CASE AUTH/2256/8/09

HEALTH AND SOCIAL CARE BOARD PRESCRIBING ADVISER v NAPP

Promotion of Targinact

A health and social care board prescribing adviser complained about a Targinact (prolonged release oxycodone and naloxone) presentation on a website (www.targetingpain.co.uk) sponsored by Napp. Targinact was indicated for the treatment of severe pain which could be adequately managed only with opioid analgesics. The usual starting dose for an opioid naïve patient was 10mg/5mg of oxycodone/naloxone at intervals of 12 hours.

Slide 7 of the presentation was headed 'How to prescribe Targinact tablets' and featured a highlighted box. The left hand side of the box stated 'Targinact tablets starting dose 10mg/5mg prolonged release 12-hourly oral tablets (total daily dose 20mg/10mg)'. The right hand side of the box was divided into two horizontally. The upper portion contained the statement 'Instead of … codeine, 8 x 30mg/500mg co-codamol tablets/day', and the lower portion contained the statement 'Instead of … tramadol 200mg/day'. Below the box the claim 'Prescribe Targinact 10mg/5mg tablets 12-hourly for patients with severe diagnosed back pain and severe osteoarthritis pain' was followed by 'The start dose of Targinact tablets is 10mg/5mg 12 hourly. This can be increased to 20mg/10mg 12 hourly if required' and 'Please refer to Targinact Summary of Product Characteristics (SPC) for further details'.

The complainant stated that the slide suggested that Targinact 10mg/5mg every 12 hours could be used instead of 8 x co-codamol 30mg codeine/500mg paracetamol tablets. The complainant alleged that this statement implied that these tablets had similar efficacy which was false and very misleading. Eight co-codamol 30/500 tablets were equivalent to 20mg morphine per day whereas Targinact 10mg/5mg twice daily was equivalent to 36mg morphine daily. This could prejudice patient safety.

The complainant stated that 8 co-codamol 30/500 was not equivalent to tramadol 200mg daily or Targinact 10mg/5mg twice daily in terms of morphine equivalence. Slide 7 did not state that Targinact was a controlled drug (Schedule 2). This information was also reproduced in printed material distributed to GPs and junior hospital doctors.

The detailed submission from Napp is given below.

The Panel noted that the Targinact SPCs stated that the usual starting dose for an opioid naïve patient was 10mg/5mg oxycodone/naloxone at 12 hourly intervals; this dose that was presented on the slide. The SPCs stated that patients already receiving opioids might be started on higher doses of Targinact depending on their previous opioid experience. The maximum daily dose of Targinact was 80mg/40mg oxycodone/naloxone.

With regard to co-codamol 30/500 the maximum daily dose of codeine was 240mg ie 8 tablets in any 24 hour period.

The Panel noted that the frequently asked question (FAQ) section of the website gave more detail than the slide. The response to the question 'How do I convert patients from other opioids?' included a table (which gave similar information about codeine and tramadol as slide 7 of the presentation) which was stated to be only a guide to the dose of Targinact that the patient might require and that inter-patient variability meant that titration to an appropriate dose might be required to provide optimal pain control. A footnote to the table gave a list of assumptions that had been used in compiling the data. Turning to the slide at issue the Panel noted that the data was presented without qualification. The phrase, 'instead of' implied that patients who had been on co-codamol 8 x 30mg/500mg or tramadol 200mg daily could be simply switched to Targinact 10mg/15mg twice a day which was not so. By Napp's own submission the conversion from one opioid to another was more complicated. Contrary to Napp's submission that all promotional material that provided conversion guidance included qualifying statements, there was no mention on the slide that the information had been provided as a guide only or of the need to individually titrate patients to an effective and well-tolerated dose. The slide did refer to increasing the dose to 20mg/10mg 12 hourly if required. In the Panel's view, although health professionals would know the difficulties of calculating equivalent doses of opioids and transferring patients from one to another it nonetheless considered that insufficient information had been given in the slide such that the comparison was misleading. The slide had to be capable of standing alone as regards the requirements of the Code. Breaches of the Code were ruled.

With regard to the alleged risk to patient safety, the Panel noted its ruling that slide 7 was misleading. Misleading material could potentially have a negative impact on patient safety. However, the Panel noted that Napp appeared to have used conservative dosage conversion ratios. It also

noted its comments above about health professionals' awareness of opioid equivalence issues and transferring patients. Targinact could be used in opioid naïve patients. The Panel did not consider that the slide warranted a further ruling of a breach on this point.

The Panel noted that Targinact was a controlled drug whereas co-codamol and Tramadol were not. The presentation did not mention that Targinact was a controlled drug. The legal classification was stated within the prescribing information which could be accessed from each page of the presentation. The Panel did not consider that the heading to the prescribing information 'Targinact tablets contain an opioid analgesic' was sufficient to ensure that readers were aware that Targinact was a controlled drug as submitted by Napp. There were opioid analgesics that were not controlled drugs. Although the Panel considered that it might have been helpful for it to be clearly stated on a page headed 'How to Prescribe Targinact' that Targinact was a controlled drug, on balance, the failure to do so was not misleading per se. No breach was ruled.

The Panel noted that the complainant referred to printed material but had not provided copies. The Panel examined the printed material supplied by Napp.

One page of a leavepiece for use with GPs and hospital specialists gave the same information as the slide at issue and included the additional statement 'This is a guide only, and patients should be individually titrated to an effective and well-tolerated dose'. The Panel noted that this qualification appeared as a footnote in small print at the bottom of the page and thus considered that it did not negate the impression that the codeine and tramadol doses could simply be changed for Targinact 10mg/5mg twice daily. The Panel considered that the leavepiece was therefore misleading and breaches of the Code were ruled. The Panel considered its comments above regarding patient safety applied to the leavepiece and no breach was ruled. Similarly the Panel considered its comments above regarding the failure to mention on the page headed 'How to prescribe Targinact' that Targinact was a controlled drug applied to the leavepiece and no breach was ruled.

Page 4 of a frequently asked questions document included a section headed 'How do I convert patients from other oral opioids?' The answer given included more information than given on slide 7 or in the leavepiece. The answer stated at the outset that the table of data was only a guide to the dose of Targinact that a patient might require and that inter-patient variability might mean that dose titration was required to provide optimal pain control. Below the table the assumptions and conversion factors applied to the table were listed. The Panel considered that this document was not misleading regarding the conversion and no breach was ruled.

A flyer used by the representatives alerted readers to the website and what was available on it. Although it was stated that the website included an introduction to Targinact there was no information given about comparable doses of co-codamol or tramadol. The Panel ruled no breach.

Overall, the Panel was concerned about the information on the website and the leavepiece. The Panel considered that high standards had not been maintained and a breach was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved for use as a sign of particular censure.

A health board prescribing adviser complained about the promotion of Targinact (prolonged release oxycodone and naloxone) by Napp Pharmaceuticals Limited. Targinact was indicated for the treatment of severe pain which could be adequately managed only with opioid analgesics. The usual starting dose for an opioid naïve patient was 10mg/5mg of oxycodone/naloxone at intervals of 12 hours.

The complainant stated that the material at issue was a presentation on www.targetingpain.co.uk/introducing-targin. Slide 7 of the presentation was headed 'How to prescribe Targinact tablets' and featured a highlighted box. In the left hand side of the box it was stated 'Targinact tablets starting dose 10mg/5mg prolonged release 12-hourly oral tablets (total daily dose 20mg/10mg)'. The right hand side of the box was divided into two horizontally. The upper portion contained the statement 'Instead of … codeine, 8 x 30mg/500mg co-codamol tablets/day', and the lower portion contained the statement 'Instead of … tramadol 200mg/day'. Below the box the claim 'Prescribe Targinact 10mg/5mg tablets 12-hourly for patients with severe diagnosed back pain and severe osteoarthritis pain' was followed by 'The start dose of Targinact tablets is 10mg/5mg 12 hourly. This can be increased to 20mg/10mg 12 hourly if required' and 'Please refer to Targinact Summary of Product Characteristics (SPC) for further details'.

COMPLAINT

The complainant stated that the promotional materials suggested that Targinact 10mg/5mg every 12 hours could be used instead of 8 x co-codamol 30mg codeine/500mg paracetamol tablets. The complainant alleged that this statement implied that these tablets had similar efficacy which was false and very misleading. Eight co-codamol 30/500 tablets were equivalent to 20mg morphine per day whereas Targinact 10mg/5mg twice daily was equivalent to 36mg morphine daily. This could pose a risk to a patient's safety.

The complainant stated that 8 co-codamol 30/500 was not equivalent to tramadol 200mg daily or Targinact 10mg/5mg twice daily in terms of morphine equivalence. It was not stated on slide 7 that Targinact was a controlled drug (Schedule 2).

This information was also reproduced in printed material distributed to GPs and junior hospital doctors.

When writing to Napp the Authority asked it to respond in relation to Clauses 2, 7.2, 7.3 and 9.1 of the Code.

RESPONSE

Napp strongly disagreed with the allegations, and did not believe that the Code has been breached, particularly in relation to Clauses 7.2, 7.3, 9.1 and 2.

With regard to the complainant's concern that the material referred to 'instead of … co-codamol 8 x 30/500mg tablets/day' or 'instead of … tramadol 200mg/day' and that promotion of Targinact in this way could 'pose a risk to patient safety', Napp referred to the Targinact SPCs which stated that the usual starting dose for an opioid naïve patient was 10mg/5mg of oxycodone/naloxone at 12-hourly intervals. Thus this dose could be used in patients with no prior experience of opioids, including codeine or tramadol. It was, therefore, not unreasonable or inconsistent with the SPCs to convert a patient who had an opioid requirement of 240mg codeine or 200mg tramadol to the recommended starting dose of 10mg/5mg Targinact tablets twice daily. The advice in the SPCs was considered appropriate and approved by the Medicines and Healthcare products Regulatory Agency (MHRA) during its appraisal of Targinact. Napp did not therefore consider that promotion in this way, which was consistent with the SPCs, posed a risk to patient safety.

The complainant stated that 8 x co-codamol 30/500mg was not equivalent to either tramadol 200mg daily or Targinact twice daily in terms of morphine equivalence. The fundamental issue related to analgesic equivalence (equianalgesia) between opioids which was based on conversion ratios. Equianalgesia referred to different doses of two agents that provided approximately equivalent pain relief. An equianalgesic dose referred to a dose that yielded roughly equivalent analgesia to a standard set in a given equianalgesic dose table. Most commonly, equianalgesic dose tables were standardised such that various opioid doses were provided relative to morphine.

Although equianalgesic dose tables were widely used to determine the new doses when converting from one opioid to another, there was a huge variation in published conversion ratios between different opioids. This was because converting opioid doses was currently based on pharmacokinetic data (such as bioavailability after oral administration) from observational and uncontrolled studies, often only using single doses, and on expert opinion and experience. Such studies often failed to account for inter-individual variations that played a prominent role in determining the appropriate ratio for each individual. Therefore the applicability of such published ratios for patients on long-term opioid therapy was the subject of much controversy and differences of opinion.

Napp had a strong heritage in the provision of opioid analgesics. Although the calculation of equianalgesic doses of opioids was a contested subject (as described above), health professionals required practical conversion guidance in order to make informed prescribing decisions. Therefore Napp believed it had a responsibility to provide guidance, where possible, in order to ensure that its opioid medicines were prescribed appropriately, whilst also highlighting that patients should be individually titrated to analgesic effect.

The material at issue suggested that Targinact 10mg/5mg twice daily could be used instead of co-codamol 8 x 30/500mg tablets per day (ie a total daily dose of 240mg codeine). This was derived from a two step process, based initially upon a conversion ratio of codeine to morphine of 6:1. So, 240mg codeine per day provided an equivalent total daily dose of 40mg morphine. The next step involved converting from morphine to oxycodone, and here a 2:1 conversion ratio had been used. Therefore it followed that a daily dose of 40mg morphine was equivalent to a daily dose of 20mg oxycodone or Targinact 10mg/5mg twice daily.

The suggestion that Targinact 10mg/5mg twice daily could be used instead of tramadol 200mg daily was based on the same process; initially a 5:1 conversion from tramadol to morphine which gave a morphine equivalence of 40mg, and subsequently the 2:1 conversion for morphine to oxycodone as described above.

Rationale for 6:1 dosage conversion ratio of codeine to morphine

Guidance for equianalgesic doses of codeine and morphine showed wide variability in the literature. As described above, this reflected the multiple inter-individual factors that were present, for example inter-patient variability in the efficacy and safety response to opioids due to tolerance and cross tolerance, pharmacokinetic and pharmacodynamic variability, use of co-analgesics and other CNS-active medicines, and psychological variables. Genetic factors also played a role, as it was known that due to polymorphisms in the hepatic microsomal CYP2D6 enzymes, approximately 7-10% of the population were poor-metabolisers of codeine and therefore obtained little or no analgesic effect from it, with 10-15% being intermediate metabolisers thus reducing the relative potency of codeine in such individuals when compared to morphine. Conversely it was also known that some individuals might be extensive (normal) or ultra-rapid metabolisers, which served to highlight the complexity that such genetic factors could add. In addition, estimates of dose equivalence were often based on single-dose studies and not repetitive dosing.

The literature suggested a wide range of

conversions for codeine to morphine when taken orally – between 3.3:1 and 10:1, with the majority of recommended conversion ratios based on clinical experience rather than firm scientific evidence. Recognising that the variation in the conversion ratios was wide, Napp used an approximate mid-point of the codeine to morphine range (ie 6:1) in order to provide some practical guidance for the physician as to where Targinact fitted in therapy relative to other products (in this case codeine) that were also used for severe non-malignant pain.

A number of references supported an approximately 6:1 dose conversion ratio of codeine:morphine. Rossi (2009) stated that 'a dose of approximately 200mg (oral) of codeine must be administrated to give analgesia approximately equivalent to 30mg (oral) of morphine' which equated to 6.7:1 codeine:morphine. This conversion ratio was also recommended by Manfredi (2005), Currie *et al* (2007) and Cherney and Foley (1996). Taking into account the dosage forms currently available for oral codeine in the UK, as well as for Targinact tablets, a 6:1 conversion provided practical guidance to the prescriber, realisable with the dosage strengths available. Indeed the Palliative Care Formulary, 3rd Edition (PCF3) recommended that, with any opioid switch, 'round the calculated dose up or down to the nearest convenient dose of the preparation concerned'.

The complainant suggested that co-codamol 8 x 30/500mg (ie 240mg codeine total) was equivalent to 20mg morphine per day. This was based on a codeine:morphine conversion ratio of 12:1. A conversion factor of 12:1 was based on the potency ratio of parenteral morphine to parenteral codeine and an assumption based on the absolute oral bioavailabilities of morphine and codeine, rather than on studies comparing the analgesic efficacy of these medicines administered orally.

Napp submitted that there were limited direct comparisons between oral oxycodone and oral codeine. Beaver *et al* (1978) looked at the oral:parenteral analgesic relative potency ratio for codeine and oxycodone independently and stated that 'whilst we are unaware of any controlled studies comparing oral oxycodone with oral codeine ... by calculating relative potencies across studies, it is possible to estimate that 10mg of oral oxycodone should be comparable in analgesic effect to 100mg of oral codeine'. This equated to a mean conversion ratio of codeine to oxycodone of 10:1 which was comparable to, and less conservative than, the 12:1 conversion ratio currently used by Napp. The 10:1 ratio of codeine:oxycodone was also employed in a study in children comparing the two in the treatment of pain due to suspected forearm fracture (Charney *et al* 2008).

Taking the above into account, Napp submitted that a dose conversion ratio of 6:1 for codeine to morphine was reasonable. Furthermore, the company was currently conducting a randomised, double-blind, clinical trial comparing the efficacy of Targinact tablets with co-codamol in the treatment of pain due to osteoarthritis and low back pain. This trial was a non-inferiority design, and compared the two treatments at doses Napp believed to be equivalent, based on a 6:1 codeine to morphine conversion, followed by a 2:1 morphine to oxycodone conversion as described above. This study had been evaluated by an independent ethics committee, and the principal investigator was an experienced pain consultant. These factors provided confidence that the relative doses of Targinact and co-codamol being used were appropriate.

Rationale for 5:1 dosage conversion ratio of tramadol to morphine

The material used a ratio of tramadol to morphine of 5:1 as Napp considered this represented standard clinical practice in the UK, as evidenced by local guidelines and the published literature.

The Targinact material referenced the conversion ratio of 5:1 for tramadol to morphine to the PCF3. However, in responding to this complaint, Napp had noted that this edition has been reprinted and now gave a conversion ratio of tramadol to morphine of 10:1. This meant that there were two versions of the PCF3 in circulation, containing different conversion ratios of tramadol to morphine. This difference between the conversion ratios had potential clinical implications, and yet the authors did not consider this significant enough to change the edition number or, at the very least, provide extensive communication of this change. Furthermore, the authors' rationale for significantly changing the conversion ratio for tramadol to morphine was based on 'extensive German clinical experience over many years', to which no specific evidence-based reference was given, thus highlighting the wide variability of such conversion ratios. A literature search identified ratios varying from 4:1 to 10:1, which showed the wide variability in the range of reported conversion ratios as for codeine.

Furthermore within individual patients, just as described for codeine, the opioid analgesic properties of tramadol were also affected by the hepatic CYP2D6 microsomal enzyme. The parent molecule was metabolised by CYP2D6 in the liver to the more potent opioid analgesic O-desmethyl tramadol. Therefore, depending on the genetic expression of CYP2D6 of the patient, they might be normal (extensive metabolisers), poor, intermediate or ultra-rapid metabolisers. This further complicated the derivation of a definitive opioid conversion ratio for tramadol.

Napp had conducted two in-house clinical studies directly comparing oral sustained release tramadol with oral prolonged release oxycodone in osteoarthritis patients with low back pain. These both demonstrated an analgesic equivalence of tramadol to oxycodone of 10:1, which was consistent with the guidance provided by the company for the relative doses of tramadol to the

oxycodone component of Targinact (ie 200mg tramadol/day was approximately equianalgesic to Targinact 10mg/5mg twice daily).

The complainant stated that '8 x co-codamol 30/500mg was not equivalent to tramadol 200mg daily' and therefore Napp had assumed that this aspect of the complaint might be directed towards the apparent equivalence between codeine and tramadol, rather than tramadol and morphine, or indeed tramadol and Targinact. As with oxycodone and codeine, there were few clinical studies comparing tramadol and codeine. While tramadol was considered more potent than codeine, Mullican and Lacy (2001) found an approximate 1:1 conversion ratio when tramadol/paracetamol was compared with codeine/paracetamol although Davis *et al* (2005) found that 200-250mg of tramadol produced the same degree of pain relief as 140mg of codeine plus 1400mg paracetamol, equivalent to a conversion ratio of approximately 1:1.5-1.8. Due to the lack of clarity regarding the relative potencies of tramadol and codeine, it was reasonable to use their respective potencies relative to morphine in order to give some guidance. On balance, Napp believed that based on the potencies of tramadol and codeine relative to morphine, as well as on the limited comparative data between the two, it was reasonable to suggest that 200mg of tramadol was approximately equivalent to 240mg of codeine.

Rationale for 2:1 dosage conversion ratio of morphine to oxycodone

There were wide inter-individual variations in the bioavailability of oral morphine and oxycodone; morphine ranged from 15 - 69%, whereas for oxycodone the mean bioavailability ranged from 37 - 87%. Thus depending on an individual's ability to absorb, distribute and metabolise morphine, the relative potency of oxycodone could in theory show a wide range. Indeed clinical studies had shown oral morphine to oxycodone conversions ratios ranged from 1:1 to 2.3:1, and therefore a 2:1 ratio reflected a conservative approach (Anderson *et al* 2001) when converting from morphine to oxycodone. Furthermore, the OxyContin (prolonged release oxycodone tablets) SPC stated that 'patients receiving oral morphine before OxyContin therapy should have their daily dose based on the following ratio: 10mg of oral oxycodone is equivalent to 20mg of oral morphine' and so a conversion ratio of 2:1 morphine:oxycodone was recommended by Napp as a guide. Using this conversion factor to convert from morphine to oxycodone, Targinact 10mg/5mg twice daily equated to 40mg and not 36mg morphine as stated by the complainant.

In summary, Napp firmly believed that the information presented for Targinact appropriately and responsibly reflected the balance of evidence regarding the comparative potency of codeine, tramadol and Targinact. The suggestion that Targinact 10mg/5mg twice daily could be used instead of total daily doses of 240mg codeine or 200mg tramadol was reasonable, supported by evidence and not misleading. Napp did not consider that it had breached Clauses 7.2 or 7.3 in this regard.

With regard to the failure to state that Targinact was a Schedule 2 controlled drug, Napp submitted that the Code required only that information relating to the legal classification of a drug be presented within the prescribing information (Clause 4.2). The legal classification of Targinact (CD (Sch2) Pom) was clearly stated in the prescribing information, to which there was a direct hyperlink on every page of the presentation on the website. Furthermore, Napp took very seriously the nature of the products that it promoted (ie controlled drugs), and for this reason the statement 'Targinact tablets contain an opioid analgesic' appeared at the top of the prescribing information to immediately alert the reader to this fact.

Slide 7 had a prominent display of the Targinact logo and non-proprietary name (ie oxycodone/naloxone) on the relevant webpage. The fact that Targinact contained the well known strong opioid oxycodone was therefore immediately obvious. In addition, the 'Overview' page of the module stated the therapeutic indication of Targinact, ie 'Severe pain, which can be adequately managed only with opioid analgesics. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut' and thus provided clear information that this product was an opioid analgesic.

Napp stated that it was unclear exactly what the complainant meant by printed material. It assumed that the complainant meant the Targinact tablets 'Your Questions Answered' booklet (UK/TA-08046), which reproduced the 'Frequently Asked Questions' section of the website, and contained the dosage conversion information. This booklet explicitly provided information to the effect that the relative doses of Targinact, co-codamol and tramadol were provided as a guide only and that due to inter-individual variability, patients should be titrated to analgesic effect.

The complainant alleged that the promotion of Targinact 10mg/5mg twice daily as being equivalent to co-codamol 8 x 30/500mg or 200mg tramadol per day posed a potential risk to patient safety. Napp appreciated, as detailed above, that the calculation of equianalgesic doses of opioids was complex and that opioid dosage conversions could only be considered as a guide. Inter-patient variability required that each patient was carefully titrated to the appropriate dose. A statement to this effect was currently included in all promotional materials that provided conversion guidance. Indeed, wording to this effect is present specifically within the 'Frequently Asked Questions' section of the 'Introducing Targinact' module of the website at issue as well as the Targinact promotional booklets referred to by the complainant (which Napp assumed to be the 'Your Questions Answered' booklet).

Napp noted that the Targinact SPCs stated that 'The usual starting dose for an opioid naïve patient is 10mg/5mg of oxycodone hydrochloride/naloxone hydrochloride at 12 hourly intervals'. This implied that this dose could be used in patients with no prior experience of opioids, including codeine or tramadol. Bearing this in mind, it was therefore not unreasonable, nor inconsistent with the SPCs, for a patient who had reached an opioid requirement of 240mg codeine or 200mg tramadol to be converted to Targinact 10mg/5mg tablets twice daily, and hence would not be considered to jeopardise patient safety when done appropriately, following the guidance as described above. Indeed the British National Formulary recommended that in opioid naïve patients, the starting dose of prolonged release morphine preparations was usually 10 - 20mg 12-hourly (considered therapeutically equivalent to Targinact 5mg/2.5mg-10mg/5mg 12-hourly), and to replace a weaker opioid analgesic the starting dose was usually 20-30mg 12-hourly (considered therapeutically equivalent to Targinact 10mg/5mg-20mg/10mg 12-hourly). This national guidance was consistent both with the Targinact SPCs and with the conversion guidance in the promotional materials.

In conclusion, published opinions varied widely regarding the most appropriate conversion ratios to use. However, Napp recognised that health professionals relied on clear and practical conversion guidance, realisable with the dosage forms available, in order to make informed clinical decisions when prescribing opioids. Therefore Napp believed it had a responsibility to provide this type of guidance, where possible, based on the balance of the available evidence in order to ensure that its opioid medicines were prescribed appropriately and responsibly.

In response to a request for further information, Napp explained that the presentation at issue was available to health professionals through the 'Targeting Pain' website. This website was initiated and funded by Napp and provided in association with Pulse as a service to pain management with Targinact promotional material only included within the section for health professionals. The website had been promoted to health professionals via digital, email and print promotion; details were provided. The website was also advertised on certain Targinact promotional items, for example, a leavepiece used with GPs and hospital specialists (ref UK/TA-09105). Sales representatives promoted the website using a flyer (ref UK/FT-09044). The website was not used proactively by sales people as a training tool.

PANEL RULING

The Panel noted that the Targinact SPCs stated that the usual starting dose for an opioid naïve patient was 10mg/5mg oxycodone/naloxone at 12 hourly intervals. It was this dose that was presented on the slide at issue. The SPCs stated that patients already receiving opioids might be started on higher doses of Targinact depending on their previous opioid experience. The maximum daily dose of Targinact was 80mg/40mg oxycodone/naloxone.

With regard to co-codamol 30/500 the maximum daily dose of codeine was 240mg ie 8 tablets in any 24 hour period.

The Panel noted Napp's comments that although equianalgesic dose tables were widely used to determine the new doses when converting from one opioid to another, it was well recognised that there was a huge variation in published conversion ratios between different opioids. There was also inter-patient variability including, *inter alia*, genetic factors which determined how quickly patients metabolised codeine or tramadol. The Panel noted Napp's submission that it believed it had a responsibility to provide guidance where possible in order to ensure that its opioid medicines were prescribed appropriately whilst also highlighting that patients should be individually titrated.

The Panel noted that the frequently asked question (FAQ) section of the website gave more detail than the slide. The response to the question 'How do I convert patients from other opioids?' included a table (which gave similar information about codeine and tramadol as slide 7 of the presentation) which was stated to be only a guide to the dose of Targinact that the patient might require and that inter-patient variability meant that titration to an appropriate dose might be required to provide optimal pain control. A footnote to the table gave a list of assumptions that had been used in compiling the data. Turning to the slide at issue the Panel noted that the data was presented without qualification. The phrase, 'instead of' implied that patients who had been on co-codamol 8 x 30mg/500mg or tramadol 200mg daily could be simply switched to Targinact 10mg/15mg twice a day which was not so. By Napp's own submission the conversion from one opioid to another was more complicated. Contrary to Napp's submission that all promotional material that provided conversion guidance included qualifying statements, there was no mention on the slide that the information had been provided as a guide only or of the need to individually titrate patients to an effective and well-tolerated dose. The slide did refer to increasing the dose to 20mg/10mg 12 hourly if required. In the Panel's view, although health professionals would know the difficulties of calculating equivalent doses of opioids and transferring patients from one to another it nonetheless considered that insufficient information had been given in the slide such that the comparison was misleading. The slide had to be capable of standing alone as regards the requirements of the Code. Breaches of Clauses 7.2 and 7.3 were ruled.

With regard to the alleged risk to patient safety, the Panel noted its ruling that slide 7 was misleading. Misleading material could potentially have a negative impact on patient safety. However, the

Panel noted that Napp appeared to have used conservative dosage conversion ratios. It also noted its comments above about health professionals' awareness of opioid equivalence issues and transferring patients. Targinact could be used in opioid naïve patients. The Panel did not consider that the slide warranted a further ruling of a breach of Clause 7.2 on this point and no breach was ruled.

The Panel noted that Targinact was a controlled drug whereas co-codamol and Tramadol were not. The presentation did not mention that Targinact was a controlled drug. The legal classification was stated within the prescribing information which could be accessed from each page of the presentation. The Panel did not consider that the heading to the prescribing information 'Targinact tablets contain an opioid analgesic' was sufficient to ensure that readers were aware that Targinact was a controlled drug as submitted by Napp. There were opioid analgesics that were not controlled drugs. Although the Panel considered that it might have been helpful for it to be clearly stated on a page headed 'How to Prescribe Targinact' that Targinact was a controlled drug, on balance, the failure to do so was not misleading per se. No breach of Clause 7.2 was ruled.

The Panel noted that the complainant referred to printed material but had not provided copies. The Panel examined the printed material supplied by Napp.

Firstly the leavepiece (ref UK/TA-09105). One of the pages gave the same information as the slide at issue and included the additional statement 'This is a guide only, and patients should be individually titrated to an effective and well-tolerated dose'. The Panel noted that this qualification appeared as a footnote in small print at the bottom of the page and thus considered that it did not negate the impression that the codeine and tramadol doses could simply be changed for Targinact 10mg/5mg twice daily. The Panel considered that the leavepiece was therefore misleading and breaches of Clauses 7.2 and 7.3 were ruled. The Panel considered its comments above regarding patient safety applied to the leavepiece and no breach of Clause 7.2 was ruled. Similarly the Panel considered its comments above regarding the failure to mention on the page headed 'How to prescribe Targinact' that Targinact was a controlled drug applied to the leavepiece and no breach of Clause 7.2 was ruled.

The frequently asked questions document (ref UK/TA-08046) included on page 4 a section headed 'How do I convert patients from other oral opioids?' The answer given included more information than given on slide 7 or in the leaflet. The answer stated at the outset that the table of data was only a guide to the dose of Targinact that a patient might require and that inter-patient variability might mean that dose titration was required to provide optimal pain control. Below the table the assumptions and conversion factors applied to the table were listed. The Panel considered that this document was not misleading regarding the conversion and no breach of Clauses 7.2 and 7.3 was ruled.

The flyer used by the representatives (ref UK/FT-09044) alerted readers to the website and what was available on it. Although it was stated that the website included an introduction to Targinact there was no information given about comparable doses of co-codamol or tramadol. The Panel ruled no breach of Clauses 7.2 and 7.3.

Overall, the Panel was concerned about the information on the website and the leavepiece. The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved for use as a sign of particular censure.

Complaint received **6 August 2009**

Case completed **5 October 2009**