TAKEDA v ASTRAZENECA

Zoladex letter

Takeda complained about a Zoladex (goserelin) letter. The letter informed readers of Zoladex price reduction and also compared the efficacy of Zoladex with, *inter alia*, Takeda's product. Prostap (leuprorelin).

Zoladex and Prostap were both luteinising hormone releasing hormone analogues (LHRHa) indicated for the treatment of prostate cancer.

Takeda alleged that the claim: *'No other LHRHa* has demonstrated survival benefit in all 3 stages of prostate cancer' was an absolute claim based on strict inclusion and exclusion criteria (ie randomized controlled trials of the UK dose comparing LHRHa monotherapy with a standard comparator, combined androgen blockade omitted) and the initial impression was altered by reading the subsequent footnote. Takeda alleged that the claim was an exaggerated and unbalanced view of the evidence and thus misleading; survival benefit in all three stages of prostate cancer with Prostap had been demonstrated and Takeda cited a number of studies in support of its position. Takeda further alleged that the claim was in bold and thus unduly emphasized.

The rationale for omitting combined androgen blockade data was unclear and did not reflect clinical practice and the totality of Prostap evidence. A long-term study comparing leuprorelin monotherapy vs continuous combined androgen blockade with leuprorelin and flutamide had demonstrated no significant differences in time to treatment failure, time to progression, or overall survival (Bono *et al* 1998).

Inclusion of trials using only the UK licensed doses of LHRH analogues provided an unbalanced view as it excluded one of the key Prostap survival outcome trials in which the US licensed dose of Prostap 7.5mg was used (D'Amico *et al* 2004). The equivalence of monthly administration of 3.75mg and 7.5mg leuprorelin had been demonstrated by Bischoff *et al* (1990). In addition, D'Amico *et al* was referred to in the Prostap summary of product characteristics (SPC). The PMCPA had previously accepted the use of data from studies that also included doses or dose regimens that were outside the UK licence.

The detailed response from AstraZeneca is given below.

The Panel noted that the letter in question, headed 'Zoladex (goserelin) price reduction from 1st October 2010', was sent to alert readers to a 12% price reduction for Zoladex 10.8mg and that Zoladex 3.6mg continued to be the least expensive one-month LHRHa. The claim at issue appeared in the second paragraph which read 'In addition to the savings Zoladex has demonstrated survival benefits in all 3 stages of prostate cancer (localised, locally advanced and metastatic). *No other LHRHa* has demonstrated survival benefits in all 3 stages of prostate cancer'. In the Panel's view, readers would assume that, the claim referred to the use of Zoladex, and any other LHRHa, as a single agent. The claim was referenced to the Zoladex 3.6mg SPC and to AstraZeneca data on file. The data on file were the results of an August 2008 search for survival data for leuprolide or triptorelin in prostate cancer. Randomized controlled clinical trials and comparisons of a single LHRHa at UK licensed doses with alternative standard therapies were included. Comparisons between different doses or formulations of the same active ingredient, trials of combined androgen blockade and abstracts/ conference proceedings were excluded. No valid randomized controlled trials for leuprorelin were found in any stage of prostate cancer.

A chart of randomized controlled clinical trials with survival endpoints at UK licensed doses comparing features of, *inter alia*, Zoladex and leuprorelin was immediately beneath the claim at issue. The features compared in the chart were whether the products' licences covered metastatic (advanced) prostate cancer; locally advanced prostate cancer, as an alternative to surgical castration; high risk localised or locally advanced prostate cancer, as a adjuvant to radiotherapy; high risk localised or locally advanced prostate cancer, as a neoadjuvant before radiotherapy and locally advanced high-risk prostate cancer at high risk for disease progression, as an adjuvant to radical prostatectomy. The total number of randomized clinical trials were given for each product; there were 11 for Zoladex and none for leuprorelin. Beneath the chart it was stated that the randomized clinical trials were of the UK dose comparing LHRHa monotherapy with a standard comparator therapy and that trials of combined androgen blockade were omitted.

The Panel noted that there was a difference in the clinical particulars listed in the SPCs for Zoladex and Prostap. The Zoladex SPC stated that survival benefit had been shown for Zoladex in metastatic, locally advanced, high-risk localised or locally advanced and locally advanced at high risk of disease progression prostate cancers. There was no similar reference to survival benefits in the Prostap SPCs. The Prostap 3.75mg SPC referred to an advantage for Prostap in relation to mean survival time in metastatic prostate cancer. In patients with metastatic disease no statistically significant difference in survival was found for patients treated with LHRH analogues compared with orchidectomy treatment.

The Prostap 3.75mg SPC referred to disease-free survival and overall survival when leuprorelin 7.5mg/month was used in combination with flutamide. The SPC stated that the higher dose was therapeutically equivalent to the European licensed dose. The SPC stated that there were no disease-free survival data or survival data for leuprorelin when used after prostatectomy in selected patients considered at high risk of disease progression. Similar statements appeared in the Prostap 11.25mg SPC.

The Panel noted that there was no footnote to the claim at issue. It was referenced to the Zoladex SPC and to an inhouse literature search but was not qualified by a footnote thus there could be no breach of the Code in this regard.

The Panel examined the data provided by both parties and considered that although Takeda had survival data from studies that had included leuprorelin, it did not have data to demonstrate survival benefits in all three stages of prostate cancer for Prostap when used as monotherapy.

The Panel thus did not consider that the claim at issue was misleading or that it failed to reflect the totality of the evidence. The claim appeared to reflect the differences in the SPCs for monotherapy with Zoladex compared with Prostap. The claim was in the context of the cost advantage for Zoladex. The Panel did not consider that the comparison was misleading as alleged. No breach of the Code was ruled.

The Panel did not consider that it was misleading *per se* to limit the trials to those using the UK licensed dose. The Panel noted Takeda's concern that this had excluded a study in which leuprorelin 7.5mg had been used. In that regard the Panel noted Takeda's submission that 3.75mg and 7.5mg leuprorelin had been shown to be equivalent. However, the objective of D'Amico *et al* was to assess the survival benefit of radiation therapy alone or in combination with 6 months of androgen suppression therapy in patients with clinically localised prostate cancer. All 98 patients on androgen suppression therapy received flutamide, ten also received goserelin and 88 received leuprorelin. There was no separate analysis of patients taking leuprorelin vs those taking goserelin.

In the Panel's view, for the purposes of the claim at issue, there were problems in using the data from D'Amico *et al* other than the fact that a dose of Prostap was used which was not within the UK licence. The Panel thus did not consider it unreasonable for the results of this study to be disregarded. Similarly the Panel did not consider it unreasonable to exclude the results of another study which used a 1mg dose of Prostap which was not in line with the UK licensed dose. The Panel did not consider that, in the circumstances, it was misleading to refer only to trials using the UK licensed dose. Thus it ruled no breach of the Code.

Takeda UK Ltd complained about a letter (ref CZ004482-ZOLA) about Zoladex (goserelin) sent by AstraZeneca UK Limited to NHS budgetary stakeholders including primary care trust pharmacists, practice managers and other payers. It was sent to medical information sources such as EMIS, BNF and MIMS, the Department of Health and other purchasing organisations and used with appropriate health professionals including oncologists, urologists, GPs and practice nurses. The letter, headed 'Zoladex (goserelin) price reduction from 1st October 2010,' was signed by a member of the AstraZeneca finance department. Inter-company dialogue had settled all but one of the points at issue. Takeda supplied Prostap (leuprorelin).

Goserelin and leuprorelin were both luteinising hormone releasing hormone analogues (LHRHa) indicated for the treatment of prostate cancer.

COMPLAINT

Takeda alleged that the use of the claim: 'No other LHRHa has demonstrated survival benefit in all 3 stages of prostate cancer' was in breach of the following clauses of the Code:

- Clause 7.2, as it was not balanced or accurate, and allowed undue emphasis
- Clause 7.3, as it was misleading
- Clause 7.10, as it was all-embracing

Further in Takeda's view the statement was contrary to the supplementary information to Clause 7, which noted that in general, claims should not be qualified by footnotes and the like.

The claim at issue was an absolute claim based on strict inclusion and exclusion criteria (ie randomized controlled trials of the UK dose comparing LHRHa monotherapy with a standard comparator, combined androgen blockade omitted) and the initial impression of the statement was altered by reading the subsequent footnote. Takeda thus alleged a breach of Clause 7.10.

Takeda believed that the claim presented readers with an exaggerated and unbalanced view of the evidence, and therefore misled by direct implication, as data demonstrated survival benefit in all three stages of prostate cancer with Prostap. In addition, the claim was in bold which allowed undue emphasis. Takeda thus alleged breaches of Clauses 7.2 and 7.3.

The rationale for omitting combined androgen blockade data remained unclear and Takeda alleged that this did not reflect clinical practice and the totality of evidence in terms of the survival benefits offered by Prostap. A long-term study comparing leuprorelin monotherapy vs continuous combined androgen blockade with leuprorelin and flutamide had demonstrated no significant differences in time to treatment failure, time to progression, or overall survival (Bono *et al* 1998) and therefore Takeda alleged that omission of this information was in breach of Clause 7.2.

Inclusion of trials using only the UK licensed doses of LHRH analogues provided an unbalanced view as it excluded one of the key Prostap survival outcome trials in which the US licensed dose of Prostap 7.5mg was used (D'Amico *et al* 2004). The equivalence of monthly administration of 3.75mg and 7.5mg leuprorelin had been demonstrated by Bischoff *et al* (1990). In addition, D'Amico *et al* was referred to in the Prostap summary of product characteristics (SPC). Therefore Takeda believed this constituted a breach of Clause 7.2. Takeda noted that in Case AUTH/1523/10/03 the PMCPA had accepted the use of data from studies that also included doses or dose regimens that were outside the UK licence.

Takeda believed the following data supported evidence of survival benefit for leuprorelin treated patients:

- Two prospective randomized efficacy and safety trials in patients with advanced prostate cancer (ie locally advanced and metastatic disease) which compared the monthly and 3-monthly formulations of leuprorelin, with long-term follow up (43 months) to evaluate median survival time and median time to progression (Wechsel *et al* 1996 and Jocham 1998).

- An open prospective multicentre trial in treatment naïve patients with advanced prostate cancer which evaluated efficacy of leuprorelin 3.75mg in maintaining castrate testosterone levels (which was the accepted surrogate marker for efficacy of hormone therapy) over a 45 month treatment period, inclusive of an evaluation of median survival time and median time to progression (Kienle *et al* 1996).

- A meta-analysis which compared LHRHa therapy to orchiectomy or diethylstilbesterol (DES), in patients with advanced prostate cancer, which supported equivalence in effectiveness among the LHRH analogues (Seidenfeld *et al* 2000).

- A prospective randomized controlled trial of leuprorelin vs DES in advanced prostate cancer. DES had been shown to be equivalent to orchiectomy in terms of overall survival outcomes and was considered the gold standard at the time of publication (Leuprolide Study Group 1984).

- A prospective randomized, controlled trial of leuprorelin as an adjuvant to 3-dimensional conformal radiotherapy (3D-CRT) vs radiotherapy (RT) alone in patients with clinically localised prostate cancer (D'Amico *et al*).

- Two sets of data presented at the American Society of Clinical Oncology (ASCO) in June 2010:

  - A 3 year multicenter, randomized phase III trial comparing a combined modality of leuprorelin and RT with leuprorelin alone in patients with locally advanced prostate cancer (Mottet *et al* 2010) and

  - An intergroup randomized phase III study of androgen deprivation therapy (including leuprorelin among other LHRH analogues) plus RT in locally advanced prostate cancer (Warde *et al* 2010).

Takeda noted that Astra Zeneca failed to include the recently presented data from ASCO in its evidence supporting its claim, which reinforced one of the inherent problems with using categorical comparative claims such as 'No other'. It was the claimant's responsibility to continuously monitor all LHRHa publications to ensure the claim could always be substantiated.

RESPONSE

AstraZeneca strongly denied the claim was in breach of Clauses 7.2, 7.3 and 7.10 as alleged. In particular AstraZeneca did not agree that the claim was not balanced or accurate, allowed undue emphasis, was misleading and all-embracing. AstraZeneca had taken into account all available data in this setting and firmly believed the claim was valid.

AstraZeneca submitted that Zoladex had the largest evidence base of any LHRHa with multiple long-term, randomized-controlled trials demonstrating survival benefit for Zoladex in all three stages of prostate cancer. This body of evidence was unique amongst the LHRH analogues and AstraZeneca noted that Takeda had not challenged the existing Zoladex dataset. Conversely, the studies submitted by Takeda did not support its assertion that Prostap had demonstrated survival benefit in all three stages of prostate cancer.

The fact that Zoladex was the only LHRHa with demonstrated survival benefits in all three stages of prostate cancer was also consistent with the current licences for the LHRH analogues. In relation to this, during a 2008 Medicines and Healthcare products Regulatory Agency (MHRA)-initiated review of the prostate cancer indications for all UK approved gonadorelin analogues, Prostap was granted an amended licence authorizing use in all three stages of prostate cancer. Subsequent to the outcome of the review for Prostap, the MHRA also allowed amended wording in Section 4.1 of the Zoladex SPC to reflect the unique evidence base that goserelin had demonstrated survival benefits in the 3 stages of prostate cancer as outlined above. This was also supported by MHRA correspondence to AstraZeneca around the time of this review:

'We highlighted that no survival claims have been approved in the Prostap SPC, whereas the Zoladex SPC now enjoys a number of new survival claims in early prostate cancer as a result of this review …'.

AstraZeneca submitted that it was thus clear that, when it did its review, the MHRA did not consider that the Prostap dataset supported survival benefit across all three stages of prostate cancer.

The fact that Zoladex had demonstrated survival benefits in all three stages of prostate cancer was also clear from review of the specific wording for the relevant Zoladex licences taken from the indication section of the SPC (emphasis added to illustrate the specific wording):

> 'In the treatment of metastatic prostate cancer where Zoladex has demonstrated comparable survival benefits to surgical castrations (see section 5.1)'.
>
> 'In the treatment of locally advanced prostate cancer, as an alternative to surgical castration where Zoladex has demonstrated comparable survival benefits to an anti-androgen (see section 5.1)'.
>
> 'As adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer where Zoladex has demonstrated improved disease-free survival and overall survival (see section 5.1)'.

Conversely, none of the other SPCs for the available LHRH analogues (ie Prostap, Decapeptyl Gonapeptyl and Vantas) referred to survival benefit across the three stages of prostate cancer. This further supported the claim for Zoladex that 'No other LHRHa has demonstrated survival benefits in all 3 stages of prostate cancer'.

Takeda alleged that the claim 'No other LHRHa has demonstrated survival benefits in all 3 stages of prostate cancer' was contrary to the supplementary information to Clause 7 as it was supported by the use of footnotes. However, the claim in the letter at issue was not qualified by a footnote and therefore AstraZeneca was unclear as to what Takeda had referred.

AstraZeneca denied a breach of Clause 7.10. The claim was carefully considered and worded to accurately reflect the available evidence base; it did not exaggerate the properties of Zoladex, nor could it be considered an all-embracing or superlative claim. Rather the claim was a simple statement of fact and was specific to treatment with LHRH analogues in all three stages of prostate cancer and substantiated with survival endpoint data from numerous randomized clinical trials and a unique licence. AstraZeneca did not agree that data had demonstrated a survival benefit in all 3 stages of prostate cancer with Prostap.

The claim had the words 'No other LHRHa …' printed in bold. Takeda had alleged that this allowed undue emphasis in breach of Clauses 7.2 and 7.3. AstraZeneca did not understand how this placed undue emphasis, but rather appropriate emphasis on the fact that only Zoladex had survival benefit in all three stages of prostate cancer.

AstraZeneca noted Takeda's concerns about the omission of combined androgen blockade data and that the claim did not reflect clinical practice. AstraZeneca stated that combined androgen blockade referred to the use of two medicines simultaneously to treat prostate cancer: an LHRHa (such as Prostap or Zoladex) and an anti-androgen (such as flutamide or bicalutamide). The claim at issue referred to single agent treatment with LHRH analogues and would be interpreted as such by health professionals. Furthermore, in routine clinical practice, combined androgen blockade was not endorsed by the National Institute for Health and Clinical Excellence (NICE) in any of the three treatment settings, and it was specifically not recommended as first line treatment in advanced disease. Therefore, AstraZeneca did not understand how the claim 'No other LHRHa has demonstrated survival benefits in all 3 stages of prostate cancer' could be interpreted as referring to combined androgen blockade, especially since this did not reflect routine clinical practice.

AstraZeneca was not aware of any studies on combined androgen blockade which demonstrated the survival benefit conferred by a single agent. Such combination studies did not allow evidence-based conclusions to be drawn regarding the survival benefit of single agents. Only studies designed to investigate single agents should be used to determine the benefit of the agent under investigation. For example, Takeda cited Bono *et al* as evidence that leuprorelin monotherapy was no different in efficacy from combined androgen blockade (leuprorelin plus flutamide). This was misleading since the study was not designed to show equivalence or non-inferiority, but to look for an advantage for combined androgen blockade (leuprorelin plus flutamide) vs leuprorelin monotherapy. The paper reported that at a cut-off analysis, when mean follow-up period was 43.7 ± (SD) 24.1 months, no statistically significant differences in terms of time to treatment failure, time to progression and death rate were detected. That the paper failed to demonstrate superiority for combined androgen blockade did not prove that leuprorelin monotherapy was equivalent in efficacy as this would require a formal pre-defined equivalence analysis.

Based on the above, AstraZeneca considered that Prostap data relating to combined androgen blockade was not relevant to the validity of the claim in question and therefore the claim was not in breach of Clause 7.2.

The only evidence provided by Takeda to support survival benefit in the localized prostate cancer came from D'Amico *et al*. Takeda claimed that this study assessed radiotherapy plus leuprorelin vs radiotherapy alone. This was factually incorrect and misleading on two counts:

- The investigational arm in the study allowed inclusion of patients on any LHRHa and of the 98 patients, 10 were on Zoladex rather than leuprorelin. Therefore this study could not demonstrate survival benefit specifically for leuprorelin.

- The study combined two active treatments in the investigational arm: flutamide in combination with either leuprorelin or goserelin. Therefore the study could not identify the relative contributions of each active treatment to survival benefit. Indeed the study itself concluded: '… the question of whether complete (LHRH agonist and nonsteroidal anti-androgen) compared with partial androgen blockade (LHRH agonist) is necessary to achieve the survival benefit noted in our study remains'. The authors had themselves concluded that the study was unable to determine whether the benefit came from flutamide or from the LHRHa.

Therefore, consistent with AstraZeneca's knowledge of the literature, Takeda had not submitted any evidence that Prostap had demonstrated survival benefit in localised prostate cancer. AstraZeneca was concerned that Takeda considered D'Amico as 'one of the key Prostap survival outcome trials'.

Takeda had stated that the exclusion of D'Amico *et al* from being referenced in the claim provided an unbalanced view. However, as stated above, AstraZeneca did not accept that this study, irrespective of the dose used, supported the conclusion that Prostap had demonstrated survival benefit in localised prostate cancer. Furthermore, the fact that this study was referred in the SPC for Prostap was not relevant to concluding that Prostap had demonstrated survival benefit in localised prostate cancer. AstraZeneca referred again to the statement in the letter from the MHRA. Therefore, AstraZeneca did not agree that the claim at issue was in breach of Clause 7.2.

AstraZeneca stated that in general, the additional studies referred to by Takeda were small and limited in the conclusions that could be drawn from them. Nevertheless, AstraZeneca had reviewed each in turn to explain why they did not provide evidence for survival benefits for Prostap in all three stages of prostate cancer.

Localised prostate cancer:

No survival data for Prostap had been submitted by Takeda in this phase of prostate cancer. AstraZeneca referred to its comments above on D'Amico *et al*.

The fact that Takeda had no data to support survival benefit in this stage of prostate cancer supported AstraZeneca's position that the dataset for Prostap did not invalidate the claim 'No other LHRHa has demonstrated survival benefits in all 3 stages of prostate cancer'.

Locally advanced prostate cancer:

Takeda had outlined three studies that it considered demonstrated survival benefits for Prostap in locally advanced disease. Each of these had been reviewed in turn: Jocham was considered in the section for advanced prostate cancer below and the two sets of data from ASCO were considered here (Warde *et al* and Mottet *et al*). AstraZeneca noted Takeda's concern that AstraZeneca failed to refer to recently presented data from ASCO. In AstraZeneca's view, the data provided by Takeda from ASCO (Warde *et al* and Mottet *et al*) were not relevant to this complaint. However, for completeness, these two studies were outlined here.

Warde *et al* was a well conducted, randomized, controlled, phase III study designed to evaluate whether adding radiotherapy to an LHRHa was beneficial for patient outcomes. The authors concluded that the addition of radiotherapy was of value to patients. The study did not measure the impact of leuprorelin on survival. Furthermore, in order to lower testosterone levels, the study allowed inclusion of any LHRHa or orchiectomy (removal of both testes) as baseline therapy and therefore could not be used to demonstrate survival benefit of leuprorelin.

Mottet *et al* evaluated the benefit of adding radiotherapy to leuprorelin vs leuprorelin alone. Although this had only been published in abstract form no survival data were presented by the authors, and the design of the study aimed to evaluate the benefit of adding radiotherapy to LHRHa and not to assess the survival benefit of Prostap monotherapy.

Advanced/metastatic prostate cancer:

Jocham was a single arm study of 37 patients who were followed up long-term following exit from a larger study. As Takeda indicated, this study recruited patients with both locally advanced and metastatic disease and therefore could not separate the survival outcomes for the two disease settings. Although the paper reported a survival time, this was a single arm study that therefore could not be used to demonstrate survival benefit. The paper made indirect comparisons of survival based on these results. However, AstraZeneca did not consider that this data was robust enough to make indirect comparisons across studies to suggest that a survival benefit existed for Prostap in this stage of prostate cancer.

Wechsel *et al* looked at two different formulations of leuprorelin (1 month vs 3 month) thus AstraZeneca failed to see how this could provide evidence of survival benefits for leuprorelin over a comparator.

Kienle *et al* was a small, non-randomized study of leuprorelin monotherapy vs a combination of leuprorelin and an anti-androgen. The study evaluated the benefit of anti-androgens to the treatment of advanced disease and demonstrated that adding an anti-androgen appeared to shorten survival. However the authors noted that the study was not randomized and therefore worse prognosis patients received combined treatment from the start and this potentially explained the poorer survival seen in this group. In any case this study was unable to demonstrate a survival benefit of leuprorelin as it was designed to measure the impact of the addition of an anti-androgen.

Seidenfeld *et al* was a systematic review of studies in advanced/metastatic disease. Ten LHRHa studies were identified including five with goserelin. Only one study of leuprorelin was identified at a dose of 1mg subcutaneous daily (the licensed dose was 3.75mg monthly). Takeda had referred to this trial (Leuprolide Study Group) as evidence of survival benefit. AstraZeneca was concerned that Takeda would use an unapproved dose of leuprorelin (and one that was unavailable in the UK) to refute a survival benefit claim for Zoladex. Although the Prostap SPC referred to equivalence of 3.75mg and 7.5mg, it did not refer to a 1mg dose of leuprorelin, which therefore remained off licence. Furthermore it would be inappropriate, due to patient safety, to infer 1mg/day (up to 31mg/month) of leuprorelin was equivalent to 3.75mg/month in the absence of any supporting data.

With regard to other supporting information, AstraZeneca submitted that during the development of the prostate cancer guidelines, the National Institute for Health and Clinical Excellence (NICE) assessed the body of survival evidence in locally advanced disease and cited a Cochrane review (Kumar *et al* 2006). Kumar *et al* cited a number of published studies which they assessed during their evaluation. There were no leuprorelin data referenced within this review, although there were two large randomized studies of Zoladex. This further emphasized AstraZeneca's assertion that no survival benefit evidence existed for Prostap in locally advanced disease. This position was consistent with the Cochrane review.

In addition, in 2010 a well recognized review body, the Midlands Therapeutics Review and Advisory Committee (MTRAC) produced a commissioning support document for Prostap. This document aimed to supersede the 2008 document which did not recommend Prostap stating a lack of evidence. The 2010 document supported the use of Prostap but stated: 'No relevant studies were identified using leuprorelin as an alternative to surgical castration in locally advanced prostate cancer, or as adjuvant therapy with either radiotherapy or prostatectomy'.

The Prostap SPC contradicted Takeda's assertion that Prostap had demonstrated survival benefit in all three stages of prostate cancer. Section 5.1 of the Prostap SPC stated '… The use of a LHRH agonist may be considered after prostatectomy in selected patients considered at high risk of disease progression. There are no disease free survival data or survival data with leuprorelin in this setting' (emphasis added).

In summary, AstraZeneca firmly believed that there was a substantial evidence base for Zoladex which demonstrated survival benefit in all three stages of prostate cancer. This was consistent with the specific licence wording, clinical trial data, clinical guidelines, systematic reviews and local formulary assessments. The position had been recognized by the MHRA in the unique range of licensed indications granted for Zoladex which underpinned the claim at issue. In contrast Prostap and all other LHRH analogues lacked evidence to demonstrate survival benefit across all three stages of prostate cancer.

AstraZeneca acknowledged that leuprorelin was an effective treatment for patients with prostate cancer. This was supported by many clinical guidelines, formularies, and current clinical practice and was based on its data for testosterone suppression. However this did not invalidate the claim for Zoladex that 'No other LHRHa has demonstrated survival benefits in all 3 stages of prostate cancer'. It remained the case that only Zoladex had such data. AstraZeneca was concerned that Takeda had considered that the studies above demonstrated survival benefits for Prostap across all 3 stages of prostate cancer (whether at unlicensed doses, in non- randomized studies or in studies assessing other active agents). These studies did not support survival benefit for Prostap across all three stages of prostate cancer and therefore did not invalidate the claim at issue.

AstraZeneca denied that the claim was in breach of Clauses 7.2 or 7.3. In addition, the claim was neither exaggerated nor all embracing; AstraZeneca denied the alleged breach of Clause 7.10.

PANEL RULING

The Panel noted that the letter in question, headed 'Zoladex (goserelin) price reduction from 1st October 2010', was sent to alert readers to a 12% price reduction for Zoladex 10.8mg and that Zoladex 3.6mg continued to be the least expensive one-month LHRHa. The claim at issue appeared in the second paragraph which read 'In addition to the savings Zoladex has demonstrated survival benefits in all 3 stages of prostate cancer (localised, locally advanced and metastatic). **No other LHRHa** has demonstrated survival benefits in all 3 stages of prostate cancer'. In the Panel's view, readers would assume that, given the purpose of the letter and the context in which the claim appeared, that the claim referred to the use of Zoladex, and any other LHRHa, as a single agent. The claim was referenced to the Zoladex 3.6mg SPC and to AstraZeneca data on file. The data on file were the results of an August 2008 EMBASE and MEDLINE search for survival data for leuprolide or triptorelin in prostate cancer. The inclusion criteria were randomized controlled clinical trials and comparisons of a single LHRHa at UK licensed doses with alternative standard therapies. The three exclusion criteria were: comparisons between different doses or formulations of the same active ingredient, trials of combined androgen blockade and abstracts/conference proceedings. No valid randomized controlled trials for leuprorelin were found in any stage of prostate cancer and no survival benefit data were found regarding the use of triptorelin in high risk localised prostate cancer.

The claim at issue was not referenced to a footnote as stated by Takeda. A chart of randomized controlled clinical trials with survival endpoints at

UK licensed doses comparing features of Zoladex, leuprorelin and triptorelin was immediately beneath the claim at issue. The features compared in the chart were whether the products' licences covered metastatic (advanced) prostate cancer; locally advanced prostate cancer, as an alternative to surgical castration; high risk localised or locally advanced prostate cancer, as a adjuvant to radiotherapy; high risk localised or locally advanced prostate cancer, as a neoadjuvant before radiotherapy and locally advanced high-risk prostate cancer at high risk for disease progression, as an adjuvant to radical prostatectomy. The total number of randomized clinical trials were given for each product; there were 11 for Zoladex, none for leuprorelin and 3 for triptorelin. Beneath the chart it was stated that the randomized clinical trials were of the UK dose comparing LHRHa monotherapy with a standard comparator therapy and that trials of combined androgen blockade were omitted.

The Panel noted that there was a difference in the clinical particulars listed in the SPCs for Zoladex and Prostap. Section 4.1, Therapeutic indications, of the Zoladex SPC stated that survival benefit had been shown for Zoladex in metastatic, locally advanced, high-risk localised or locally advanced and locally advanced at high risk of disease progression prostate cancers. There was no reference to survival benefits in the indication section of the Prostap SPCs. Section 5.1 of the Prostap 3.75mg SPC referred to an advantage for Prostap in relation to mean survival time in metastatic prostate cancer. In patients with metastatic disease no statistically significant difference in survival was found for patients treated with LHRH analogues compared with orchidectomy treatment.

The Prostap 3.75mg SPC referred to disease-free survival and overall survival when leuprorelin 7.5mg/month was used in combination with flutamide. The SPC stated that the higher dose was therapeutically equivalent to the European licensed dose. The SPC stated that there were no disease-free survival data or survival data for leuprorelin when used after prostatectomy in selected patients considered at high risk of disease progression.

Similar statements appeared in the Prostap 11.25mg SPC.

With regard to the alleged breach of Clause 7.10, the Panel noted that there was no footnote to the claim at issue. It was referenced to the Zoladex SPC and to an inhouse literature search but was not qualified by a footnote. As there was no footnote there could be no breach of the Code in this regard. Thus the Panel ruled no breach of Clause 7.10.

The Panel noted AstraZeneca's comments about Wechsel *et al*. The study was designed to compare the efficacy, safety and tolerability of the two formulations of Prostap (3.75mg monthly or 11.25mg monthly) and to investigate whether they were able to lower testosterone effectively and persistently to the castrate level in the same way. The patients all had a life expectancy of >12 months; the study only lasted for 9 months. The authors stated that in relation to long-term prognosis, the reduction in prostate-specific antigen (PSA) might be regarded as clinically very important. There was no direct mention of survival benefits in this study.

The Panel examined the data provided by both parties and considered that although Takeda had survival data from studies that had included leuprorelin, it did not have data to demonstrate survival benefits in all three stages of prostate cancer for Prostap when used as monotherapy.

The Panel thus did not consider that the claim at issue was misleading or that it failed to reflect the totality of the evidence. The claim appeared to reflect the differences in the SPCs for monotherapy with Zoladex compared with Prostap. The claim was in the context of the cost advantage for Zoladex. The Panel did not consider that the comparison was misleading as alleged. No breach of Clauses 7.2 and 7.3 were ruled.

The Panel did not consider that it was misleading *per se* to limit the trials to those using the UK licensed dose. The Panel noted Takeda's concern that this had excluded the results of D'Amico *et al* in which a dose of 7.5mg leuprorelin had been used. In that regard the Panel noted Takeda's submission that 3.75mg and 7.5mg leuprorelin had been shown to be equivalent. However, the objective of D'Amico *et al* was to assess the survival benefit of radiation therapy alone or in combination with 6 months of androgen suppression therapy in patients with clinically localised prostate cancer. All 98 patients on androgen suppression therapy received flutamide, ten also received goserelin and 88 received leuprorelin. There was no separate analysis of patients taking leuprorelin vs those taking goserelin.

In the Panel's view, for the purposes of the claim at issue, there were problems in using the data from D'Amico *et al* other than the fact that a dose of Prostap was used which was not within the UK licence. The Panel thus did not consider it unreasonable for the results of this study to be disregarded. Similarly the Panel did not consider it unreasonable to exclude the results of the Leuprolide Study Group because the Prostap dose used, 1mg daily, was not in line with the UK licensed dose. The Panel did not consider that, in the circumstances, it was misleading to refer only to trials using the UK licensed dose. Thus it ruled no breach of Clause 7.2.

Complaint received **28 February 2011**

Case completed **5 May 2011**