MEN'S HEALTH PHYSICIAN/GENERAL PRACTITIONER v IPSEN

Conduct of representative

A men's health physician/general practitioner complained that an Ipsen representative had told him that Decapeptyl (triptorelin) could be used in patients with prostate cancer which had spread beyond the gland. The complainant stated that this would therefore include both locally advanced and advanced cancer. Advanced prostate cancer was metastatic; it was considered M1 using standard criteria. Locally advanced cancer was not considered M1 but was present when the cancer had spread beyond the prostatic capsule with or without regional lymph node involvement.

The complainant stated that the representative might have been confused but it was important that representatives and companies quoted specifically the licensed indications for a medicine and did not mislead as to their spectrum of use.

The Panel noted that Decapeptyl was indicated *inter alia* for the treatment of advanced prostate cancer. There appeared to be a difference of opinion as to the definition of advanced prostate cancer. Ipsen submitted that it was any cancer which had spread beyond the prostatic capsule and noted that the Decapeptyl clinical trial data included very few patients with cancer confined to the prostatic capsule; most had disease which extended beyond it but without apparent local nodal involvement or distant metastases. Data in support of the licence application showed that of 485 Decapeptyl patients, 20% were pre-metastatic, 60% were metastatic and the disease status of the rest was unknown. The representatives' briefing material acknowledged that there was some confusion about the term and stated that the licence had been granted on patients with prostate cancer grades C and D meaning that Decapeptyl was licensed for locally advanced and metastatic prostate cancer. The Panel noted the NHS R&D Health Technology Assessment definition which supported Ipsen's submission.

The Panel noted that both the complainant's account of what the representative had said and the representative's briefing material were consistent with Ipsen's definition of advanced prostate cancer ie anything which had gone beyond the prostatic capsule.

On the information before it, the Panel did not consider that the representative had promoted Decapeptyl beyond its licensed indication or had misled the complainant in that regard. However, it was not possible to determine exactly what had happened. Thus no breach of the Code was ruled.

A men's health physician/general practitioner complained about what a representative of Ipsen Ltd had told him about Decapeptyl (triptorelin). Decapeptyl was licensed for, *inter alia*, the treatment of advanced prostate cancer.

COMPLAINT

The complainant alleged that the representative misled as to the licensed indication for Decapeptyl at a recent UK prostate cancer educational meeting supported by medical device and pharmaceutical companies. The complainant believed the meeting was held in early January at the Institute of Physics.

The complainant stated that he met the representative at the Ipsen stand and issues relating to Decapeptyl, which was licensed for advanced prostate cancer were discussed. The representative stated that Decapeptyl could be used in patients with prostate cancer when the cancer had spread beyond the gland. The complainant stated that this would therefore include both locally advanced and advanced cancer. Advanced prostate cancer was metastatic; it was considered M1 using the standard tumour, nodes, metastasis (TNM) criteria. Locally advanced cancer was not considered M1 but was present when the cancer had spread beyond the prostatic capsule with or without regional lymph node involvement.

The complainant stated that there might have been some confusion on the part of the representative but it was important that representatives and their companies quoted specifically the licensed indications for their medicine and did not mislead wittingly or otherwise as to their spectrum of use.

In considering this matter Ipsen was asked to respond in relation to Clauses 3.2, 7.2 and 15.2 of the Code.

RESPONSE

Ipsen stated that the 3rd National Conference on Prostate Cancer: Meeting the Challenge had been held in December 2005 at the Institute of Physics. Two representatives were present at the meeting to staff an Ipsen stand. Ipsen submitted that all information provided to the doctor was consistent with the training the representatives had received on this subject and in line with Decapetyl's licensed indications.

The essence of the case depended on what constituted advanced prostate cancer. The term was not clinically precise and there continued to be genuine debate over exactly what was included in this description. Ipsen sympathised with the complainant as the nomenclature was not used consistently within the medical community. Ipsen stated that advanced prostate cancer was not synonymous with metastatic (M1) cancer, as stated by the complainant.

Prostate cancer – the disease and staging

Ipsen explained that prostate cancer was the most common cancer in men in the UK. The clonal theory of cancer considered the clinical course of prostate carcinoma to begin with a single malignant cell in the prostate gland. Under permissive conditions, this single, aberrant cell grew to form a microscopic focus of cancer within the gland. With time, these cells developed into macroscopic nodules of malignant disease, which were initially confined entirely within

the prostate gland. When large enough, this macroscopic growth could produce the signs and symptoms of prostate enlargement that might lead to its early detection and treatment. Indeed, at this stage whilst the cancer was completely contained within the tough, fibrous prostatic capsule, the treatment target was cure by ablation or extirpation of the tumour. Hormonal manipulation with Decapeptyl was not promoted for this early, localised stage.

However, if the diagnosis at this stage was missed, or treatment was unduly delayed or failed, the continued, unregulated growth of the cancer eventually allowed malignant cells to breach the physical barrier of the prostatic capsule and spread into tissue outside the prostate gland. Initially, these malignant deposits were most likely to be in close proximity to the gland, involving structures such as the seminal vesicle(s), bladder neck and regional lymph nodes. Later, distant metastatic spread via blood and lymphatics carried malignant cells to other locations beyond the pelvis to invade non-regional lymph nodes, bone and soft tissue organs such as the liver, lungs and brain.

Classification of these various steps in the clinical course of prostate cancer were objectively described in the staging of the disease. Two main scales described this staging: the TNM (newer, and more common in Europe) and the Whitmore-Jewett (older, and more common in the USA). Their abbreviated description and equivalence were:

Whitmore-Jewett		**TNM**	
Stage A	Histological (incidental) cancer confined to the prostate	T1	Histological (incidental) cancer confined to the prostate
Stage B	Clinical (palpable or visible) cancer confined to the prostate	T2	Clinical (palpable or visible) cancer confined to the prostate
Stage C	Extracapsular cancer	T3	Tumour extends through the prostatic capsule
C1	No invasion of seminal vesicles	T3a	Extracapsular extension (unilateral/ bilateral)
C2	Invasion of seminal vesicles	T3b	Tumour invaded seminal vesicle(s)
		T4	Tumour fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall
Stage D	Metastatic cancer		
D1	Invasion of pelvic lymph nodes or urethral obstruction causing ureterohydro-nephrosis	N1-3	Involvement of the regional lymph nodes
D2	Bone, visceral or lymph node distant metastases	M1	Invasion to distant metastases
		N0 no regional lymph node involvement	
		M0 no distant metastatic disease	

By combining clinical assessments of the disease stage, histological tumour grade (Gleason score), biochemical markers (prostate-specific antigen levels, serum alkaline phosphatase, prostatic acid phosphatase), life expectancy and the presence of symptoms, internationally recognised treatment algorithms had been developed, and were widely followed. The therapeutic role for hormone manipulation in symptomatic stage C, T3 and T4, and metastatic prostate cancer was firmly established.

However, the description 'advanced' was not used in either scale, and there was no universally agreed point in this clinical spectrum at which local disease, which was confined entirely to the prostate gland, became advanced. Indeed, each step in the staging of this disease could be described as more advanced than that preceding it. By this definition, every stage from stage B or T2 onwards could be considered as advanced. In anatomical terms though, the event that most significantly impacted the prognosis, clinical management and treatment selection in prostate cancer was extension of the tumour through the prostatic capsule. By this practical definition, every stage from stage C or T3 might be thought of as advanced. This approach was supported by the NHS R&D Health Technology Assessment Programme definition which included in the advanced category, prostate cancers which had locally invaded through the prostatic capsule, and/or had involved lymph nodes, and/or had metastases in bone or other organs. However, there was little consensus on the use of this term in scientific publications or in discussion within the medical community.

Clinical trials used for the original licence, Decapeptyl SR 3mg

Ipsen stated that the marketing authorization for Decapeptyl SR 3mg for advanced prostate cancer was granted in 1994. Decapeptyl SR 11.25mg was subsequently granted a licence for the same indication in 2002.

Ten clinical trials were included for assessment in support of the licence application. They included 688 patients and of these, 485 received Decapeptyl SR. At least 95 (20%) had pre-metastatic disease (stage C, M0

or earlier). In 106 Decapeptyl patients the metastatic status was not defined.

When the first Decapeptyl SR marketing authorization for the treatment of prostate cancer was applied for, the term advanced was used and approved in the labelling to conservatively refer to this heterogeneous patient population. Very few patients had locally confined disease (stage A or B; T1 or T2), a significant proportion had disease extending through the prostatic capsule, but without apparent local nodal involvement or distant metastases (stage C; T3, N0, M0 or T4, N0, M0). In recent years, the term locally advanced had been suggested to describe this clinical situation, but this was not commonly used when the UK licence was granted. There remained differences in the use of this new terminology between different research groups and between Europe and the USA. Despite these terminological variations, it was clear that the marketing authorization for Decapeptyl SR was supported and approved on a basis wider than metastatic prostate cancer alone, as feared by the complainant.

Representatives' briefing

Ipsen stated that because of the complexities detailed above and because feedback from prescribers suggested that some clinicians were confused about the interpretation of this approved indication for Decapeptyl SR, a detailed briefing for Ipsen representatives on this subject was prepared last year. A copy was provided.

Stand materials from the meeting

Materials from the stand at the meeting, together with a copy of the graphics used on the stand panels, and the programme from the meeting were provided. This same issue was discussed during much of the second day's agenda. Interestingly, although locally advanced disease (session I) and advanced disease (session II) were handled separately on this day, so too was metastatic prostate cancer (session IV), suggesting that none of these clinical descriptions completely included the others. Furthermore, a review of locally advanced disease was included in the advanced disease session, suggesting the former was a legitimate subset of the latter. In addition, the mechanisms of metastasis were described in the session on locally advanced disease, which by definition should be M0. This illustrated some of the inconsistency in the terminology, even between experts, and might, in part, explain the complainant's concerns if the information provided on classification did not exactly fit with the terminology heard at the meeting.

Conclusions

Ipsen submitted that the Decapeptyl marketing authorization for the treatment of advanced prostate cancer was supported and approved on a wide clinical basis that included many patients with pre-metastatic disease. The licensed description advanced prostate cancer was not used in current staging classifications, and did not have a precise, clinical meaning, other than to exclude early cancers confined to the prostate gland itself. Decapeptyl SR had never been promoted for the treatment of localised prostate disease. Promotion at the meeting was therefore in accordance with its marketing authorization and summary of product characteristics (SPC) (Clause 3.2).

The two representatives who attended the meeting were unable to recall this actual incident. Ipsen was satisfied that their conversation with the complainant on this matter would have been accurate, balanced and fair, and not misleading either directly or by implication (Clause 7.2).

Both representatives would have discharged their responsibilities, to Ipsen specifically and the pharmaceutical industry more generally, ethically and with integrity, in compliance with Clause 15.2 of the Code.

PANEL RULING

This case was considered in relation to the 2003 edition of the Code using the procedure set out in the 2006 Constitution and Procedure.

The Panel noted that Decapeptyl was indicated *inter alia* for the treatment of advanced prostate cancer. There appeared to be a difference of opinion as to the definition of advanced prostate cancer. Ipsen submitted that advanced prostate cancer was any cancer which had spread beyond the prostatic capsule. The company had further stated that the Decapeptyl clinical trial data included very few patients with cancer confined to the prostatic capsule; most had disease which extended beyond the prostatic capsule but without apparent local nodal involvement or distant metastases. An appendix of data showing the patient types included in support of the licence application showed that of 485 Decapeptyl patients, 20% were pre-metastatic, 60% were metastatic and the disease status of the rest was unknown. The representatives' briefing material acknowledged that there was some confusion about the term and stated that the licence had been granted on patients with prostate cancer grades C and D meaning that Decapeptyl was licensed for locally advanced and metastatic prostate cancer. The Panel noted the NHS R&D Health Technology Assessment definition which supported Ipsen's submission.

The Panel noted that the identity of the complainant had not been revealed to Ipsen. The representatives could not remember speaking to the complainant. The Panel noted that both the complainant's account of what the representatives had said and the representative's briefing material were consistent with Ipsen's definition of advanced prostate cancer ie anything which had gone beyond the prostatic capsule.

On the information before it, the Panel did not consider that the representatives had promoted Decapeptyl beyond its licensed indication or had misled the complainant in that regard. However, it was not possible to determine exactly what had happened. Thus no breach of Clauses 3.2 and 7.2 of the Code was ruled. No breach of Clause 15.2 of the Code was also ruled.

Complaint received **2 February 2006**

Case completed **10 March 2006**