about the use of Prostap DCS (either formulation) in patients with breast cancer. Information on the use of the two formulations had been included in the indication section within the Formulary Decision Guide. The first bullet point in that section stated 'Prostap SR DCS and Prostap 3 DCS are licensed for breast cancer as follows:' and so it was immediately clear to the reader that the information which followed would relate to both formulations. The second bullet point, however, was presented in a different style and stated 'Preservation of ovarian function:' without making it clear at the outset as to which formulation the information which followed referred. That it only referred to Prostap SR DCS was in the sentence which followed. The Panel considered that some readers might read the preservation of ovarian function indication and assume that it applied to both formulations particularly if they did not go on to read the text below.**

**The Panel considered that when two formulations of one product had differing indications such that one formulation was licensed for use where the other one was not, particular care needed to be taken to avoid any confusion. In the Panel's view, such differences should be made abundantly clear to ensure the rational use of each formulation. The Panel noted that Prostap 3 DCS had not been granted a licence for use in the preservation of ovarian function due to lack of efficacy data and so in that regard it was extremely important that clinicians did not use it for such. The Panel noted that the**

**MHRA had required additional text to be added to the Prostap 3 DCS SPC stating that 'Prostap 3 should not be used for preservation of ovarian function'. Although there was no statement in the Formulary Decision Guide that Prostap 3 DCS could be used for the preservation of ovarian function there was also no statement that it should not be so used, thus drawing readers' attention to the very clear distinction between the two Prostap formulations in that regard. The Panel accepted that it was unusual for material to state what a product was not licensed for but, given the reference in the Formulary Decision Guide to the use of Prostap SR DCS for the preservation of ovarian function and the MHRA's requirement that the Prostap 3 DCS SPC include a statement that it should not be used for such, the Panel considered that by not clearly and unambiguously stating that Prostap 3 DCS should not be used for the preservation of ovarian function, Takeda had failed to maintain high standards and a breach of the Code was ruledthat was upheld on appeal.**

**The Panel noted that the layout of the combined Prostap SR DCS and Prostap 3 DCS prescribing information dated May 2019 was such that emboldened sub-headings distinguished between the breast cancer indications for Prostap SR DCS and Prostap 3 DCS and the indication of preservation of ovarian function for just Prostap SR DCS. Although it noted Takeda's submission that there was no requirement in the Codeto refer to any therapeutic indications for which a product was not licensed, the Panel considered that patient safety and the rational use of medicine was paramount and in that regard any possibility of confusion must be avoided. The Panel noted that the Code required prescribing information to include, among other things, 'serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement'. In the Panel's view, the statement required by the MHRA that Prostap 3 DCS should not be used to preserve ovarian function, although not within Section 4.3 of the Prostap 3 DCS SPC (Contra-indications), was an important precaution relevant to the indications referred to in the Formulary Decision Guide and in that regard should have been included in the prescribing information to reinforce to readers that Prostap 3 DCS should not be used to preserve ovarian function. The prescribing information thus did not include the required information and so a breach of the Code was ruled that was upheld following an appeal from Takeda. The Panel ruled a further breach as high standards had not been maintained. Upon appeal from Takeda the Appeal Board considered that its concerns were adequately covered by the prior ruling of a breach of the Code and therefore it ruled no breach the Code in relation to high standards.**

**Although the Panel considered that more should have been done to ensure that prescribers were clear that Prostap 3 DCS should not be used to preserve ovarian function, it nonetheless did not consider that, on the evidence before it, the product had been promoted for that use as alleged. No breach of the Code was ruled.**

**The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its concerns above but considered that, on balance, a ruling of a breach of Clause 2 was not warranted. No breach of the Code was ruled.**

A complainant, who described him/herself as a concerned UK health professional, complained about Prostap (leuprorelin acetate) material produced by Takeda UK Limited hosted on the website of the journal 'Guidelines in Practice'. Prostap was available in two formulations,

Prostap SR DCS (dual chamber syringe) and Prostap 3 DCS; both were indicated for use in certain patients with breast cancer. Additionally, Prostap SR DCS was indicated for the preservation of ovarian function in pre-menopausal women with neoplastic disease undergoing chemotherapy treatment that could cause premature ovarian insufficiency.

**COMPLAINT**

The complainant drew attention to a webpage on the Guidelines in Practice website which presented a Formulary Decision Guide on Prostap DCS and provided details of the link to the prescribing information. The complainant stated that neither the Formulary Decision Guide nor the prescribing information included the statement that was added to Section 5.1 of the summary of product characteristics (SPC) in August 2019 that Prostap 3 DCS should not be used for preservation of ovarian function. The complainant stated that, in that regard, the Formulary Decision Guide promoted an off-licence indication as it listed ovarian preservation as an indication for use. The complainant considered that patient safety was at issue.

When writing to Takeda, the Authority asked the company to consider the requirements of Clauses 3.2, 4.1, 4.2, 9.1 and 2 of the Code.

**RESPONSE**

Takeda noted that the complaint concerned two promotional items for Prostap DCS which were available on the internet (refs UK/PRS/1905/0010b (website landing page) and UK/PRS/1905/0010 (Formulary Decision Guide)).

Takeda noted that the Formulary Decision Guide was available as a hard copy or an electronic leavepiece. The Guide was also published online via a Guidelines in Practice landing page. The items were intended for use by various primary and secondary care health professionals including general practitioners, nurses and oncologists and also by other relevant decision makers in the procurement of medicines. Both items, barring the initial mention of the preservation of ovarian function indication, promoted Prostap DCS for use in the treatment of breast cancer.

Takeda noted that it marketed two separate formulations within the Prostap DCS range, ie Prostap SR DCS and Prostap 3 DCS. Prostap SR DCS was administered monthly, whereas Prostap 3 DCS was administered every 3 months. Both formulations had indications that included prostate cancer, endometriosis, central precocious puberty and breast cancer. There were some differences, however, with Prostap SR DCS additionally indicated for the treatment of uterine fibroids and the preservation of ovarian function.

Takeda noted that the preservation of ovarian function indication was granted for Prostap SR DCS in March 2019 as follows:

> ‘Preservation of ovarian function in pre-menopausal women with neoplastic disease undergoing chemotherapy treatment that can cause premature ovarian insufficiency. Prostap SR is not a replacement for standard fertility-preservation methods. Treatment with a GnRH analogue should be proposed after careful evaluation, in each case, of the benefit/risk profile.’

Prostap 3 DCS did not receive a corresponding indication for preservation of ovarian function at that time. As Takeda did not intend to actively promote Prostap SR DCS for the new preservation of ovarian function indication, the prescribing information was not immediately updated to include that particular indication.

A salesforce briefing was sent out to inform the representatives of this new indication (copy provided) and making it clear that as they had not been trained, they could not mention the new indication proactively. The briefing also made it clear that the preservation of ovarian function licence was only for Prostap SR DCS and not Prostap 3 DCS to ensure there was no confusion in responding to any reactive enquires.

Both the Prostap SR DCS and Prostap 3 DCS brands received breast cancer indications on 9 May 2019 as follows:

> 'As treatment in pre- and perimenopausal women with advanced breast cancer suitable for hormonal manipulation.
>
> As adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in pre- and perimenopausal women at higher risk of disease recurrence (young age, high grade tumour, lymph node involvement). In women who have received chemotherapy, premenopausal status must be confirmed after completion of chemotherapy.'

On 24 May 2019 a new combined prescribing information for both formulations, covering only the breast cancer and preservation of ovarian function indications was certified for use in promotional materials about breast cancer. This prescribing information stated that both Prostap SR and 3 DCS were indicated in breast cancer and that Prostap SR DCS was specifically indicated for preservation of ovarian function and read as follows:

> **'Indications: Prostap SR DCS /Prostap 3 DCS**: As treatment in pre- and perimenopausal women with advanced breast cancer suitable for hormonal manipulation; As adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in pre- and perimenopausal women at higher risk of disease recurrence (young age, high grade tumour, lymph node involvement). In women who have received chemotherapy, premenopausal status must be confirmed after completion of chemotherapy. **Prostap SR DCS** also indicated for preservation of ovarian function in pre-menopausal women with neoplastic disease undergoing chemotherapy treatment that can cause premature ovarian insufficiency. Prostap SR DCS is not a replacement for standard fertility preservation methods. Treatment with a GnRH analogue should be proposed after careful evaluation, in each case, of the benefit/risk profile.'

In August 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) declined to grant a preservation of ovarian function indication for Prostap 3 DCS. The MHRA's assessment report stated that that was primarily due to lack of Prostap 3 DCS efficacy data. In the assessment report the MHRA stated that 'No new or unexpected safety concerns were identified'.

Given that there were two formulations of Prostap DCS, only one of which was indicated for preservation of ovarian function (ie Prostap SR DCS), the MHRA requested that additional text be included in the Prostap 3 DCS SPC (copy provided).

The MHRA required that text be included in Section 4.2 of the Prostap 3 DCS SPC stating that:

> 'Prostap 3 should not be used for preservation of ovarian function.'

Section 5.1 of the Prostap 3 DCS SPC was also updated with the following:

> 'There are no data demonstrating effectiveness of the 3-monthly formulation of leuprorelin for ovarian function preservation in premenopausal women undergoing chemotherapy treatment.'

Takeda queried, at that time, whether this SPC change required a change to the Prostap DCS prescribing information but considered that as the prescribing information already clearly stated that only the SR formulation was licensed for preservation of ovarian function, there was negligible risk of health professionals being confused in that regard. As a result, further changes to the prescribing information were deemed unnecessary.

In addition to the prescribing information, both the Formulary Decision Guide and website landing page included prominent indication sections containing the following text:

' • Prostap SR DCS and Prostap 3 DCS are licensed for breast cancer as follows:

  – as treatment in pre- and perimenopausal women with advanced breast cancer suitable for hormonal manipulation

  – as adjuvant treatment, in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in pre- and perimenopausal women at higher risk of disease recurrence (young age, high grade tumour, lymph node involvement). In women who have received chemotherapy, premenopausal status must be confirmed after completion of chemotherapy

• Preservation of ovarian function:

  – Prostap SR DCS is indicated for use in premenopausal women with neoplastic disease undergoing chemotherapy treatment that can cause premature ovarian insufficiency. It is not a replacement for standard fertility-preservation methods. Treatment with a GnRH analogue should be proposed after careful evaluation, in each case, of the benefit/risk profile

• For other indications, please refer to the SPCs at: www.medicines.org.uk/emc/.'

Takeda considered that the indication statements on the promotional materials and the prescribing information made it abundantly clearly that only the SR formulation of Prostap DCS was indicated for the preservation of ovarian function.

In conclusion, Takeda submitted that both the Formulary Decision Guide and the website landing page contained text, in both the prescribing information and main advertising copy,

which accurately stated relevant licensed indications for the two Prostap DCS formulations. There was no ambiguity that could lead to confusion as to whether Prostap 3 DCS should be used for preservation of ovarian function.

Takeda disagreed with the complainant's assertion that the prescribing information (or the items themselves) had not been updated to reflect the contents of the respective SPCs. The items were not misleading and did not imply that Prostap 3 DCS was indicated for the preservation of ovarian function. Takeda thus denied a breach of Clause 3.2.

The Prostap DCS prescribing information accurately described relevant licensed indications for both Prostap SR DCS and 3 DCS. Takeda noted that Clause 4.2 of the Code specified what must be included within the prescribing information; there was no requirement to specify any therapeutic indications for which a product was not licensed. Takeda therefore denied a breach of Clauses 4.1 and 4.2.

Takeda considered that it had maintained high standards and had not brought discredit upon, or reduced confidence in, the pharmaceutical industry. Takeda therefore denied a breach of Clauses 9.1 and 2.

**PANEL RULING**

The Panel noted that the material at issue was primarily about the use of Prostap DCS (either formulation) in patients with breast cancer. Information on the use of the two formulations had been included in the indication section within the Formulary Decision Guide, a link to which was provided by the complainant. The first bullet point in that section stated 'Prostap SR DCS and Prostap 3 DCS are licensed for breast cancer as follows:' and so it was immediately clear to the reader that the information which followed would relate to both formulations. The second bullet point, however, was presented in a different style and stated 'Preservation of ovarian function:' without making it clear at the outset as to which formulation the information which followed referred. That it only referred to Prostap SR DCS was in the sentence which followed. The Panel considered that some readers might read the preservation of ovarian function indication and assume that it applied to both formulations particularly if they did not go on to read the text below.

The Panel considered that when two formulations of one product had differing indications such that one formulation was licensed for use where the other one was not, particular care needed to be taken to avoid any confusion. In the Panel's view, such differences should be made abundantly clear to ensure the rational use of each formulation. The Panel noted that Prostap 3 DCS had not been granted a licence for use in the preservation of ovarian function due to lack of efficacy data and so in that regard it was extremely important that clinicians did not use it for such. The Panel noted that the MHRA had required additional text to be added to the Prostap 3 DCS SPC stating that 'Prostap 3 should not be used for preservation of ovarian function'. Although there was no statement in the Formulary Decision Guide that Prostap 3 DCS could be used for the preservation of ovarian function there was also no statement that it should not be so used, thus drawing readers' attention to the very clear distinction between the two Prostap formulations in that regard. The Panel accepted that it was unusual for material to state what a product was not licensed for but, given the reference in the Formulary Decision Guide to the use of Prostap SR DCS for the preservation of ovarian function and the MHRA's requirement that the Prostap 3 DCS SPC include a statement that it should not be used for such, the Panel considered that by not clearly and unambiguously stating that Prostap 3 DCS should not be

used for the preservation of ovarian function, Takeda had failed to maintain high standards and a breach of Clause 9.1 was ruled. This ruling was appealed.

The Panel noted that the layout of the combined Prostap SR DCS and Prostap 3 DCS prescribing information dated May 2019 was such that emboldened sub-headings distinguished between the breast cancer indications for Prostap SR DCS and Prostap 3 DCS and the indication of preservation of ovarian function for just Prostap SR DCS. Although it noted Takeda's submission that there was no requirement in Clause 4.1 to refer to any therapeutic indications for which a product was not licensed, the Panel considered that patient safety and the rational use of medicine was paramount and in that regard any possibility of confusion must be avoided. The Panel noted that Clause 4.2 required prescribing information to include, among other things, 'serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement'. In the Panel's view, the statement required by the MHRA that Prostap 3 DCS should not be used to preserve ovarian function, although not within Section 4.3 of the Prostap 3 DCS SPC (Contra-indications), was an important precaution relevant to the indications referred to in the Formulary Decision Guide and in that regard should have been included in the prescribing information to reinforce to readers that Prostap 3 DCS should not be used to preserve ovarian function. The Panel considered that the prescribing information thus did not include the information as set out in Clause 4.2 and so a breach of Clause 4.1 was ruled. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. These rulings were appealed.

Although the Panel considered that more should have been done to ensure that prescribers were clear that Prostap 3 DCS should not be used to preserve ovarian function, it nonetheless did not consider that, on the evidence before it, the product had been promoted for that use as alleged. No breach of Clause 3.2 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its concerns above but considered that, on balance, a ruling of a breach of Clause 2 was not warranted. No breach of Clause 2 was ruled.

**APPEAL BY TAKEDA**

Takeda submitted that it did not accept the Panel's view that 'some readers might read the preservation of ovarian function indication and assume that it applied to both formulations particularly if they did not go on to read the text below.' The preservation of ovarian function indication was presented in the Formulary Decision Guide as a full bullet point, which clearly differentiated the text relating to the preservation of ovarian function indication from that relating to the breast cancer indication. Immediately below this bullet was a sub-bullet making clear that it was only the Prostap SR DCS preparation which was licensed for use in this indication, as well as providing details regarding the indication itself. The font size used for the sub-bullet was only slightly smaller than for the bullet point itself.

Given the minimal information conveyed by the bullet point 'Preservation of ovarian function:', Takeda submitted that it found it difficult to imagine that a clinician intending to use Prostap DCS for the preservation of ovarian function indication would not go on to read the sub-bullet in its entirety.

Takeda submitted that it understood the Code requirement to ensure that claims in promotional materials were capable of standing alone in terms of accuracy and that general claims should

not be qualified by the use of footnotes and the like (Clause 7, Supplementary information). However, in this instance, given that the clarifying text was presented directly below the main bullet point introducing the preservation of ovarian function indication, Takeda considered that the item unambiguously made it clear that only Prostap SR DCS was indicated for the treatment of preservation of ovarian function.

As outlined in Takeda's initial response to the PMCPA, the Prostap 3 DCS preservation of ovarian function assessment report from the MHRA stated that 'No new or unexpected safety concerns were identified.' The additional text that the MHRA required to be added to the Prostap 3 DCS SPC, on the basis of lack of efficacy data to support the preservation of ovarian function indication, was as follows: 'Prostap 3 should not be used for preservation of ovarian function'. Takeda submitted that in its view there was an important distinction between the SPC and the Formulary Decision Guide and accompanying prescribing information which were the subject of this complaint. SPCs existed as separate stand-alone documents for the various available preparations of a particular medicine. It was therefore conceivable that had the MHRA not requested this SPC change, a health professional who was already aware that Prostap SR DCS was licensed for the preservation of ovarian function indication might have reviewed the SPC for Prostap 3 DCS without noticing that this preparation was not, in fact, licensed for this particular indication. In contrast, the Formulary Decision Guide and accompanying prescribing information made reference to both the Prostap SR DCS and Prostap 3 DCS preparations and, in Takeda's opinion, made abundantly clear to the reader that only the Prostap SR DCS preparation was licensed for the preservation of ovarian function indication.

Takeda submitted that it was concerned that the Panel's view could cause significant confusion for those certifying promotional materials in future. Clause 7.2 of the Code required that '[promotional] material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'. When considering whether this requirement had been met, those certifying promotional materials habitually assumed that the reader would read at least all the text in the main body of the material, though they might be less diligent in their reading of footnotes and lists of references for example. The Panel's ruling in this case appeared to suggest that those certifying this material should have taken into account the fact that a significant portion of the main body of the text contained within this item might be skipped over by readers.

Takeda submitted that in was difficult to understand how a signatory could ever assess compliance with Clause 7.2 of the Code without making the assumption that the main body of the material would be read in full, since reading only part of any promotional item was unlikely to furnish the reader with sufficient information to 'form their own opinion of the therapeutic value of a medicine'.

Takada submitted that the Formulary Decision Guide fully complied with the requirements of the Code. Takeda therefore denied a breach of Clause 9.1 of the Code in respect of the complaint made regarding the Indications section of this item.

The prescribing information which was subject to this complaint covered both breast cancer and POF indications for both the Prostap 3 DCS and Prostap SR DCS preparations. The indication section of the prescribing information started by stating the two breast cancer indications which were common to both preparations. This was then followed by the text: 'Prostap SR DCS also indicated for preservation of ovarian function…'. Takeda submitted that it was highly unlikely that any health professional reading this prescribing information would be left with the erroneous

impression that Prostap 3 DCS was also indicated for POF. Indeed, the Panel noted that 'the layout of the combined Prostap SR DCS and Prostap 3 DCS prescribing information dated May 2019 was such that emboldened sub-headings distinguished between the breast cancer indications for Prostap SR DCS and Prostap 3 DCS and the indication of preservation of ovarian function for just Prostap SR DCS.'

Takeda submitted that it disagreed with the Panel's view that a statement to the effect that Prostap 3 DCS was not indicated for preservation of ovarian function should have been included within this prescribing information. Clause 4.2 of the Code listed the matters which were required to be included within the prescribing information. The sub-sections of this clause which might be relevant to this complaint were as follows:

> 'iii) [prescribing information should include] at least one authorized indication for use consistent with the summary of product characteristics
>
> v) a succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of product characteristics, together with a statement that prescribers should consult the summary of product characteristics in relation to other adverse reactions
>
> vi) any warning issued by the Medicines Commission, the Commission on Human Medicines, the Committee on Safety of Medicines or the licensing authority, which was required to be included in advertisements'

Takeda submitted that in respect of point (iii) and as previously described, the prescribing information included details of the breast indications for both Prostap SR DCS and Prostap 3 DCS formulations, along with the preservation of ovarian function indication for the Prostap SR DCS formulation only. Takeda submitted that it would be unusual, and in this case unnecessary, to additionally specify conditions for which a medicine was not indicated. In this regard it was important to consider that the purpose of the prescribing information was to summarise, not simply duplicate, the SPC.

Takeda submitted that in respect of point (v) and in common with usual industry practice, common and serious adverse reactions included in section 4.8 of the SPC along with contra-indications and special warnings and precautions taken from sections 4.3. and 4.4 of the SPC respectively had been summarised in the prescribing information. In respect of point (vi) Takeda confirmed that the regulatory authorities had never required the company to include any warning pertaining to the preservation of ovarian function indication in advertising materials.

Takeda submitted that the prescribing information which formed part of the Formulary Decision Guide had been prepared in line with the requirements of the Code and thus denied any breach of either Clause 4.1 or Clause 9.1 in respect of the complaint made regarding the prescribing information .

Takeda submitted that in this instance the PMCPA had requested that Takeda respond to Clauses 9.1 and 4.1. Takeda duly responded to the complaint on this basis. However, the ruling made by the Panel suggested that its main concern related to the presentation of claims, in particular the clarity with which the preservation of ovarian function indication was described,

rather than any concern that the item overall was of an unacceptably poor standard. Therefore, it appeared that Clause 7 was much more relevant here than Clause 9.1. Takeda submitted that Clause 9.1 should be reserved for materials which were of generally poor standard and should not be used where other more specific clauses were more relevant.

Takeda submitted that it was fully committed to complying with both the letter and spirit of the Code and therefore took complaints that suggested the Code might have been breached extremely seriously.

Takeda submitted that the nature of its response to this complaint reassured the Panel that this complaint was thoroughly investigated by the company. After much consideration, and despite the ruling of the Panel, Takeda submitted that this piece of promotional material fully complied with the requirements of the Code. It was for this reason that Takeda had taken the decision to appeal the Panel's ruling.

**COMMENTS FROM THE COMPLAINANT**

There were no comments from the complainant.

**APPEAL BOARD RULING**

The Appeal Board noted the MHRA's decision in August 2019 that required additional text to be added to Section 4.2 of the Prostap 3 DCS SPC stating that 'Prostap 3 should not be used for preservation of ovarian function'. Section 5.1 of the SPC was also updated to state 'There are no data demonstrating effectiveness of the 3-monthly formulation of leuprorelin for ovarian function preservation in premenopausal women undergoing chemotherapy treatment'. The Appeal Board noted from the company representatives at the appeal that at the relevant time the company had assessed both the Formulary Decision Guide and the prescribing information at issue and decided that no revision was required.

The Appeal Board considered that it was likely that a general practitioner would favour a three-monthly injection with Prostap 3 DCS over the monthly injection of Prostap SR DCS. In that regard the Appeal Board noted that in response to a question the company representatives stated that the balance of prescribing was around 3 to 1 in favour of the 3-monthly injection. The Appeal Board considered that when two formulations of a product had differing indications, as in this instance where one formulation was licensed for one use and the other formulation was not so licensed because its efficacy in that indication was unproven, particular care needed to be taken to avoid any confusion. In the Appeal Board's view, such differences should be made abundantly clear to enable good clinical judgement and the rational use of each formulation.

The Appeal Board noted that the Formulary Decision Guide was primarily about the use of Prostap DCS (either formulation) in patients with breast cancer. Information on the use of the two formulations was included in the indication section. The first bullet point in that section stated 'Prostap SR DCS and Prostap 3 DCS are licensed for breast cancer as follows:' and so it was immediately clear to the reader that the information which followed would relate to both formulations. The second bullet point, however, was presented differently and stated 'Preservation of ovarian function:' without making it clear at the outset to which formulation the statement referred. Although the sentence below stated that Prostap SR DCS was indicated for use in preservation of ovarian function, there was no clear statement that Prostap 3 DCS was

not so indicated. The Appeal Board considered that some readers might read the preservation of ovarian function indication and not unreasonably assume that it applied to both formulations and some readers might be unaware that Prostap 3 DCS should not be used for that indication.

Although there was no statement in the Formulary Decision Guide that Prostap 3 DCS could be used for the preservation of ovarian function there was also no statement that it should not be so used. The Appeal Board considered that by not clearly and unambiguously stating that Prostap 3 DCS should not be used for the preservation of ovarian function, the Formulary Decision Guide was unclear and consequently it upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

The Appeal Board noted that Clause 4.2 (v) required prescribing information to include, 'serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement'. Clause 4.2 (iv) required the prescribing information to include a succinct statement of *inter alia* the information in the summary of product characteristics relating to the dosage and method of use relevant to the indications quoted in the advertisement and, where not otherwise obvious, the route of administration.

The Appeal Board noted that the layout of the combined Prostap SR DCS and Prostap 3 DCS prescribing information dated May 2019 was such that emboldened sub-headings distinguished between the breast cancer indications for Prostap SR DCS and Prostap 3 DCS and the indication of preservation of ovarian function which applied solely to Prostap SR DCS. The Appeal Board noted Takeda's submission that there was no requirement in Clause 4.1 to refer to any therapeutic indications for which a product was not licensed. The Appeal Board noted that the MHRA had required the statement that Prostap 3 DCS should not be used to preserve ovarian function, although not within Section 4.3 of the Prostap 3 DCS SPC (Contra-indications), it was in Section 5.1 and given the context, it was important information relevant to the indications referred to in the Formulary Decision Guide. The Appeal Board considered that the joint prescribing information should have made it clear that Prostap 3 DCS should not be used to preserve ovarian function. Otherwise the Appeal Board considered that there was potential to mislead. The Appeal Board considered that because this was a combined prescribing information for two formulations of a medicine with different indications, the combined Prostap SR DCS and Prostap 3 DCS prescribing information needed to be clear about the use in both indications to ensure the rational use of the medicine.

The Appeal Board noted its comments above regarding the practicality of the 3-monthly dose. The Appeal Board considered in the particular circumstances of this case that the prescribing information thus did not include the required information as set out in Clause 4.2 and therefore upheld the Panel's ruling of a breach of Clause 4.1. The appeal on this point was unsuccessful. The Appeal Board did not consider that this omission amounted to a breach of Clause 9.1. The Appeal Board considered that its concerns were adequately covered by the ruling of a breach of Clause 4.1 and therefore ruled no breach of Clause 9.1 of the Code. The appeal on this point was successful.

**Complaint received** **11 March 2020**

**Case completed** **30 July 2020**