CASE AUTH/2961/6/17

INDIVIOR v MARTINDALE

Promotion of Espranor and information to the public

Indivior complained about the promotion of Espranor oral lyophilisate (buprenorphine) by Martindale Pharmaceuticals. The materials at issue were two detail aids, a patient leaflet and a website. Indivior marketed Subutex (buprenorphine sublingual tablets). Both Espranor and Subutex were indicated for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

The detailed response from Martindale is given below.

Indivior noted that the landing page to the Espranor website included the claim 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment'. The claim was directly visible to all visitors ie patients and health professionals worldwide. At the bottom of the homepage, the options to enter the website as 'a UK health professional' or 'not a health professional' were visible. The 'not a health professional' option opened a new page which appeared to be a general page for patients whether taking Espranor or not. Indivior was concerned that the website was promotional and encouraged patients to request Espranor and that important safety information from the summary of product characteristics (SPC) with regard to Espranor not being directly interchangeable with other buprenorphine products, was not addressed.

The Panel noted that the patient section of the website stated that it was for 'patients interested in opioid substitution therapy (OST) and Espranor' and considered that its audience was therefore wider than just patients who had been prescribed the product as submitted by Martindale. The website was open access and the homepage would potentially be seen by a broad audience. This was not unacceptable so long as the website complied with the Code and relevant parts were suitable for the general public. The Panel noted that the website was directed at not only health professionals and those who had been prescribed the medicine but also the general public. Irrespective of the intended audience, the open access homepage should be suitable for the general public. The Panel noted that the claim in question 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment' would be seen by this wide audience and considered that it promoted a prescription-only medicine to, *inter alia*, members of the public and encouraged them to ask their doctor to prescribe it. Breaches of the Code were ruled.

The Panel noted that the part of the website which stated that it was for patients interested in OST and Espranor, contained information about Espranor and a link to the patient leaflet, rather than general information about OST and all relevant treatments. In the Panel's view, this section of the website might be generally suitable for patients for whom Espranor had been prescribed, rather than the general public and it encouraged the general public to seek a prescription for it. A breach of the Code was ruled.

The Panel noted Indivior's concern that the section of the website for patients interested in OST and Espranor' did not include important safety information, identified in the SPC, such as 'Espranor is not directly interchangeable with other buprenorphine products'. The Panel noted that the webpage in question gave top line information about Espranor and stated that readers should speak to their doctor if they had any specific questions about their treatment. A reference to the Yellow Card Scheme appeared at the bottom of the page. A link to the patient information leaflet (PIL) was provided and this included the warning 'Espranor is not interchangeable with other oral buprenorphine products and the dose of Espranor may differ from the dose of other buprenorphine products'. The Panel noted its comments above about the unclear nature of the intended audience and its rulings of breaches of the Code. The page in question described Espranor as a new wafer form of buprenorphine and referred to its use as a substitute for opiate drugs such as morphine or heroin. The Panel noted Martindale's submission about the vulnerable nature of those being treated for opioid dependence and that any change to medication would cause anxiety. The Panel considered that the statements about Espranor might encourage patients to consider interchangeability. The Panel considered that the web page should stand alone as regards the medicine's risk/benefit profile and compliance with the Code and could not rely on the PIL in that regard. Readers would not necessarily click on the link. In addition, the Panel noted the emphasis in the EU Risk Minimisation Plan for Espranor that it should not be swapped for sublingual buprenorphine, or vice versa, without health professional advice. Given the prominence given to the interchangeability warning in the PIL, that the webpage appeared to be directed at, *inter alia*, patients and the points raised above including the vulnerable nature of such patients, the Panel considered the omission of such information meant that this section was not presented in a balanced way. A breach of the Code was ruled.

Indivior noted that the claim 'This renders the buprenorphine dose impossible to remove from the mouth once administered' appeared in one detail aid and 'No delay, No diversion, No nonsense buprenorphine' appeared in the other.

Indivior stated that misuse (intentional and inappropriate use not in accordance with the authorised product information which could be accompanied by harmful physical or psychological effects) and diversion (the unsanctioned supply of regulated medicines from legal sources to the illicit drug market, or to a user for whom the drugs were not intended) of medicines used in opioid use disorder was a well-known and accepted adverse event that occurred with opioid agonists, including buprenorphine.

Indivior noted that in response to a query related to the claim' 'impossible to remove from the mouth once administered' Martindale referred to the SPC which stated: 'Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue'. Indivior alleged that the claim was exaggerated, misleading, inaccurate and not supported by the evidence provided; it was harmful to prescribers and patients as it created the illusion that it was not possible to remove the medication once on the tongue.

The Panel noted that it had asked both parties to define, *inter alia*, 'dispersal', 'dissolution', 'disintegrate' and 'dissolve'. The parties' definitions were not wholly dissimilar. However, the Panel queried whether Martindale had applied sufficient rigour to the consistent application of the terms throughout the materials such that their meanings were clear. The Panel noted that this matter was further complicated as the use of certain terms also appeared to be inconsistent in the various studies and public documents.

The Panel noted that the claims at issue 'This renders the buprenorphine dose impossible to remove from the mouth once administered' and 'No delay, No diversion, No nonsense buprenorphine' implied that there was absolutely no possibility that a dose could be removed from the mouth following supervised administration (diversion) which was not so. The Espranor SPC stated 'Removal of Espranor from the mouth following supervised administration is *virtually* impossible due to its rapid dispersal on the tongue' (emphasis added) which implied that that there was a potential for the dose to be removed from the mouth following its supervised administration. The Panel further noted clinical data (Strang *et al* 2017) regarding the disintegration time of Espranor ie that time when 'the tablet could no longer be removed intact'. 96.3% of Espranor administrations achieved partial disintegration on the tongue in ≤ 15 seconds' and 'the median time for complete [Espranor] tablet disintegration was 2 minutes ...'. This meant that 3.7% of administrations took longer than 15 seconds to achieve partial disintegration leaving potential for the dose to be removed. By 2 minutes, Espranor had completely disintegrated in 58% of administrations. In four recordings either partial or complete disintegration was noted at 15 minutes.

The Panel noted the qualified statement in a clinical study that a benefit of the reduced time to disintegration with Espranor was 'the *reduced potential* for concealment and diversion' (emphasis added). The Panel considered that the claims in question 'No diversion.' and 'This renders the buprenorphine dose impossible to remove from the mouth once administered' were too dogmatic and implied there was absolutely no possibility of diversion, however small, and that was not so. This implication was compounded in relation to the latter claim as it appeared beneath the unqualified heading 'Espranor *prevents* the most common route of diversion' (emphasis added). The Panel considered that the claims in question were misleading and could not be substantiated, breaches of the Code were ruled.

The Panel further noted Indivior's allegation that the information about adverse events (in this case misuse and diversion of buprenorphine) did not reflect the available evidence. The Panel considered that the claims in question might potentially be harmful to patients as doctors might assume that it was absolutely impossible for patients to remove the dose which was not necessarily so. However, the clause cited by Indivior related to the requirement that claims about adverse reactions must reflect available evidence and not state that there were no adverse reactions, toxic hazards or risks of addiction or dependency. The Panel noted Indivior's submission that, *inter alia*, diversion was a well-known and accepted adverse event with opioid agonists including buprenorphine. The Panel noted diversion was not listed in Section 4.8, Undesirable effects, of the Espranor SPC. In the Panel's view, the claims in question did not fall within the remit of the cited clause and so it ruled no breach of that clause.

Indivior stated that Martindale had been unable to provide data to support a number of claims that Espranor instantly disintegrated when placed on the tongue eg '…buprenorphine that instantly disintegrates on the tongue …'. In fact, the evidence it provided showed that this was not the case. Indivior noted that conflicting claims were presented side-by-side in the PIL which stated 'Instant Disintegration', followed by 'Average time to complete disintegration (median): 2 minutes', further confusing patients. Indivior alleged that the claims were inaccurate, misleading and misrepresented the data which was unsubstantiated by the published evidence. Indivior further noted that the SPC stated 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds'.

The Panel noted its general comments above about the definition and inconsistent use of, *inter alia*, 'disintegration'. It considered its comments above about diversion were relevant to the claims now at issue about instant disintegration.

The Panel considered that most of the claims made for instant disintegration were too dogmatic and implied that the tablets completely disintegrated instantly on every administration which was not so. Context was important. Further information should be given about disintegration times, the meaning of the term and clinical study results so that readers could properly assess the claims. In the Panel's view, 5 of the 6 claims in question were each misleading and could not be substantiated; breaches of the Code were ruled.

The Panel noted that further information about partial disintegration time and dissolution time vs sublingual buprenorphine was provided alongside the claim 'Instant disintegration' on page 3 of the one of the detail aids. In that regard the Panel considered that the context was such that this claim was materially different to the others at issue. However, on balance, the Panel considered that the prominent claim 'Instant disintegration' was misleading insofar as it gave the immediate visual impression that tablets completely disintegrated instantly on each administration and that was not necessarily so. This immediate impression was not capable of substantiation. Breaches of the Code were ruled.

Indivior noted that it had highlighted above the importance of misuse and diversion in patients receiving OST. Martindale had not provided evidence to support claims that Espranor eliminated or prevented the opportunity for removal of the medicine. A video on the Espranor website showed that the product remained on the tongue and available for removal for at least the eight seconds; the product was shown largely unchanged on the tongue. The SPC stated: 'Removal of Espranor from the mouth following supervised administration is *virtually* impossible due to its rapid dispersal on the tongue' (emphasis added). Indivior did not accept that this statement could be converted into the claim that the product 'eliminates' the opportunity for diversion. Indivior alleged that such claims were inaccurate, misleading and not substantiated.

The Panel noted its general comments and rulings above in relation to instant disintegration and diversion claims. The Panel noted that it might be difficult for a patient to remove Espranor from the mouth once administered but considered that it was misleading to state that Espranor and its 'instant disintegration' completely eliminated the opportunity for such removal. The Panel considered that such claims were too dogmatic. Insufficient information was given to enable a reader to assess the data. The Panel further noted the SPC statements above and considered that the claims at issue were misleading and not capable of substantiation; breaches of the Code were ruled. Indivior referred to the claims 'Espranor is not interchangeable with other buprenorphine products' which appeared on the website and 'Espranor was not directly interchangeable with other forms of buprenorphine' which appeared in each of the detail aids. Indivior stated that efficacy data confirmed that 'Espranor is not interchangeable with other buprenorphine products'. This was prominently featured on the packaging the SPC and PIL (either in bold, or in a boxed warning) and so should be similarly displayed on all materials to enable prescribers and patients to make informed choices. Indivior did not consider that Martindale had not gone to sufficient lengths to highlight that Espranor was not interchangeable with other buprenorphines used in OST; the text was not sufficiently prominent and this important information was not provided early enough in all of the materials in question and was not in the patient leaflet at all. Indivior alleged that Martindale had brought discredit upon the industry by underplaying a key prescribing issue and thus misleading prescribers.

The Panel noted that a boxed warning that Espranor was not interchangeable with other buprenorphine products was included in Section 4.2 of the SPC. A boxed warning appeared at the beginning of Section 2 (What you need to know before you take Espranor) of the PIL which read 'Espranor is not interchangeable with other oral buprenorphine products and the dose of Espranor may differ from the dose of other buprenorphine products'. This latter boxed warning was also part of the labelling on the product packaging as referred to in the PAR. The Panel noted that the EU Risk Management Plan discussed the prevention of error due to the wrong medication and noted the higher bioavailability of buprenorphine from Espranor than from Subutex. Medication errors were listed as an important potential risk in the summary of safety concerns.

The Panel disagreed with Indivior's contention that the warning in question should make it clearer that Espranor was not interchangeable with other buprenorphines used in OST. The Panel noted that some other buprenorphine products were licensed to treat, *inter alia*, moderate to severe cancer pain and severe pain which did not respond to non-opioid analgesics. The Panel noted Espranor's licensed indication, substitution treatment for opioid dependence, and that each item at issue was either promotional material for the product or for patients who had been prescribed it and discussed its licensed use. The Panel thus did not consider that the non-interchangeability warning at issue needed to qualify the reference to buprenorphines by stating that it applied to those used in OST. High standards had been maintained on this point. No breach of the Code was ruled.

The Panel disagreed with Martindale's submission that the warning in one of the detail aids, 'Espranor is not directly interchangeable with other forms of buprenorphine', stood out as the header because it was highlighted in blue. The Panel noted that all five subheadings on the page were in the same pale blue font. Two main headings were in purple font and the text was otherwise black. The Panel considered that the pale blue font colour and the overall design of the page, including the position of the warning in question as the subheading to the final paragraph at the bottom of the page, meant that it was not sufficiently prominent. Although, as submitted by Martindale, the warning in the Espranor SPC was in the same size as the rest of the text on that page, it was also within a box and 'Not

interchangeable with other buprenorphine products' was emboldened. The Panel considered that the warning should have been made more prominent given the therapy area, the vulnerable nature of the patients and its prominence in the SPC. A breach of the Code was ruled.

The Panel noted that the warning 'Espranor is not directly interchangeable with other buprenorphine products' was in the other detail aid followed by the prescribing information. Despite the use of emboldened font within the warning, the Panel considered that it should have been presented earlier in the detail aid given that the preceding pages discussed how Espranor delivered buprenorphine in OST more effectively than hard, compressed, sublingual formulations and compared its dissolution time to that of Subutex. The Panel considered that its comments above about the need for the warning to be more prominent were relevant here. High standards had not been maintained. A breach of the Code was ruled.

With regard to the Espranor website, the Panel noted that although the warning in the SPC had been reproduced in full and was within an outlined box, it was only presented towards the end of the health professional section. As above the Panel considered that it should have been presented earlier; high standards had not been maintained and a breach of the Code was ruled.

The Panel noted that Indivior had also alleged that the warning was not sufficiently prominent on page 15 of the website which comprised prescribing information. In this regard, the Panel noted that the prescribing information did not include the SPC. The Code dictated the content of prescribing information which included precautions and contraindications and warnings issued by, *inter alia*, the licensing authority which were required to be in advertisements and it also required prescribing information to be provided in a clear and legible manner. There was no reference in the relevant clauses about prominence of particular elements of the prescribing information. The Panel noted that the warning, 'Espranor is not interchangeable with other buprenorphine products' was in the same font size as the rest of the prescribing information within the Dosage and administration section. It was underlined as were 10 other phrases or sentences in the first column of prescribing information. It was not prominent such that it caught the reader's eye. Although the Panel considered that it would have been helpful if the warning had been visually more prominent in the absence of a specific direction or requirement of the Code, on balance, it did not consider that the company had failed to maintain high standards. No breach of the Code was ruled.

The Panel noted that the absence of the warning on the patient section of the website was covered by its ruling above.

With regard to the patient leaflet the Panel noted its relevant comments above including the content of the EU Risk Minimisation Plan and in particular noted the vulnerability of the patients and considered that in these particular circumstances it was important to ensure that all relevant information was made available. The Panel considered that the failure to include the verbatim warning (or similar) in the patient information leaflet was such that high standards had not been maintained. A breach of the Code was ruled.

The Panel noted the vulnerability of the patient population and that the highlighted warning was a prominent part of the SPC, PIL and the product pack. The Panel noted its comments above on the lack of prominence given to the warning across several materials and that it was not on the patient materials at issue at all. The Panel noted that prejudicing patient safety was given as an example of an activity likely to be in breach of Clause 2 of the Code. A breach of that clause was ruled.

Indivior alleged that Martindale misrepresented dissolution and disintegration data for Subutex when comparing it with Espranor, implying that there were greater differences in dissolution time to that shown by the head-to-head data. According to Indivior, Martindale also suggested that the difference was clinically important without providing any supportive evidence. Indivior referred to the SPC and clinical data and stated that dissolution and disintegration were not comparable nor interchangeable in this context. Indivior alleged that Martindale was misleading with this comparison; it had distorted the data, exaggerated and given undue emphasis to the benefits of Espranor compared with Subutex.

The Panel noted Indivior's submission that the SPC for Subutex stated 'The tablet should be kept under the tongue until dissolved, which usually occurs within 5 to 10 minutes'. The Espranor SPC stated that 'The oral lyophilisate should be … placed whole on the tongue until dispersed, which usually occurred within 15 seconds, and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes ... Patients should not consume food or drink for 5 minutes after administration'. The SPC further noted that physicians must advise patients that the oromucosal route of administration was the only effective and safe route of administration for Espranor. If the oral lyophilisate or saliva containing buprenorphine were swallowed, the buprenorphine would be metabolised and excreted and have minimal effect. The Panel noted its comments above about the clinical data regarding disintegration and diversion.

In relation to the website claim 'Unlike conventional hard compressed buprenorphine sublingual tablets which take up to 10 minutes to dissolve, Espranor instantly disintegrates within 15 seconds of being placed on the tongue resulting in rapid dissolution (median time 2 minutes)', the Panel noted that the latter part of the claim 'resulting in rapid dissolution (median time 2 minutes)' appeared at the top of the following page on the version provided by the complainant. The Panel noted its ruling of a breach of the Code in relation to a claim about instant disintegration within 15 seconds above. The Panel noted the reference to 5-10 minutes in the

Subutex SPC and considered that readers would probably compare the stated 'instant disintegration' of Espranor with the stated 'up to 10 minutes' dissolution time for the comparator. The Panel noted Indivior's submission that dissolution and disintegration were not comparable in this context and noted the parties' definition of terms. The Panel queried whether 'up to 10 minutes' was a fair reflection of the Subutex SPC. Those readers who saw the entire claim, which concluded on page 4, might compare Espranor's median dissolution time of 2 minutes with 'up to 10 minutes' for Subutex. The Panel considered that the claim in question 'Unlike conventional hard compressed buprenorphine sublingual tablets which take up to 10 minutes to dissolve, Espranor instantly disintegrates within 15 seconds of being placed on the tongue resulting in rapid dissolution (median time 2 minutes)' exaggerated the differences between the products and was misleading in this regard. The claim could not be substantiated. Breaches of the Code were ruled.

In relation to the website claim 'Buprenorphine is currently only available as hard compressed sublingual tablets which take up to 10 minutes to dissolve,' the Panel noted that whilst the claim itself did not refer to Espranor, the preceding paragraphs discussed Espranor and referred to its 'rapid dissolution' and 'Instant disintegration ...'. Closely similar claims about instant disintegration had been ruled in breach of the Code above. The Panel noted its comments above about the Subutex SPC and the phrase 'up to 10 minutes'. In the Panel's view, readers were invited to compare the stated 'up to' 10 minutes' dissolution time of the comparator with the stated instant disintegration of Espranor which were misleading and exaggerated the differences between the products. This comparison was incapable of substantiation. A breach of the Code ruled.

The Panel noted that the claim 'Conventional, hard, compressed, sublingual buprenorphine tablets take up to 10 minutes to dissolve' on the front page of one of the detail aid immediately followed the claim 'Espranor oral lyophillsate has been specifically designed to disintegrate instantly and dissolve rapidly when placed on the tongue'. This preceding claim, including the phrase 'disintegrate instantly', had been ruled in breach of the Code above. The emboldened unqualified claims on the front page of the detail aid included 'No delay. No diversion'. The Panel noted its comments above about the Subutex SPC and the phrase 'up to 10 minutes'. The Panel considered readers were invited to compare the stated 'up to' 10 minute dissolution time for Subutex with the stated instant disintegration of Espranor which gave a misleading and exaggerated comparison of the two which could not be substantiated. Breaches of the Code were ruled. The Panel noted that the claim 'In the UK, licensed buprenorphine is currently only available as hard-compressed sublingual tablets, which take up to 10 minutes to dissolve and may compromise supervised administration' was in the introductory section of one of the detail aids that discussed barriers to buprenorphine use (page 3). Whilst the preceding page and subsequent sections on the page in question discussed Espranor, the Panel noted that the only relevant statement in relation to Espranor across both pages was the first bullet point at the top of page 2 which read 'Espranor oral lyophilisate is a novel freeze dried wafer formulation of buprenorphine which disintegrates instantly and rapidly when placed on the tongue'. As noted above, claims about instant disintegration had been ruled in breach of the Code. The Panel noted the detailed information given across pages 2 and 3 of the A4 detail aid. Other than the aforementioned bullet point, there was no other mention of disintegration and dissolution. Visually no prominence was given to the aforementioned bullet point at the top of page 2 such that the Panel considered, on the balance of probabilities, that the claim in question on page 3, 'In the UK, licensed buprenorphine is currently only available as hard-compressed sublingual tablets, which take up to 10 minutes to dissolve and may compromise supervised administration' would not be read in light of the first bullet point on the preceding page and thus not a comparison with it. The design of the page was relevant. The Panel ruled no breach of the Code.

In relation to the allegation about the comparison on page 3 of the other detail aid, the Panel noted the page was prominently headed 'Espranor: rapid by design'. Beneath the left-hand column and the prominent subheading 'Instant disintegration' a clock face depicted that 96% of Espranor patients vs 72% with Subutex (p=0.0002) had partial disintegration (no longer removable from the mouth) at ≥15 seconds. The figure of 96% was prominent and in the same purple font as the claims 'rapid by design and instant disintegration'. The right-hand column was headed 'Rapid dissolution' beneath which the average time to complete disintegration (median) was visually depicted showing Espranor as 2 minutes and Subutex as 10 minutes, p<0.0001. The data was referenced to the Espranor SPC and Strang *et al* (2015). The Panel noted its comments on this page above. The Panel noted its comments above on the wording in the Subutex SPC. The Panel noted that the bar chart did not reflect the range of 5-10 minutes within which Subutex usually dissolved as stated in its SPC. The Panel noted that there were differences between the products in relation to disintegration and dissolution in favour of Espranor. The prominent subheading 'Instant disintegration' had previously been ruled in breach of the Code. The Panel noted that more comparative data was given on this page than for the claims at issue above. Nonetheless, the Panel considered that the failure to fairly reflect the Subutex SPC in conjunction with the prominent claim 'instant disintegration' meant that the comparison was misleading and exaggerated the differences between the products. The comparison was not capable of substantiation. Breaches of the Code were ruled.

The Panel noted the allegation that Martindale suggested that the above comparisons were clinically relevant which was not supported by the data. However, the Panel noted that whilst

claims had to be capable of substantiation, the burden was on Indivior to show that, on the balance of probabilities, such claims were not clinically relevant. It had not identified any data and Martindale had not responded to this point. The Panel noted that the studies before it in relation to different matters in this case included discussion of supervision times. In the Panel's view, Indivior had not discharged the burden of proof. The Panel ruled no breach of the Code.

Indivior noted claims regarding the reduced supervision time afforded by Espranor and that in support of such claims Martindale had referred to an excerpt of its clinical study report which was a key reference for multiple claims in its materials, but this had not been provided in a full enough form to confirm or deny the claim. It surmised: 'The faster speed of disintegration with [Espranor] *will* reduce the supervision time required compared to [sub-lingual buprenorphine], providing a greater convenience for both the patient and clinician, and the *potential for reduced supervision costs* in both the healthcare and prison systems' (emphasis added). Indivior did not consider that there was evidence to support the claims and again noted that the Espranor SPC stated '… Swallowing should be avoided for 2 minutes … Patients should not consume food or drink for 5 minutes after administration' which increased the required supervision time to at least 5 minutes.

The Panel noted Indivior's reasoning that, given wording in the Espranor SPC, supervision time should be at least 5 minutes. In the Panel's view, the aim of supervision was to ensure that the patient did not remove a dose for diversion. It was well-known that patients removed doses of buprenorphine from supervised consumption in creative ways.

The Panel considered that its comments above about the time taken to achieve partial and complete disintegration and diversion were relevant here.

The Panel noted Martindale's submission that there was no statement in the SPC to suggest supervision for 5 minutes to ensure that food was not consumed after taking Espranor; the only reference to supervision was during the initiation of treatment. Daily supervision of dosing was recommended to ensure proper placement of the dose on the tongue and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

The Panel noted that Strang *et al* (2017) concluded that 'Espranor's rapid disintegration and consequent greater ease of supervised dosing may increase the feasibility of buprenorphine treatment in busy community and custodial settings when supervised dosing is considered important. This now needs to be explored clinically'. The authors subsequently stated that 'hopefully rapid-dissolving variants of buprenorphine may increase the range of settings in which buprenorphine can safely be delivered such as settings where it is unrealistic to expect full supervision of dosing over several minutes'. These contexts would warrant attention in future studies. The Panel noted that the page of the clinical study report that had previously been disclosed to Indivior was more dogmatic, it stated 'The faster speed of disintegration with [Espranor] will reduce the supervision time required compared to the comparator, providing a greater convenience for both the patient and clinician, and the potential for reduced supervision costs in both the healthcare and prison systems'.

The Panel noted that there were differences between the products which were relevant to supervision time. The Panel considered that the phrase 'reduces the time required.' had to be considered in the context in which it was used.

The Panel noted that the website claim 'Rapid dissolution reduces the time required for supervised administration' was one of two bullet points and appeared immediately above the claim 'Instant disintegration eliminates the opportunity for removal from the mouth once administered' which was ruled in breach of the Code above in relation to the elimination claim. In addition, the phrase 'instant disintegration' was closely similar to matters ruled in breach of the Code above. In the Panel's view, the context including the unqualified claim about instant disintegration and elimination implied that the reduction in time required for supervision would be greater than it in fact was. In this regard, the claim 'Rapid dissolution reduces the time required for supervised administration' was misleading and incapable of substantiation. Breaches of the Code were ruled.

In relation to the claim 'Instant disintegration of Espranor reduces the time required by pharmacists for supervised self-administration of buprenorphine' in one of the detail aids, the Panel considered that its comments in relation to the first claim above applied here. 'Instant disintegration' was part of the claim at issue. Breaches of the Code were ruled.

The Panel noted that the third claim 'Minimises supervision time and reduces potential diversion for misuse.' was a prominent claim at the bottom of page 3 of the other detail aid on the same page as matters ruled in breach of the Code above in relation to comparative dissolution times and the claim 'Instant disintegration'. The Panel considered that the term 'minimises' was different to the term 'reduces'. It implied reduction to an almost irreducible amount. In the Panel's view, this implication was compounded by the other claims ruled in breach on the page. Overall, the Panel considered the claim misleading and incapable of substantiation. Breaches of the Code were ruled.

Indivior referred to the claim 'Equivalent safety and efficacy to sublingual buprenorphine' which appeared on page 8 of one of the detail aids and to 'Clinical trials show that Espranor is as effective as conventional compressed sublingual forms of buprenorphine at treating opioid dependence with a comparable safety profile' which appeared on the website. Indivior submitted that these claims

were in contrast to the statement '56.5% of patients reported mild AEs [adverse events] with Espranor compared with 7.7% of patients taking [sublingual buprenorphine]' found in both detail aids. Indivior also noted that Strang *et al* (2017) stated '… more AEs and Treatment-Emergent AEs with [Espranor] (mostly "mild")' and 'However, a greater proportion of [Espranor] subjects experienced at least one AE and similarly for TEAE (73.9 and 69.6%, respectively) compared to the [sublingual buprenorphine] group'. Indivior was concerned that Martindale had misrepresented the safety data on its website. It also noted that Martindale had additional risk minimisation measures stipulated in its risk management plan, as stipulated in the Public Assessment Report (PAR). Martindale did not address these in any of the materials Indivior had seen. Indivior further noted that there was no safety information in the patient leaflet.

The Panel noted that the first claim at issue was a subheading and read 'Equivalent safety and efficacy to sublingual buprenorphine'. It appeared on page 8 of one of the detail aids. The Panel noted Martindale's submission that the key safety concern facing any new formulation of buprenorphine was respiratory depression and the Espranor safety study which aimed to investigate this concern stated that whilst administration of Espranor did not result in a higher risk of respiratory depression when compared to sublingual buprenorphine a higher number of mild treatment-emergent adverse events (TEAEs) were reported in the Espranor group. Strang *et al* (2017) stated that a greater proportion of Espranor subjects experienced at least one AE and similarly for TEAE (73.0 and 69.6% respectively).

The Panel noted that although information about the greater incidence of mild adverse events with Espranor vs Subutex appeared on page 6 of the detail aid, the claim at issue 'Equivalent safety and efficacy to sublingual buprenorphine' appeared on page 8. The Panel considered that the claims and data on page 8 had to be able to stand alone in relation to the requirements of the Code and, in this regard, considered that the phrase 'Equivalent safety …' was not a fair overall reflection of the adverse event data given the difference in the incidence in mild adverse events and was misleading in this regard. The claim was incapable of substantiation and did not reflect the available evidence. Breaches of the Code were ruled.

The second claim at issue on page 7 of the website read 'Clinical trials show that Espranor is as effective as conventional compressed sublingual forms of buprenorphine at treating opioid dependence with a comparable safety profile' and was referenced to Strang *et al* (2015). There was no further discussion of the products' adverse event profiles. The Panel considered that its comments immediately above about the adverse event data applied here. The Panel considered that the claim at issue was not a fair reflection of the adverse event data in relation to mild adverse events. The claim was incapable of substantiation and did not reflect the available evidence. Breaches of the Code were ruled.

The Panel noted Martindale's submission that the patient leaflet was for those prescribed Espranor as a 'how to administer' guide and provided details of how to report side-effects. The patient would also have the Espranor patient information leaflet with the full list of adverse events. The Panel noted that the leaflet had to be able to stand alone with regard to the requirements of the Code. It was headed 'This leaflet is intended for patients that have been prescribed Espranor'. No information about the product was given other than a diagrammatic illustration of its administration and information on how to report side effects. Given its limited circulation to patients for whom the product had been prescribed and specific purpose to illustrate administration, the Panel, on balance, did not consider that it was necessary to include safety data as alleged. No breach of the Code was ruled.

Indivior presumed that Martindale chose to use its clinical study report to reference significant claims in its materials because Strang *et al* (2017) was not available at the time. Indivior asked a number of times for fully marked up references to support the claims. Martindale subsequently sent 6 out of at least 123 pages of the study report, which did not support the claims referenced, around 5 weeks later. Indivior was concerned that some claims were taken from extracts of the preamble of the study report and not from any data itself, and that other claims supported by the study report would require verification. Indivior had not seen the full report and was concerned at the length of time taken to receive final comments from Martindale.

Indivior was very concerned at the strength of some of the claims given that they appeared to be based on opinion and summation rather than data or peer-reviewed evidence.

The Panel noted that the Code required that substantiation for any information, claim or comparison must be provided as soon as possible, and certainly within ten working days, at the request of members of the health professions or other relevant decision makers. The Panel noted that the relevant clause had not been raised and so Martindale not been asked to comment on it and the Panel could make no rulings in that regard.

The Panel noted Indivior's concern with regard to the strength of some claims but also noted that Indivior had not identified the claims at issue; it was not for the Panel to identify the claims. In the Panel's view, it did not have a valid complaint to consider and thus ruled no breach of the Code.

Overall, Indivior alleged that high standards had not been maintained with regard to the launch campaign for Espranor. Indivior submitted that the alleged breaches were overall very serious and some in particular brought discredit upon, and reduced confidence in, the pharmaceutical industry. With regard to dependency therapy the NHS was under significant resource constraints, making it particularly important for the pharmaceutical industry to provide credible evidence based information to prescribers and patients alike about its products. Indivior alleged a breach of Clause 2.

The Panel noted its comments and rulings above and considered that Martindale had failed to maintain high standards; a breach of Clause 2 had also been ruled above.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. Examples of activities that were likely to be in breach of Clause 2 included, *inter alia*, prejudicing patient safety and/or public health.

The Panel noted its rulings of breaches and comments above. The Panel noted the vulnerability of the patient population and the therapy area. The Panel noted Indivior's reference to the need for evidence-based information and, in this regard, noted the difficulties of undertaking studies in this patient population. The Panel noted the small study size, Espranor n=23 and sublingual buprenorphine, n=13 and that it was unblinded. The Panel considered that further information about the study should have been provided in the materials to enable the reader to assess the data. This was particularly so given the strong unqualified nature of some of the claims at issue. In addition, the Panel considered that the cumulative effect of advertising Espranor to the public and encouraging patients to ask for it, implying that there was absolutely no possibility of diversion, and claims in relation to reduced supervision time due to the instant disintegration of Espranor, which was not so, prejudiced patient safety and a further breach of Clause 2 was ruled.

Indivior complained about the promotion of Espranor (oral lyophilisate) by Martindale Pharmaceuticals Limited. Indivior marketed Subutex (buprenorphine sublingual tablets). Both Espranor and Subutex were indicated for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

At issue were two Espranor detail aids, one entitled 'Product Overview (ADD/11/2016/122)', the second entitled 'Straight to the Point (ADD/01/2017/130)'; a patient leaflet (ADD/12/2016/127) and an Espranor website, www.espranor.com (ADD/01/2017/133).

Martindale noted that in its correspondence Indivior referred to the use of the product names Xprenor and Espranor. To clarify, the original market authorization (MA) holders of this product made the initial submission to the Medicines and Healthcare products Regulatory Agency (MHRA) under the brand name Xprenor. The submission was subsequently withdrawn and Martindale, who took over as the market authorization holder, performed both safety studies under the name of Xprenor. The UK and Indian studies in the clinical study report were also carried out as per MHRA guidance, using the product name Xprenor. However, a trademark conflict was subsequently discovered, so the product name was changed to Espranor in 2015. Hence the product originally named Xprenor in the clinical studies was subsequently licensed and launched as Espranor.

Indivior stated that after inter-company dialogue which dated back to 1 March 2017, it was unable to accept Martindale's responses and therefore submitted a complaint.

1 Promotion to the public on the Espranor website

The landing page of the Espranor website (espranor.com), was headed 'Welcome to Espranor (Buprenorphine oral lyohilisate)' followed by 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment'. The following paragraph stated 'This site provides information on Espranor for UK-based healthcare professionals and patients. Please select from the buttons below to tailor the content to your needs'. The options given were 'I am a UK healthcare professional' and 'I am NOT a healthcare professional'.

The page that the reader was taken to if they selected 'I am NOT a healthcare professional' was headed 'This website is for patients interested in opioid substitution therapy and Espranor'.

COMPLAINT

Indivior noted that the landing page to the Espranor website (last accessed 23 June 2017) included an unreferenced claim 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment'. This claim was directly visible to all visitors to the website ie patients and health professionals worldwide. When a reader scrolled down on the homepage, the options to enter the website as 'a UK health professional' or 'not a health professional' were visible at the bottom.

Indivior stated that the 'not a health professional' section linked to a new page which appeared to be a general page for patients whether they were on Espranor or not. This 'general patient' section of the website on page 17 was entitled 'This website is for patients interested in opioid substitution therapy and Espranor'. Indivior was concerned that the website was promotional and encouraged patients to request Espranor, rather than make an informed decision in consultation with their health professional. Indivior was also concerned that important safety information, identified in the summary of product characteristics (SPC), such as 'Espranor is not directly interchangeable with other buprenorphine products', was not addressed on this page.

Indivior stated that Martindale was advertising directly to the public. In Indivior's view the website encouraged patients to ask for Espranor, rather than assist patients already on Espranor. As highlighted in matters below, Indivior considered that the claim 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid

dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment' was misleading and not supported by evidence, in breach of Clauses 7.2, 26.1 and 26.2.

RESPONSE

Martindale refuted Indivior's allegation of breaches of the Code and submitted that the Espranor website was created for health professionals and patients who had been prescribed Espranor. The landing page clearly stated that it 'provides information on Espranor for UK based healthcare professionals and patients'. There was a clear button to select the appropriate page relevant to the viewer. This website would only be accessed by someone who knew the name Espranor by receiving a prescription for it. It was never intended for anyone who had not already received a prescription for Espranor. The website directed patients to speak to their doctor if they had any specific questions about their health or treatment. There was no link from the Martindale Pharma website to the Espranor website, so members of the public would not accidentally find this website when they sought information about the company or its products.

Martindale strongly refuted the allegation that it was advertising directly to the public and submitted that statements on the patient page were supported by clinical data.

Patients already on opioid substitution therapy (OST) were clearly dependent on their current medication. They were vulnerable and any change in their medication was likely to cause anxiety. It was well recognised that in any consultation with a health professional, a patient would only retain approximately 50% of the verbal information they were given. The aim of the website was to provide relevant information for those patients who had already been prescribed a new OST product, in this case Espranor.

In response to a request for further information, Martindale reiterated that the website was created for health professionals and patients who had been prescribed Espranor; it provided information for UK based health professionals and patients and would only be accessed by someone who knew the name Espranor by receiving a prescription for it. The website was not intended for those who had not already been prescribed Espranor. There was no link from the Martindale Pharma website to the Espranor website, so members of the public would not accidentally find this website when seeking information about the company or its products.

Martindale further submitted that there were currently no materials given to health professionals regarding the Espranor website. Health professionals would only be told about the website if they asked if there was one.

Martindale submitted that the name Espranor was not derived from the word buprenorphine and hence would not be intuitively found. An OST patient who was prescribed Espranor was likely to Google the name which would lead them to the website which was not mentioned on the Martindale Pharma website.

Martindale aimed to create a user friendly website, that acknowledged that the patient was interested enough to have found the name of their new medication. Martindale submitted that the patient group accessing the website was one and the same (being prescribed Espranor and interested enough to use it).

PANEL RULING

The Panel noted that this point solely concerned the website. The Panel noted that the page numbers on the printed version of the website provided by the complainant differed to those on the printed version provided by Martindale. At all points in its ruling the Panel referred to the page numbers as they appeared in the version provided by the complainant.

The Panel noted Indivior's concern that the claim 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It was licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment' on the Espranor website landing page promoted Espranor to the public and encouraged members of the public to ask for it.

The Panel noted Martindale's submission that the website in question would only be accessed by someone who knew the product name Espranor after receiving a prescription for it. The Panel noted that the patient section of the website stated that it was for 'patients interested in opioid substitution therapy and Espranor' and considered that its audience was therefore wider than just patients who had been prescribed the product. The Panel noted that the website was open access and the homepage would potentially be seen by a broad audience. This was not unacceptable so long as the website complied with the Code and relevant parts were suitable for the general public: the supplementary information to Clause 28.1, 'Access' was relevant. The Panel noted that the website was directed at not only health professionals and patients for whom the medicine had been prescribed, but also the general public. Irrespective of the intended audience, the open access homepage should be suitable for the general public. The Panel noted that the claim in question on the landing page 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment' would be seen by this wide audience and considered that it promoted a prescription-only medicine to, *inter alia*, the public and encouraged them to ask their doctor to prescribe it. Breaches of Clauses 26.1 and 26.2 were ruled.

In relation to that part of the website which stated that it was for patients interested in OST and Espranor, the Panel noted that it contained information about Espranor and a link to the patient leaflet rather than general information about OST and all relevant treatments. In the Panel's view, this section of the website might be generally suitable for patients for whom Espranor had been prescribed, rather than the general public and it encouraged the general public to seek a prescription for it. A breach of Clause 26.2 was ruled.

The Panel further noted Indivior's concern that the claim 'Espranor is a novel formulation of buprenorphine which allows instant disintegration and rapid dissolution when placed on the tongue. It is licensed as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment' was misleading and not supported by evidence. Indivior did not provide detailed allegations or evidence in support but referred to later complaints. Martindale had not responded to this matter at point 1. It was not possible to consider the complaint on this matter at this point in the absence of detail from either party. The matter in relation to the phrase 'instant disintegration' and Clause 7.2 was thus covered by the Panel's ruling at point 3 below. The Panel noted that Indivior had not cited Clause 7.3 in relation to substantiation.

The Panel noted Indivior's concern that page 17 of the website headed 'This website is for patients interested in opioid substitution therapy and Espranor' did not include important safety information, identified in the SPC, such as 'Espranor is not directly interchangeable with other buprenorphine products'. The Panel noted that the webpage in question gave top line information about Espranor including its indication and administration and stated that readers should speak to their doctor if they had any specific questions about their treatment. A reference to the Yellow Card Scheme appeared at the bottom of the page. A link to the patient information leaflet (PIL) was provided for further information on the following page in a section entitled 'Resources'. The PIL included the warning 'Espranor is not interchangeable with other oral buprenorphine products and the dose of Espranor may differ from the dose of other buprenorphine products' in an outlined box at Section 2 on the first page. The Panel noted its comments above about the unclear nature of the intended audience and its rulings of breaches of the Code. The page in question (page 17) described Espranor as a new wafer form of buprenorphine and referred to its use as a substitute for opiate drugs such as morphine or heroin. The Panel noted Martindale's submission about the vulnerability of OST patients and that any change to medication would cause anxiety. The Panel considered that the statements about Espranor might particularly encourage patients to consider the issue of interchangeability. The Panel considered that the page ought to be capable of standing alone as regards the medicine's risk/benefit profile and compliance with the Code and could not rely on the patient information leaflet in that regard. Readers would not necessarily click on the link. In addition, the Panel noted that the EU Risk Minimisation Plan discussed medication errors noting the higher bioavailability of buprenorphine in Espranor compared with Subutex. The Risk Minimisation Plan included a patient guide, page 2 of which featured a boxed statement which included the warning that 'You should not swap Espranor for sublingual buprenorphine, or the other way around, without your health professional's advice. Given the prominence given to the interchangeability warning in the PIL, that the content of the page appeared to be directed at, *inter alia*, patients and the points raised above including the vulnerability of those patients, the Panel considered the omission of such information meant that this section was not presented in a balanced way. In the Panel's view, the non-interchangeability warning did not necessarily need to be reproduced verbatim however, closely similar information should be conveyed. A breach of Clause 26.2 was ruled.

2 Diversion claims

Claim 'This renders the buprenorphine dose impossible to remove from the mouth once administered' appeared in page 8 of the 'Product Overview' detail aid.

Claim 'No delay, No diversion, No nonsense buprenorphine' appeared in page 1 of the 'Straight to the Point' detail aid.

COMPLAINT

Indivior stated that misuse (intentional and inappropriate use not in accordance with the authorised product information which could be accompanied by harmful physical or psychological effects) and diversion (the unsanctioned supply of regulated medicines from legal sources to the illicit drug market, or to a user for whom the drugs were not intended) of medicines used in opioid use disorder was a well-known and accepted adverse event that occurred with opioid agonists, including buprenorphine. It was well-established that patients removed doses of buprenorphine from supervised consumption in creative ways. Larance *et al* (2011) showed that 23% of OST patients reported having removed a supervised dose and for those on buprenorphine, 90% of doses had been removed directly from the patient's mouth. This was seen equally with a tablet and with wafer/film formulations. This data highlighted the significant challenge health professionals, payors and carers faced with diversion of opioid medication.

Indivior noted that Martindale had not provided evidence to support the claims. In response to queries related to the claim 'This renders the buprenorphine dose impossible to remove from the mouth once administered', Martindale referred to the SPC which stated: 'Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue'. Indivior alleged that the claim was not only exaggerated, but was not supported by the evidence

provided. Indivior stated that this information was harmful to prescribers and patients as it created the illusion that it was not possible to remove the medication once on the tongue.

Indivior submitted that Martindale's claim, the phrase 'No diversion' was not substantiated with any evidence or clinical trial data. Indivior did not consider that the claims were accurate and, as such, they were misleading and not substantiated by clinical evidence. Information about adverse events (in this case misuse and diversion of buprenorphine) did not reflect the available evidence. Indivior alleged breaches of Clauses 7.2, 7.4, 7.6 and 7.9.

RESPONSE

Martindale submitted that Larance *et al* was an Australian study, which used products from other companies. The entire basis of the Espranor product development related to the oral lyophilisate technology, producing 'instant dissolution' as per Seager (1998). This was developed to specifically target the misuse and diversion issues encountered with existing licensed buprenorphine products. Larance *et al* was published before Espranor was licensed. Indivior submitted that the results of this study could not, therefore, be presumed to apply to the Espranor oral lyophilisate formulation. As stated earlier, the formulation of Espranor was specifically developed to provide clinicians and patients with a clinically effective formulation of OST which would reduce the risk of diversion and abuse. The data contained in the Clinical Study Report confirmed the rapid disintegration of the formulation when it touched the tongue, minimising the risk of diversion through the removal of a supervised dose.

Martindale noted that, as an oral lyophilisate, Espranor needed careful handling; each individual freeze-dried 'oral lyophilisate' of buprenorphine was foil wrapped in a blister. Once the blister was opened, it was recommended that the oral lyophilisate was placed on the tongue immediately as the wafer was very sensitive to moisture and susceptible to disintegration. Espranor oral lyophilisate was able to be handled with dry hands. Once the oral lyophilisate touched saliva on the tongue, 96.3% partially disintegrated in ≤15 seconds rendering it unable to be removed from the mouth (this was because it would have dissolved in saliva). The definition of partial disintegration according to the Clinical Study Report was that the formulation could no longer be removed from the mouth.

This was represented in the SPC with the following wording:

> 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds, and then absorbed through the oromucosa' and "Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue"'.

The study protocol, which Martindale had not provided to Indivior as it was commercially sensitive in its entirety, referred to a paper by Seager, which was the basis of the product development for Espranor. This paper stated the following with regard to the Zydis technology and the 'instant disintegration: The Zydis fast-dissolving dosage form was a unique freeze dried medicinal tablet, made from well-known and acceptable materials. When Zydis units are put into the mouth, the freeze dried structure disintegrates instantaneously releasing the drug which dissolved or dispersed in the saliva'.

Martindale provided Indivior with page 116 of the Clinical Study Report headed 'Discussion and Conclusions' which contained the following information, which was also provided to Indivior:

> 'This study demonstrates that the Xprenor tablet starts to disintegrate on the tongue in ≤15 seconds in 96.3% of administrations, with a median time to complete Xprenor tablet disintegration of 2 minutes compared to 10 minutes with Subutex. The faster speed of disintegration with Xprenor will reduce the supervision time required compared to Subutex, providing a greater convenience for both the patient and clinician, and the potential for reduced supervision costs in both the healthcare and prison systems.'

Taking the study data into account, it was difficult to see how the product would be removed from the mouth when in 96.3% of administrations the product had started to disintegrate on the tongue in ≤15 seconds. If the product could not be removed from the mouth, it could not be diverted.

In response to a request for further information Martindale provided the following dictionary definitions with references for dispersal, dissolution, disintegration and dissolving:

A Disperse: (Chemistry) Distribute (small particles) uniformly in a medium Synonym: Dissolve

B Dissolution:
- The action or process of dissolving or being dissolved
- Disintegration; Decomposition

Synonym(s): Dissolving, Disintegration

C Disintegrate: Break up into small parts as a result of impact or decay Synonym: Dissolve

D Dissolve: (with reference to a solid) become or cause to become incorporated into a liquid so as to form a solution Synonym(s): Disintegrate, Disperse.

Martindale noted that its clinical study report defined time to partial disintegration as no longer able to remove from the mouth.

FURTHER INFORMATION FROM INDIVIOR

In response to a request for information, Indivior clarified its understanding of the terms: dispersal, dissolution, disintegration and dissolving.

Indivior assumed that the Panel was referring to these in relation to the unresolved complaints below and what Indivior believed was the direct marketing of some of those claims to patients on the patient website:

- Unresolved Complaint 2: Impossible to remove and NO Diversion;
- Unresolved Complaint 3: Instant disintegration (multiple claims)
- Unresolved Complaint 4: Instant disintegration eliminates the opportunity for removal from the mouth.

Indivior stated that it was in that context that it was responding. Indivior noted that given the context in which the terms were used, it had analysed and interpreted the meaning of such words in the context of what might be understood by the general public and health professionals on reading such terms and, in a more specific context, to assess whether this provided any further clarity.

Indivior stated that the reader of the material was likely to be a patient affected by opioid use disorder, a carer of such a patient, or a health professional involved in the care of such patients applying their general understanding without reference to specific medical definitions (such as those in relation to bioequivalence mentioned below). Thus, Indivior considered that a general definition of these terms was best understood, assessed and defined by the Oxford English Dictionary definitions as detailed below:

1 Dispersal (n): The action or process of distributing or spreading things [or people] over a wide area.
2 Dissolution (n): The action or process of dissolving or being dissolved.
3 Disintegration (n): The process of coming to pieces.
4 Dissolving (v-dissolve): (with reference to a solid). Become or cause to become incorporated into a liquid so as to form a solution.

Notwithstanding the above, Indivior had specifically analysed the relevant terms in a medical context to assess any alternate interpretation to provide further clarity.

- **Dissolution**

  The EMA Guideline on the Investigation of Bioequivalence used the term 'dissolution' and Indivior considered that the associated specific medical definition was 'the rate of drug release from a dosage form'; hence medicines could be described in terms of dissolution time, or dissolution profile. In this context, Indivior noted that the Espranor Public Assessment Report (PAR) confirmed that '[Espranor's] bioequivalence to [Subutex] has not been demonstrated' but Martindale had received a biowaver and a requirement to place a boxed warning on packaging stating 'Espranor is not interchangeable with other buprenorphine ...'. As such, there was a different dissolution of the Espranor product compared to the mono-buprenorphine sublingual tablets.

- **Dissolving and Disintegration**

  Indivior believed the term 'dissolving' to be intrinsically linked to the term 'dissolution'; they seemed impossible to separate (as seen by the Oxford English Dictionary definitions). Indeed, 'dissolving' might be seen as the process to achieve 'dissolution'. Accordingly, Indivior did not believe there to be any material differences between 'dissolving' and 'dissolution', nor in the way Martindale used the terms.

  The Espranor Public Assessment Report (PAR) used the terms 'dissolving' and 'disintegration' seemingly interchangeably and as a general principle, Indivior did not take issue with that (indeed the pivotal paper, Strang *et al* 2017 provided earlier used the terms interchangeably). Moreover, given the meaning of 'disintegration' highlighted above, 'the process of coming to pieces', it was logical that 'disintegration was a necessary part of (if not a pre-requisite for) 'dissolving'. Accordingly, whilst it was possible that from a medical point of view there might be subtle differences between 'dissolving' and 'disintegration'; given the general public understanding highlighted above, and the context in which such statements were used by Martindale, Indivior did not believe such differences were material.

  However, Indivior noted that the disputed Martindale claims were not supported by the PAR. The report highlighted that the mean time for complete disintegration was 2 minutes. Hence, as identified in complaints 3 and 4, references to 'instant disintegration' could not be supported.

- **Dispersal**

  In a medical context and building on the general public understanding, Indivior considered it logical to interpret 'dispersal' as meaning the physical distribution/dissemination of a medical material following administration. Accordingly, this was slightly different from 'dissolving', 'dissolution' and 'disintegration'. Indivior stated that in applying logic, one could conclude that dispersal could only occur following the dissolution, dissolving or disintegration of the relevant material to some extent, and might only be completely dispersed following complete dissolution, dissolving or disintegration.

  Indivior stated that through the above, it could be seen that (save for the technical definition associated with 'Dissolution' taken from EMA bioequivalence testing) there was little difference between the medical and general understanding of these terms.

Impact of definitions in context

A Infer a relationship of dissolution (which implied bioequivalence)/disintegration and subsequent benefits

Indivior noted that Martindale made disputed claims that were associated with the 'instant disintegration' claims (unresolved complaint 4 in its letter of 26 June 2017) for example, 'eliminating the opportunity for removal from the mouth once administered' and 'instant disintegration eliminates the opportunity for removal ...' amongst other such claims. Indivior was concerned that the reader would believe these disputed claims, and infer benefit which was associated with bioequivalence (and dissolution/ disintegration).

B Confusion as to the instant properties of Espranor

Indivior noted that the words being assessed had been used interchangeably by Martindale in its materials. Whilst arguably such use was not in line with the EMA definition, the concern was that the use of such terms inferred a relationship to bioequivalence and subsequent benefits which were not substantiated, particularly with reference to 'instant' which could not be substantiated.

Indivior believed that in Martindale claiming Espranor's instant dispersal, dissolution, disintegration and dissolving, Martindale made the association that the product had been completely taken, as if it were ingested or impossible to divert; this implication was self-evident from the claims 'impossible to remove from the mouth once administered' and 'No delay, No Diversion'. However, this was not substantiated:

a) Espranor's PAR acknowledged that the mean time for complete disintegration was 2 minutes; and
b) It was acknowledged the active ingredient (buprenorphine) in fact remained on the tongue for up to 15 minutes before 'complete disintegration' [Strang *et al* 2017, figure 2].

Whilst Indivior believed that the differences in time above related to the differences between disintegration of the physical delivery system/film and the disintegration of the buprenorphine itself, it was evident that neither of these were 'instant'. As such, the indication that the product had been completely taken as if ingested or impossible to divert was consequently erroneous.

In that context, Martindale used the above terms in relation to Espranor without drawing a distinction between the dispersal, dissolution, disintegration and dissolving of the physical delivery system used to administer the active ingredient and the dispersal, dissolution, disintegration and dissolving of the active ingredient itself. Notwithstanding that reference to 'instant' dispersal, dissolution, disintegration and dissolving was not substantiated, the implications of Martindale's use of such terminology in relation to Espranor, especially when predicated by reference to 'instant', was that there was instant dispersal, dissolution, disintegration and dissolving of the medicine; when in reality, the active ingredient (the fundamental issue and aspect most liable to misuse and diversion) did not benefit from such instant dispersal, dissolution, disintegration and dissolving.

C Misleading impact on the risk of misuse and diversion of the Espranor product and active ingredient

Indivior noted that building on the above, Martindale went further and claimed that Espranor was 'As easy to administer and take as methadone', which was a liquid for ingestion, and therefore incorrectly inferred that Espranor could not be diverted or removed from the mouth. It was noted that Martindale made indirect (and in some cases) associations with terms that implied bioequivalence (ie dissolution, which was used interchangeably with the other terms) with mono-buprenorphine/Subutex sublingual tablets and also stated that Espranor 'renders the buprenorphine dose impossible to remove from the mouth once administered' and so clearly claimed that with Espranor it was not possible to divert the active ingredient, however, it was also acknowledged that, in fact, it remained on the tongue for up to 15 minutes before 'complete disintegration'; [Strang *et al* 2017, Figure 2].

Indivior being aware that the mono-buprenorphine was a highly desirable medication that was often diverted and misused and, in its experience, took 5-10 minutes to dissolve in the mouth, was concerned that health professionals and carers would be misled by the claims that Martindale was making which were unsubstantiated by evidence. It was unclear how 'instant dissolution', even if it were true of the physical delivery system itself, would prevent someone from removing the 'dispersed'/'dissolving'/'dissoluted'/'disintegrated' product from the tongue with active ingredient (and/ or saliva containing such active ingredient), and misusing it, or diverting it.

PANEL RULING

The Panel noted that it had asked both Martindale and Indivior to define certain terms including dispersal, dissolution, disintegrate and dissolve. The parties' definitions were not wholly dissimilar. However, the Panel queried whether Martindale had applied sufficient rigour to the consistent application of the terms throughout the materials such that their meanings were clear. The Panel noted that this matter was further complicated as the use of certain terms also appeared to be somewhat inconsistent in the various studies and public documents. In this regard, the Panel noted Indivior's submission that dissolving and disintegration were used seemingly interchangeably in the Espranor PAR and Strang *et al* (2017). The Panel, of course, was only concerned with the materials produced by Martindale which had to comply with the Code.

The Panel noted that the parties referred to Strang *et al* (2015), the Clinical Study Report (2014) and Strang *et al* (2017). The Panel noted that all three related to the same study data. Strang *et al* (2015) was a presentation based on data from the Clinical Study Report and the published 2017 paper was the published record of the Clinical Study Report and bore the same EudraCT number. The Panel noted that the materials at issue appeared to pre-date the publication of the 2017 paper although not its

submission for publication in 2016. The Panel noted that materials had to reflect evidence available at the point of certification. Papers published subsequently were relevant if it meant that materials no longer complied with the Code and required amendment/ withdrawal. In this regard, Strang *et al* (2017) did not appear to be new data – it summarised and was the published record of the 2014 Clinical Study Report.

The Panel considered that its general comment above at point 1 about the page numbers applied to the website by the complainant were relevant here. The Panel adopted the page numbering applied by the complainant.

The Panel noted that the claims at issue 'This renders the buprenorphine dose impossible to remove from the mouth once administered' and 'No delay, No diversion, No nonsense buprenorphine' implied that there was absolutely no possibility that a dose could be removed from the mouth following supervised administration (diversion) which was not so. At Section 4.4, Special Warnings and Precautions For Use, Diversion, the Espranor SPC stated 'Removal of Espranor from the mouth following supervised administration is *virtually* impossible due to its rapid dispersal on the tongue' (emphasis added) which implied that that there was a potential for the dose to be removed from the mouth following its supervised administration. The Panel further noted that Strang *et al* (2017) defined disintegration as the point when 'the tablet could no longer be removed intact' and stated that over all periods, 96.3% of [Espranor] administrations achieved partial disintegration on the tongue in ≤ 15 seconds' and 'The median time for complete [Espranor] tablet disintegration was 2 minutes ...'. This meant that 3.7% of administrations took longer than 15 seconds to achieve partial disintegration leaving potential for the dose to be removed. By 2 minutes, Espranor had completely disintegrated in 58% of administrations. According to the Clinical Study Report on which Strang *et al* (2017) was based, there were four recordings of either partial or complete disintegration at 15 minutes. The Clinical Study Report also differed from Strang *et al* in that partial disintegration was defined as 'no longer able to remove from the mouth'. The reason for the difference was not explained in either publication. The authors' discussion in the published paper referred to 'remarkably rapid disintegration with complete disintegration by 3 minutes for more than 75% of Espranor administrations ...'. The authors also noted that on the first days some anxious patients had very dry mouths resulting in slower disintegration.

The Panel noted its comments above. The Panel noted that the definition of disintegration in Strang *et al* (2017) only referred to the impossibility of removing the intact tablet and in this regard noted Indivior's comment about removing the disintegrated product or saliva containing the dissolved product. The Panel noted the qualified statement in the Clinical Study Report that a benefit of the reduced time to disintegration with Espranor was 'the *reduced potential* for concealment and diversion' (emphasis added). Similarly, on page 3 of the Straight to the Point detail aid the qualified phrase '... reduces potential diversion for misuse' appeared. The Panel considered that the claims in question 'No diversion.' and 'This renders the buprenorphine dose impossible to remove from the mouth once administered' were too dogmatic and implied there was absolutely no possibility of diversion, however small, and that was not so. This implication was compounded in relation to the latter claim as it appeared beneath the unqualified heading 'Espranor *prevents* the most common route of diversion' (emphasis added). The Panel considered that the claims in question were misleading and could not be substantiated, breaches of Clauses 7.2 and 7.4 were ruled in relation to each claim.

Clause 7.6, as raised by Indivior, stated that when promotional material referred to published studies, clear references must be given. Clause 7.6 applied to references to published material, including the use of quotations, tables, graphs and artwork. The Panel noted that Indivior had not identified the reference/s in the material to published studies. It was not for the Panel to identify the references for Indivior. In the Panel's view, it did not have a valid complaint to consider and thus ruled no breach of Clause 7.6.

The Panel further noted Indivior's allegation that the information about adverse events (in this case misuse and diversion of buprenorphine) did not reflect the available evidence. The Panel considered that the claims in question might potentially be harmful to patients as doctors might assume that it was absolutely impossible for patients to remove the dose which was not necessarily so. However, Clause 7.9 of the Code related to claims about adverse reactions reflecting available evidence and not stating that there were no adverse reactions, toxic hazards or risks of addiction or dependency. The Panel noted Indivior's submission that, *inter alia*, diversion was a well-known and accepted adverse event with opioid agonists including buprenorphine. The Panel noted diversion was not listed in Section 4.8, Undesirable effects, of the Espranor SPC. In the Panel's view, the claims in question did not fall within the remit of Clause 7.9, they related to the likelihood of the product's diversion rather than adverse reactions and risk of dependency etc which might arise after administration of the product post diversion and ruled no breach of that Clause accordingly.

3 Instant disintegration claims

Claim 'Espranor allows instant disintegration and rapid dissolution when placed on the tongue'. This appeared on the home page of the website. Indivior also referenced alongside this claim 'disintegrate instantly' and 'instant disintegration' which each appeared in the 'Straight to the Point' detail aid on pages 1 and 2 respectively.

Claim 'Espranor oral lyophilisate is a novel freeze-dried wafer formulation of buprenorphine which disintegrates instantly and rapidly dissolves when placed on the tongue' which appeared on page 2 of the Product Overview detail aid.

Claim '… has been specifically designed to disintegrate instantly and dissolve rapidly when placed on the tongue' which appeared on the front page of the 'Straight to the Point' detail aid.

Claim 'Instant disintegration of Espranor reduces the time required by pharmacists for supervised self-administration of buprenorphine' which appeared on page 8 of the 'Product Overview' detail aid.

Claim Espranor instantly disintegrates within 15 seconds …' which appeared on page 3 of the website. Alongside this claim Indivior referred to 'Instant disintegration' on page 3 of the Straight to the Point detail aid.

Claim '… buprenorphine that instantly disintegrates on the tongue …' which appeared on page 6 of the website. Alongside this claim Indivior referred to 'dissolve instantly' which appeared on page 17 of the website.

COMPLAINT

Indivior stated that Martindale had been unable to provide data to support claims that Espranor instantly disintegrated when placed on the tongue. In fact, the evidence it provided showed that this was not the case. Martindale referred to Strang *et al* (2015) which stated '[Espranor] completely disintegrating within 2 minutes in 58% of administrations' and later provided Strang *et al* (2017) which stated 'Over all periods, 96.3% of [Espranor] administrations achieved partial disintegration on the tongue in ≤15' with a quotation including a question mark in figure 2 stating 'Partial or complete disintegration at 15 s?'. Indivior reproduced a figure from Strang et al (2017) which showed that complete disintegration occurred at 15 minutes. The same figure was also included in the 'Product Overview' detail aid.

Indivior stated that Martindale referred to the proprietary Zydis technology website which was the basis of its product and stated 'The Zydis ODT (orally dissolving tablet) fast-dissolve formulation, is a unique, freeze-dried oral solid dosage form that *disperses almost instantly in the mouth* – no water required' (emphasis added) and Seager (1998) to support the instant disintegration claim. Martindale took no account of the fact that the active ingredient buprenorphine was also present in Espranor, and that there was no data to show that buprenorphine together with Zydis technology resulted in 'instant disintegration'. In fact, complete disintegration of Espranor took 15 minutes according to Martindale's own data.

Indivior noted that conflicting claims were presented side-by-side in the PIL which stated 'Instant Disintegration', followed by 'Average time to complete disintegration (median): 2 minutes', further confusing patients.

Indivior considered that the claims were inaccurate, misleading and misrepresented the data which was unsubstantiated by the published evidence in breach of Clauses 7.2, 7.4 and 7.6.

Given the data Martindale provided, Indivior was furthermore confused that the SPC stated 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds'.

RESPONSE

Martindale submitted that the Espranor oral lyophilisate formulation had characteristics that were very different to that of a tablet. It was a fragile, freeze-dried 'wafer' which had been individually foil wrapped in a blister. Once the blister was opened, it was suggested that the oral lyophilisate was placed on the tongue immediately, as the wafer was very sensitive to moisture and susceptible to disintegration. Espranor oral lyophilisate was to be handled with dry hands. It was clear, therefore, that once the oral lyophilisate touched saliva on the tongue, 96.3% partially disintegrated in ≤15 seconds rendering it unable to be removed from the mouth (this was because it would have dissolved in saliva). The definition of partial disintegration, according to the Clinical Study Report, was that the formulation could no longer be removed from the mouth. Martindale submitted that the study data supported the claim, in the context of both the fragile structure of the wafer and the definition of partial disintegration. This was represented in Section 4.4 of the SPC which stated that 'Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue'. Martindale noted that this wording was reviewed and approved by the Medicines and Healthcare products Regulatory Agency (MHRA) based on the study data.

As stated earlier, Seager (1998), which was the basis of the product development for Espranor, stated the following with regards to the Zydis technology and the 'instant disintegration':

> The Zydis fast-dissolving dosage form is a unique freeze dried medicinal tablet, made from well-known and acceptable materials. When Zydis units are put into the mouth, the freeze dried structure disintegrates instantaneously releasing the drug which dissolves or disperses in the saliva.

Martindale noted that Indivior stated that there was no data to show that buprenorphine with the Zydis technology resulted in instant disintegration. However, the first time point measured in the Espranor Phase II study was 15 seconds, no data was available prior to this time point, as it was not measured. According to the published study results, 'Oral disintegration time of (Espranor) and [a sublingual buprenorphine], was measured by direct observation, measuring (a) time to disintegration (i.e., tablet could no longer be removed intact) and (b) time until completely dissolved'.

At 15 seconds, results showed that 96.3% of Espranor administrations achieved partial disintegration on the tongue vs 71.8% with the competitor, ($p < 0.001$). The definition of partial

disintegration, according to the Clinical Study Report, was that the formulation could no longer be removed from the mouth.

Section 4.2 of the Espranor SPC stated:

> 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds, and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes. The oral lyophilisate should be taken immediately after opening the blister. *Patients should not consume food or drink for 5 minutes after administration'.* (emphasis added).

Martindale noted that this wording was reviewed and approved by the MHRA based on the study data.

PANEL RULING

The Panel noted its general comments at point 2 above including the parties' definition of relevant terms and the adoption of website page numbers in the printed version provided by the complainant. The Panel also noted that its comments at point 2 above about diversion were relevant to the claims presently at issue about instant disintegration.

The Panel noted that this matter was further complicated by apparently inconsistent use of the term disintegration. For instance, as noted by Indivior, the patient information leaflet referred to both instant disintegration and that the average time taken to complete disintegration was 2 minutes. The Panel, as stated at point 2 above, was only concerned with the materials produced by Martindale.

The Panel noted that the Clinical Study Report and Strang *et al* (2017) stated that 'over all periods, 96.3% of [Espranor] administrations achieved partial disintegration on the tongue in ≤ 15 seconds' and 'The median time for complete [Espranor] tablet disintegration was 2 minutes ...'. The data showed that at 2 minutes, [Espranor] had completely dissolved in 58% of administrations. The Panel also noted that, as stated at point 2 above, the Clinical study report showed that there were four recordings of partial or complete disintegration at 15 minutes.

In addition, the Panel noted that the voice-over on the video on the health professionals section of the website 'How to Dispense in a Supervised Setting' stated that 'You may want to offer your patient a small drink of water as this aids the dissolving of Espranor, once administered'.

The Panel considered that the six claims listed above for instant disintegration (save the claim 'Instant disintegration' in the 'Straight to the Point' detail aid mentioned above, alongside the fifth claim) were too dogmatic and implied that the tablets completely disintegrated instantly on every administration which was not so. Context was important. Further information should be given about disintegration times, the meaning of the term and the study so that readers could properly assess the claims. In the Panel's view, the claims in question were each misleading and could not be substantiated. The Panel ruled breaches of Clauses 7.2 and 7.4 in relation to each claim in question.

The Panel noted that further information was provided alongside the claim 'Instant disintegration' on the left-hand side of page 3 of the 'Straight to the Point' detail aid. Immediately beneath the claim in question it stated '% of individuals with partial disintegration (no longer removable from the mouth): ≤15 secs' above a depiction of a clock face highlighting 15 seconds. Adjacent to this was the claim '96% vs 72% with Subutex'. The right-hand side of the same page beneath the subheading 'Rapid dissolution' depicted a bar chart showing that that the average time to complete dissolution with Espranor was 2 minutes vs 10 minutes with Subutex. The Panel considered that the context was such that this claim was materially different to the other claims at issue. Further information had been provided. However, on balance, the Panel considered that the prominent claim 'Instant disintegration' was misleading insofar as it gave the immediate visual impression that tablets completely disintegrated instantly on each administration and that was not necessarily so. This immediate impression was not capable of substantiation. A breach of Clauses 7.2 and 7.4 was ruled.

Clause 7.6, as raised by Indivior, stated that when promotional material refered to published studies, clear references must be given. Clause 7.6 applied to references to published material, including the use of quotations, tables, graphs and artwork. The Panel noted that Indivior had not identified the reference/s in the material to published studies. It was not for the Panel to identify the references for Indivior. In the Panel's view, it did not have a valid complaint to consider and thus ruled no breach of Clause 7.6.

4 Elimination of the opportunity for removal from the mouth

Claim 'Eliminating the opportunity for removal from the mouth once administered' which appeared on page 4 of the website.

Claim 'Instant disintegration eliminates the opportunity for removal …' which appeared on page 7 of the website.

Claim 'Espranor prevents the most common route of diversion' which appeared on page 8 of the 'Product Overview' detail aid.

COMPLAINT

Indivior highlighted earlier the importance of the issue of misuse and diversion in patients receiving OST. Indivior noted that Martindale had not provided evidence to support the claim with regard to how the opportunity for removal of the drug was 'eliminated'. A review of the video on the Espranor website showed that even without the active ingredient buprenorphine present, the product remained on the tongue and appeared to be available for removal for at least the eight seconds the product was shown largely unchanged on the tongue. Martindale

referred to the SPC which stated: 'Removal of Espranor from the mouth following supervised administration is *virtually* impossible due to its rapid dispersal on the tongue' (emphasis added). There was no evidence to substantiate this statement. Indivior did not accept that this statement could be converted into the claim that the product 'eliminates' the opportunity. Indivior alleged that the claims made were inaccurate, misleading and were not faithfully substantiated by the clinical evidence and that Martindale was in breach of Clauses 7.2 and 7.4.

RESPONSE

Martindale provided Indivior with several references to substantiate the claims above, none of which were accepted as outlined below:

Martindale noted that the oral lyophilisate needed careful handling. Each individual freeze dried 'oral lyophilisate' of buprenorphine was individually foil wrapped in a blister. Once the blister had been opened, it was suggested that the oral lyophilisate was placed on the tongue immediately, as the wafers were very sensitive to moisture and susceptible to disintegration. Espranor oral lyophilisate were to be handled with dry hands. It was clear, therefore, that once the oral lyophilisate touched saliva on the tongue, 96.3% partially disintegrated in ≤15 seconds rendering it unable to be removed from the mouth. This was represented in the SPC, with the following wording:

> 'Removal of Espranor from the mouth following supervised administration is virtually impossible due to its rapid dispersal on the tongue.'

Seager (1998), which was the basis of the product development for Espranor, stated the following with regards to the Zydis technology and the 'instant disintegration': The Zydis fast-dissolving dosage form was a unique freeze-dried medicinal tablet, made from well-known and acceptable materials. When Zydis units were put into the mouth, the freeze dried structure disintegrated instantaneously releasing the drug which dissolved or dispersed in the saliva.

It was important to note that the first time point measured in the Espranor Phase II study was 15 seconds, no data were available prior to this time point as it was not measured. According to the published study results, 'Oral disintegration time of [Espranor] and [a sublingual buprenorphine] was measured by direct observation, measuring (a) time to disintegration (i.e., tablet could no longer be removed intact) and (b) time until completely dissolved'. 'At 15 seconds, results showed that 96.3% of [Espranor] administrations achieved partial disintegration on the tongue vs. 71.8% with [a sublingual tablet], ($p < 0.001$)'. The definition of partial disintegration according to the Clinical Study Report was that the formulation could no longer be removed from the mouth.

PANEL RULING

The Panel noted its general comments at point 2 and, in addition, its comments and rulings in points 2 and 3 above and considered that they were relevant here.

The Panel noted that it might be difficult for a patient to remove Espranor from the mouth once administered but considered that it was misleading of Martindale to state that Espranor and its 'instant disintegration' (and at claim 3 above, in conjunction with its rapid dissolution) completely eliminated the opportunity for such removal. The Panel considered that each claim was too dogmatic. Insufficient information was given to enable a reader to assess the data. The Panel further noted that the SPC stated 'Removal of Espranor from the mouth following supervised administration is *virtually impossible* due to its rapid dispersal on the tongue' (emphasis added). The Panel therefore considered that claims 1-3 above were each misleading and were not capable of substantiation and therefore ruled breaches of Clauses 7.2 and 7.4 in relation to each.

5 Lack of visibility of interchangeability information

Claim 'Espranor is not interchangeable with other buprenorphine products' which appeared on pages 10 and 15 of the website.

Claim 'Espranor is not directly interchangeable with other forms of buprenorphine'. This appeared on page 2 of the 'Product Overview' detail aid and page 4 of the 'Straight to the Point' detail aid.

COMPLAINT

Indivior stated that the Martindale efficacy data confirmed that 'Espranor is not interchangeable with other buprenorphine products'. This was prominently featured on the packaging and the SPC and PIL (either in bold, or in a boxed warning) and as such, should be similarly and prominently featured on all materials so that prescribers and patients could make informed choices.

Indivior stated that Martindale had made some concessions and changes to the website following Indivior's initial request. Currently, Martindale placed this warning as set out above.

Indivior, however, considered that Martindale had not gone to sufficient lengths to highlight that Espranor was not interchangeable with other buprenorphines used in OST, did not make the text prominent enough and did not provide this important information early enough in all of the materials seen to date. Further, this information was not present in the patient leaflet.

Indivior did not consider that the display of safety information for a new product was prominent enough, despite the changes to the website. Indivior alleged that Martindale had purposefully misled prescribers by underplaying a key prescribing issue and had thus brought discredit upon the industry in breach of Clauses 2, 7.9 and 9.1.

RESPONSE

Martindale submitted that in the product overview, which was the focus of Indivior's initial complaint, the warning from the SPC that 'Espranor is not directly interchangeable with other forms of buprenorphine' was highlighted in blue in the text so that it stood out as the header. This sentence was presented on page 2 of the 'Product Overview'. Page 1 did not contain any claims other than the title of the document and the name of the product. In addition, the warning in the Espranor SPC was mentioned on the 'Product Overview' under the header 'Espranor is not directly interchangeable with other forms of buprenorphine' in a size that was no different to the rest of the text on that page.

The text 'Espranor is not directly interchangeable with other forms of buprenorphine' was included on the website in a box in the health professional pages. For the patient there was a direct link to the SPC and the PIL and page 1 of the PIL contained the safety information in a box in a similar manner to that presented in the SPC.

With regards to the appropriate risk minimisation measures in this context, Martindale had extensive discussion with the MHRA about a post-authorization safety study which involved four questionnaires. In August 2016 the MHRA finally agreed that it would be extremely difficult to gather any useful additional clinical data other than through a good pharmacovigilance system. It was satisfied with all the warnings in the SPC, PIL and carton.

With regards to the patient leaflet, this was not part of the inter-company dialogue. Martindale noted that this material had a clear header that stated 'This leaflet is intended for patients that have been prescribed Espranor'. Espranor was a prescription-only medicine. Patients receiving this leaflet would have been prescribed Espranor and informed by their health professional that 'Espranor is not directly interchangeable with other forms of buprenorphine'. Martindale agreed that health professionals needed to be aware that 'Espranor is not directly interchangeable with other forms of buprenorphine', hence this information was prominently featured in all materials, the SPC, PIL and packaging.

PANEL RULING

The Panel noted that the warning 'Espranor is **not interchangeable with other buprenorphine products**. **Different buprenorphine products** have different bioavailability. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a certain product (brand), the product cannot be readily exchanged with another product' appeared as a boxed warning at Section 4.2 of the SPC. A boxed warning appeared at the beginning of Section 2 (What you need to know before you take Espranor) of the patient information leaflet which read 'Espranor is not interchangeable with other oral buprenorphine products and the dose of Espranor may differ from the dose of other buprenorphine products'. This latter boxed warning was also part of the labelling on the product packaging as referred to in the PAR. The Panel noted that the EU Risk Management Plan discussed the prevention of error due to the wrong medication (Section SVI.4 Potential for medication errors) noting the higher bioavailability of buprenorphine from Espranor than from Subutex. Medication errors were listed as an important potential risk in the summary of safety concerns.

The Panel noted that Indivior had cited Clause 7.9 which related to claims and information about adverse reactions. It also required that companies could not state that a product had no adverse reactions, toxic hazards or risks of addiction or dependency. The matters raised at this point did not relate to adverse events or other matters covered by Clause 7.9. The Panel considered that Clause 7.9 was not relevant and thus considered the matters raised under Clause 9.1 which had been cited. No breach of Clause 7.9 was ruled in relation to each claim.

The Panel considered that its general comment above at point 1 about the page numbers applied to the website by the complainant were relevant here. The Panel adopted the page numbering applied by the complainant.

The Panel disagreed with Indivior's contention that the warning in question should make it clearer that Espranor was not interchangeable with other buprenorphines used in OST. The Panel noted that some other buprenorphine products were licensed to treat, *inter alia*, moderate to severe cancer pain and severe pain which did not respond to non-opioid analgesics. The Panel noted Espranor's licensed indication, substitution treatment for opioid dependence, and that each item at issue was either promotional material for the product or for patients who had been prescribed it and discussed its licensed use. In such circumstances, the Panel did not consider that the non-interchangeability warning at issue needed to qualify the reference to buprenorphines by stating that it applied to those used in opioid substitution therapy. High standards had been maintained on this point. No breach of Clause 9.1 was ruled.

The Panel disagreed with Martindale's submission that the warning on page 2 of the 'Product Overview' detail aid 'Espranor is not directly interchangeable with other forms of buprenorphine' stood out as the header because it was highlighted in blue text. The Panel noted that all five subheadings on the page were in the same pale blue font. Two main headings were in purple font and the text was otherwise in black font. The Panel considered that the pale blue font colour and the overall design of the page, including the position of the warning in question as the subheading to the final paragraph at the bottom of the page, meant that it was not sufficiently prominent. Although, as submitted by Martindale, the warning in the Espranor SPC was in a size that was no different to the rest of the text on that page, it was also within a box and the phrase 'not interchangeable with other buprenorphine products' was emboldened. The Panel considered that the warning should have been made more prominent given the therapy area, the vulnerable nature of the

patients and its prominence in the SPC. A breach of Clause 9.1 was ruled.

The Panel noted that the warning 'Espranor is **not directly interchangeable** with other buprenorphine products was on page 4 of the 'Straight to the Point' detail aid followed by the prescribing information. Although 'not directly interchangeable' was emboldened within the warning, the Panel considered that the warning should have been presented earlier in the detail aid given that the preceding pages discussed how Espranor delivered buprenorphine in OST more effectively than hard, compressed, sublingual formulations and compared its dissolution time to that of Subutex. The Panel noted its comments above about the need for the warning to be more prominent and considered that those reasons were relevant here. High standards had not been maintained. A breach of Clause 9.1 was ruled.

In relation to page 10 of the website, the Panel noted that although the warning in the SPC had been reproduced in full and was within an outlined box, it was only presented on page 10, towards the end of the health professional section of the Espranor website. The Panel considered that it should have been presented earlier for the same reasons as stated above in relation to each of the detail aids; high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that Indivior had also alleged that the warning was not sufficiently prominent on page 15 of the website which comprised prescribing information. In this regard, the Panel noted that the prescribing information did not include the summary of product characteristics. Clause 4.2 dealt with the content of prescribing information which included precautions and contraindications and warnings issued by, *inter alia*, the licensing authority which were required to be in advertisements. Clause 4.1 required prescribing information to be provided in a clear and legible manner. There was no reference in either Clause 4.1 or 4.2 about prominence to particular elements of the prescribing information. The Panel noted that the warning in question 'Espranor is not interchangeable with other buprenorphine products' was in the same font size as the rest of the prescribing information within the Dosage and administration section. It was underlined as were 10 other phrases or sentences in the first column of prescribing information. It was not prominent such that it caught the reader's eye. Although the Panel considered that it would have been helpful if the warning in question had greater visual prominence in the absence of a specific direction or requirement in Clauses 4.1 and 4.2 of the Code, on balance, it did not consider that the company had failed to maintain high standards. No breach of Clause 9.1 was ruled.

The Panel noted that the absence of the warning on the patient section of the website was covered by its ruling at point 1 above.

The Panel noted that Indivior was also concerned that the warning was not included in the patient leaflet, a double-sided A5 sheet intended for patients who had been prescribed Espranor. Page 1 dealt with reporting of side-effects and page 2 explained how to administer Espranor. The Panel noted its relevant comments including the content of the EU Risk Minimisation Plan and ruling of a breach of the Code at point 1 above in relation to the failure to include the warning on the patient section of the website. The Panel noted, in particular, the vulnerability of these patients and considered that in these particular circumstances it was important to ensure that all relevant information was made available. The Panel considered that the failure to include the warning in the patient information leaflet was such that high standards had not been maintained. In the Panel's view, the non-interchangeability statement from the SPC did not necessarily need to be reproduced verbatim, however, closely similar information should be conveyed. A breach of Clause 9.1 of the Code was ruled.

The Panel noted the vulnerability of the patient population and that the highlighted warning was a prominent part of the SPC, PIL and the product pack. The Panel noted its comments above on the lack of prominence given to the warning across several materials and that it was not on the patient materials at issue at all. The Panel noted that prejudicing patient safety was given as an example of an activity likely to be in breach of Clause 2. A breach of Clause 2 was ruled.

6 Misleading comparison with Subutex and dissolution time

Claim 'In the UK, licensed buprenorphine is currently only available as hard-compressed sublingual tablets, which take up to 10 minutes to dissolve and may compromise supervised administration'. This appeared on page 3 of the 'Product Overview' detail aid.

Claim 'Unlike conventional hard compressed buprenorphine sublingual tablets which take up to 10 minutes to dissolve'. This appeared on page 3 of the website.

Claim 'Buprenorphine is currently only available as hard compressed sublingual tablets which take up to 10 minutes to dissolve'. This appeared on page 7 of the website.

Claim 'Conventional, hard, compressed, sublingual buprenorphine tablets take up to 10 minutes to dissolve'. This appeared on page 1 of the 'Straight to the Point' detail aid.

In addition, the visual comparison of the disintegration and dissolution times of Subutex and Espranor on page 3 of the 'Straight to the Point' detail aid was the subject of complaint.

COMPLAINT

Indivior alleged that Martindale misrepresented the Subutex data when comparing it with Espranor implying that there were greater differences in

dissolution time to that shown by the head-to-head data. Martindale also suggested that the difference was clinically important without providing any supportive evidence. The Subutex SPC stated 'The tablet should be kept under the tongue until dissolved, which usually occurs within 5 to 10 minutes'. The Espranor SPC stated that Espranor was dispersed '… which usually occurs within 15 seconds, and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes …. Patients should not consume food or drink for 5 minutes after administration'. As highlighted earlier under point 3, Strang *et al* (2017) showed that complete disintegration occurred at 15 minutes. Thus, according to the SPC, a reasonable supervision time was at least 5 minutes after administration of Espranor, which was not substantially different to 5-10 minutes for Subutex and even longer if factoring in the complete disintegration time of Espranor of 15 minutes as highlighted in Strang *et al* (2017). Dissolution and disintegration were not comparable nor interchangeable in this context.

Indivior alleged that Martindale was misleading with this comparison, distorted the data, exaggerated and gave undue emphasis to the benefits of Espranor compared with the reference product. Indivior alleged that this was in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Martindale submitted that all data that it represented came directly from the Clinical Study Report (MD2012/01XP). This data was published in a peer-reviewed journal (Strang *et al* 2017). The text to which Indivior referred clearly stated that hard compressed sublingual tablets took 'up to 10 minutes' to dissolve. Nowhere in the Espranor materials did it state 'it takes 10 minutes' for sublingual tablets to dissolve. There was a clear distinction here and Martindale submitted that the statement was fair and in line with the references provided.

The published study results (Strang *et al* 2017) stated the following:

> 'Over all periods, 96.3% of "[Espranor]" administrations achieved partial disintegration on the tongue in ≤ 15 vs. 71.8% with "[a sublingual buprenorphine]" ($p < 0.001$). At 2 min, "[Espranor]" had completely dissolved in 58.0% of administrations versus only 5.1% ("[sublingual buprenorphine]"; $p < 0.0001$). The median time for tablets to completely disintegrate was 2.0 min for "[Espranor]" versus 10 min for "[sublingual buprenorphine]" ($p < 0.0001$).'

These results were presented in the materials in both text form and as figures. Martindale submitted that the reader was not misled in any way as to the results that were presented.

Section 4.2 of the Espranor SPC stated the following:

> 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds, and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes. The oral lyophilisate should be taken immediately after opening the blister. Patients should not consume food or drink for 5 minutes after administration.'

Martindale noted that it was important to understand that the principle of OST was supervised administration. Supervision was likely to last as long as the buprenorphine product took to dissolve which, in the case of Espranor, was a shorter mean time than that of Subutex. There was no statement suggesting supervision for 5 minutes in the Espranor SPC to ensure that food was not consumed.

The point of avoiding swallowing with Espranor was so that the patient did not swallow saliva containing Espranor before it was absorbed, as otherwise the buprenorphine content would undergo first pass metabolism. This did not mean supervision was required during this time. The same applied to food and drink.

PANEL RULING

The Panel considered that its general comment above at point 1 about the page numbers applied to the website by the complainant were relevant here. The Panel adopted the page numbering applied by the complainant.

The Panel noted Indivior's submission that the Subutex SPC stated 'Administration is sublingual. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this drug. The tablet should be kept under the tongue until dissolved, which usually occurs within 5 to 10 minutes'. The Panel noted that the Espranor SPC stated that the oral lyophilisate should be taken from the blister unit with dry fingers and placed whole on the tongue until dispersed, which usually occurred within 15 seconds and then absorbed through the oromucosa. Swallowing should be avoided for 2 minutes. The oral lyophilisate should be taken immediately after opening the blister. Patients should not consume food or drink for 5 minutes after administration. The SPC further noted that physicians must advise patients that the oromucosal route of administration was the only effective and safe route of administration for this medicinal product. If the oral lyophilisate or saliva containing buprenorphine were swallowed, the buprenorphine would be metabolised and excreted and have minimal effect. The Panel noted its comments above at points 2 and 3 about the comments and findings in the clinical study report and Strang *et al* (2017).

In relation to the claim 'Unlike conventional hard compressed buprenorphine sublingual tablets which take up to 10 minutes to dissolve, Espranor instantly disintegrates within 15 seconds of being placed on the tongue resulting in rapid dissolution (median time 2 minutes)', the Panel noted that the latter part of the claim 'resulting in rapid dissolution (median time 2 minutes)' appeared at the top of

the following page on the version provided by the complainant. The Panel noted its ruling of a breach of the Code in relation to the phrase 'instantly disintegrates within 15 seconds' at point 3 above (claim 3), which misleadingly implied that Espranor tablets dissolved instantly on each administration which was not so. The Panel noted the reference to 5-10 minutes in the Subutex SPC and considered that readers would probably compare the stated 'instant disintegration' of Espranor with the stated 'up to 10 minutes' dissolution time for Subutex. The Panel noted Indivior's submission that dissolution and disintegration were not comparable in this context and noted the parties' definition of terms at point 2 above. The Panel queried whether 'up to 10 minutes' was a fair reflection of the Subutex SPC. Those readers who saw the entire claim, which concluded on page 4, might compare Espranor's median dissolution time of 2 minutes with 'up to 10 minutes with Subutex'. The Panel noted that for a comparison to be valid, like must be compared with like. The Panel considered that the claim in question 'Unlike conventional hard compressed buprenorphine sublingual tablets which take up to 10 minutes to dissolve, Espranor instantly disintegrates within 15 seconds of being placed on the tongue resulting in rapid dissolution (median time 2 minutes)' exaggerated the differences between the products and was misleading in this regard. A breach of Clauses 7.2 and 7.3 was ruled. The claim was incapable of substantiation. A breach of Clause 7.4 was ruled.

In relation to the claim on page 7 of the website 'Buprenorphine is currently only available as hard compressed sublingual tablets which take up to 10 minutes to dissolve,' the Panel noted that whilst the claim itself did not refer to Espranor, the preceding paragraphs discussed Espranor and referred to its 'rapid dissolution' and 'Instant disintegration ...'. Closely similar claims about instant disintegration had been ruled in breach of the Code at point 3 above. The Panel noted its comments above about the Subutex SPC and the phrase 'up to 10 minutes'. The Panel considered that the reader was invited to compare the stated 'up to' 10 minutes' dissolution time of Subutex with the stated instant disintegration of Espranor. In the Panel's view, this comparison was misleading and exaggerated the differences between the products. A breach of Clauses 7.2 and 7.3 were ruled. This comparison was incapable of substantiation. A breach of Clause 7.4 was ruled.

The Panel noted that the claim 'Conventional, hard, compressed, sublingual buprenorphine tablets take up to 10 minutes to dissolve' on the front page of the Straight to the Point detail aid immediately followed the claim 'Espranor oral lyophillsate has been specifically designed to disintegrate instantly and dissolve rapidly when placed on the tongue'. This preceding claim, including the phrase 'disintegrate instantly', had been ruled in breach of the Code at point 3 above. The emboldened unqualified claims on the front page of the detail aid included 'No delay. No diversion'. The Panel noted its comments above about the Subutex SPC and the phrase 'up to 10 minutes'. The Panel considered that the reader was invited to compare the stated 'up to' 10 minute dissolution time of Subutex with the stated instant disintegration of Espranor. In the Panel's view, this comparison was misleading and exaggerated the differences between the products. A breach of Clauses 7.2 and 7.3 were ruled. The claim could not be substantiated. A breach of Clause 7.4 was ruled.

The Panel noted that the claim 'In the UK, licensed buprenorphine is currently only available as hard-compressed sublingual tablets, which take up to 10 minutes to dissolve and may compromise supervised administration' on page 3 of the 'Product Overview' detail aid was within an introductory section that discussed barriers to buprenorphine use. Whilst the preceding page and subsequent sections on page 3 discussed Espranor, the Panel noted that the only relevant statement in relation to Espranor across both pages was the first bullet point at the top of page 2 which read 'Espranor oral lyophilisate is a novel freeze dried wafer formulation of buprenorphine which disintegrates instantly and rapidly when placed on the tongue'. As previously stated, closely similar claims about instant disintegration had been ruled in breach of the Code. The Panel noted the detailed information given across pages 2 and 3 of the A4 booklet. Other than the aforementioned bullet point, there was no other mention of disintegration and dissolution. Visually no prominence was given to the aforementioned bullet point at the top of page 2 such that the Panel considered, on the balance of probabilities, that the claim in question on page 3 'In the UK, licensed buprenorphine is currently only available as hard-compressed sublingual tablets, which take up to 10 minutes to dissolve and may compromise supervised administration' would not be read in light of, and therefore was not a comparison with, the first bullet point on the preceding page. The design of the page was relevant. The Panel ruled no breach of Clauses 7.2, 7.3 and 7.4 of the Code.

In relation to the allegation about the comparison on page 3 of the 'Straight to the Point' detail aid, the Panel noted the page bore the prominent heading 'Espranor: rapid by design'. Beneath the left-hand column and the prominent subheading 'Instant disintegration' a clock face depicted that 96% of Espranor patients vs 72% with Subutex ($p=0.0002$) at ≥15 seconds had partial disintegration (no longer removable from the mouth). The figure of 96% was prominent and in the same purple font as the claims 'Rapid by design' and 'Instant disintegration'. The right-hand column was headed 'Rapid dissolution' beneath which the average time to complete disintegration (median) was visually depicted showing Espranor as 2 minutes and Subutex as 10 minutes, $p<0.0001$. The data was referenced to the Espranor SPC and Strang et al (2015). The Panel noted its comments on this page at point 3 above. The Panel noted the wording in the Subutex SPC set out above and its comments thereon. The Panel noted that the bar chart did not reflect the range of 5-10 minutes within which Subutex usually dissolved as stated in its SPC. The Panel noted that there were differences between the products in relation to disintegration and dissolution in favour of Espranor. The prominent subheading 'Instant disintegration' had previously been ruled in breach of the Code.

The Panel noted that more comparative data was given on this page than for the claims at issue above. Nonetheless, the Panel considered that the failure to fairly reflect the Subutex SPC in conjunction with the prominent claim 'Instant disintegration' meant that the comparison was misleading as it exaggerated the differences between the products. A breach of Clauses 7.2 and 7.3 were ruled. The comparison was not capable of substantiation. A breach of Clause 7.4 was ruled.

In relation to the allegation that Martindale suggested that the above comparisons were clinically relevant which was not supported by the data, the Panel noted that Indivior bore the burden of proof. Whilst claims made by Martindale had to be capable of substantiation, the burden was on Indivior to show that, on the balance of probabilities, such claims were not clinically relevant. It had not identified any data and Martindale had not responded to this point. The Panel noted that the studies before it in relation to different matters in this case included discussion of supervision times. In the Panel's view, Indivior had not discharged the burden of proof. The Panel ruled no breach of Clause 7.2.

7 Reduces supervision time

Claim 'Rapid dissolution reduces the time required for supervised **administration**'. This appeared on page 7 of the website.

Claim 'Instant disintegration of Espranor reduces the time required by pharmacists for supervised self-administration of buprenorphine'. This appeared on page 8 of the 'Product Overview' detail aid.

Claim 'Minimises supervision time'. This appeared on page 3 of the 'Straight to the Point' detail aid.

COMPLAINT

Indivior noted that in response to its requests on 1 March 2017, Martindale provided evidence to support the claim by reference to an excerpt of its Clinical Study Report, which was a key reference for multiple claims in its materials and had not, so far, been provided in a full enough form to confirm or deny the claim. It surmised: 'The faster speed of disintegration with Xprenor (Espranor) will reduce the supervision time required compared to Subutex, providing a greater convenience for both the patient and clinician, and the potential for reduced supervision costs in both the healthcare and prison systems'. Indivior did not consider that there was evidence to support the claims. The same argument, as identified in the point above, applied in that the Espranor SPC stated '… Swallowing should be avoided for 2 minutes … Patients should not consume food or drink for 5 minutes after administration' which increased the required supervision time to at least 5 minutes. Indivior alleged that these claims were in breach of Clauses 7.2, 7.4, 7.6 and 7.9.

RESPONSE

Martindale submitted that it had provided Indivior with page 116 of the clinical study report; the heading on this page was 'DISCUSSION AND CONCLUSIONS', which was clearly not a preamble to the study report as Indivior suggested but contained the key study findings:

> 'This study demonstrates that the Xprenor tablet starts to disintegrate on the tongue in ≤15 seconds in 96.3% of administrations, with a median time to complete Xprenor tablet disintegration of 2 minutes compared to 10 minutes with Subutex. The faster speed of disintegration with Xprenor will reduce the supervision time required compared to Subutex, providing a greater convenience for both the patient and clinician, and the potential for reduced supervision costs in both the healthcare and prison systems.'

Martindale noted that Indivior was concerned about the advice in the SPC regarding food or drink after Espranor administration. Section 4.2 of the Espranor SPC stated the following:

> 'The oral lyophilisate should be taken from the blister unit with dry fingers, and placed whole on the tongue until dispersed, which usually occurs within 15 seconds, and then absorbed through the oromucosa. *Swallowing should be avoided for 2 minutes*. The oral lyophilisate should be taken immediately after opening the blister. *Patients should not consume food or drink for 5 minutes after administration'* (emphasis added).

Martindale submitted that it was important to understand that the principle of OST was supervised administration. Supervision was likely to last as long as the buprenorphine product took to dissolve, which in the case of Espranor was a shorter mean time than that of Subutex. There was no statement suggesting supervision for 5 minutes in the SPC for Espranor to ensure that food was not consumed.

The point of avoiding swallowing with Espranor was so that the patient did not swallow saliva containing Espranor before it was absorbed, as otherwise the buprenorphine content underwent first pass metabolism. This did not mean supervision was required during this time. The same applied to food and drink.

With regard to the supply of the full study report, Martindale provided, in good faith, the relevant pages from the clinical study report, which it considered were sufficient for the issue at hand. Furthermore, the study results were published in March 2017 and a copy of this was provided to Indivior. Martindale considered that Indivior had all the literature it needed to substantiate the claims made concerning the Espranor study results.

PANEL RULING

The Panel noted that its general comment above at point 1 about the page numbers applied to the website by the complainant were relevant here.

The Panel noted Indivior's statement that given the Espranor SPC stated '… Swallowing should be avoided for 2 minutes …. Patients should

not consume food or drink for 5 minutes after administration', this increased the required supervision time to at least 5 minutes.

In the Panel's view, the aim of supervision was to ensure that the patient did not remove a dose for diversion. It was well-established that patients removed doses of buprenorphine from supervised consumption in creative ways.

The Panel considered that its comments at Points 2, 3, 4 and 6 above about the time taken to achieve partial and complete disintegration and diversion were relevant here.

The Panel noted Martindale's submission that there was no statement suggesting supervision for 5 minutes in the SPC for Espranor to ensure that food was not consumed and noted the only reference to supervision was during the initiation of treatment. Daily supervision of dosing was recommended to ensure proper placement of the dose on the tongue and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

The Panel noted that Strang et al (2017) concluded that 'Espranor's rapid disintegration and consequent greater ease of supervised dosing may increase the feasibility of buprenorphine treatment in busy community and custodial settings when supervised dosing is considered important. This now needs to be explored clinically'. The authors subsequently stated that 'hopefully rapid-dissolving variants of buprenorphine may increase the range of settings in which buprenorphine can safely be delivered such as settings where it is unrealistic to expect full supervision of dosing over several minutes'. These contexts would warrant attention in future studies. The Panel noted that the page of the clinical study report that had previously been disclosed to Indivior was more dogmatic, stating 'The faster speed of disintegration with [Espranor] will reduce the supervision time required compared to [sublingual competitor], providing a greater convenience for both the patient and clinician, and the potential for reduced supervision costs in both the healthcare and prison systems'. The Panel noted that Indivior had emphasised 'potential for reduced supervision costs' but considered that cost was not directly relevant to the claims at issue.

The Panel noted that there were differences between the products which were relevant to supervision time. The Panel considered that the phrase 'reduces the time required' had to be considered in the context in which it was used.
The Panel noted that the claim 'Rapid dissolution reduces the time required for supervised administration' was one of two bullet points and appeared immediately above the claim 'Instant disintegration eliminates the opportunity for removal from the mouth once administered' which was ruled in breach of the Code at point 4 in relation to the elimination claim. In addition, the phrase 'Instant disintegration' was closely similar to matters ruled in breach of the Code at point 3. In the Panel's view, the context including the unqualified claim about instant disintegration and elimination implied that the reduction in time required for supervision would be greater than it in fact was. In this regard, the claim in question 'Rapid dissolution reduces the time required for supervised administration' was misleading and incapable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled.

In relation to the second claim at issue 'Instant disintegration of Espranor reduces the time required by pharmacists for supervised self-administration of buprenorphine' in the 'Product Overview' detail aid, the Panel considered that its comments in relation to the first claim above applied here. 'Instant disintegration' was part of the claim at issue. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that the third claim 'Minimises supervision time and reduces potential diversion for misuse.' was a prominent claim at the bottom of page 3 of the 'Straight to the Point' detail aid on the same page as matters ruled in breach of the Code at point 6 above in relation to comparative dissolution times and at point 3 above in relation to the claim 'Instant disintegration'. The Panel considered that the term 'minimises' was different to the term 'reduces'. It implied reduction to an almost irreducible amount. In the Panel's view, this implication was compounded by the other claims ruled in breach on the page. Overall, the Panel considered the claim misleading and incapable of substantiation. A breach of Clauses 7.2 and 7.4 was ruled.

Clause 7.6, as raised by Indivior, stated that when promotional material refers to published studies, clear references must be given. Clause 7.6 applied to references to published material, including the use of quotations, tables, graphs and artwork. The Panel noted that Indivior had not identified the reference/s in the material to published studies. It was not for the Panel to identify the references for Indivior. In the Panel's view, it did not have a valid complaint to consider and thus ruled no breach of Clause 7.6.

The Panel noted that Indivior had cited Clause 7.9 which related to claims and information about adverse reactions. It also required that companies could not state that a product had no adverse reactions, toxic hazards or risks of addiction or dependency. The matters raised at this point did not relate to adverse events or other matters covered by Clause 7.9. The Panel considered that Clause 7.9 was not relevant and thus ruled no breach of Clause 7.9 in relation to each claim cited above.

8 Comparable safety profile

Claim 'Equivalent safety and efficacy to sublingual buprenorphine'. This appeared on page 8 of the 'Product Overview' detail aid.

Claim 'Clinical trials show that Espranor is as effective as conventional compressed sublingual forms of buprenorphine at treating opioid dependence with a comparable safety profile'. This appeared on page 7 of the website.

COMPLAINT

Indivior noted that the claims above were in contrast to the statement '56.5% of patients reported mild AEs with Espranor compared with 7.7% of patients taking Subutex' on page 3 of the 'Straight to the Point' detail aid and page 6 of the Product Overview detail aid which showed large differences in mild adverse events (AEs). Indivior noted that the Strang *et al* (2017) also stated '… more AEs and Treatment-Emergent AEs with "[Espranor]" (mostly "mild")' and 'However, a greater proportion of "[Espranor]" subjects experienced at least one AE and similarly for TEAE (73.9 and 69.6%, respectively) compared to the [Subutex] group'.

Indivior was concerned that Martindale had misrepresented the safety data on the website. It also noted that Martindale had additional risk minimisation measures stipulated in its risk management plan, as stipulated in the PAR. It was noted that Martindale did not take the opportunity to address these in any of the materials Indivior had seen.

Indivior further noted that there was no safety information provided in the patient leaflet.

Indivior alleged that Martindale was in breach of Clauses 7.2, 7.3, 7.4 and 7.9.

RESPONSE

Martindale submitted that licensed buprenorphine had been available in the UK since 1978 and had an established safety profile. The key safety concern facing any new formulation of buprenorphine was respiratory depression and the investigation of this safety concern was the aim of the Espranor safety study, as the MHRA required evidence that the increased bioavailability with Espranor was not associated with an increased risk of respiratory depression. The study confirmed that this was not an issue for Espranor. The 'Product Overview' detail aid contained a full table of the study adverse events for both products. It was clear that there was no significant difference in moderate adverse events between the products, no severe adverse events and no deaths. No patients withdrew secondary to Treatment-Emergent Adverse Events (TEAEs).

Patients in OST were very vulnerable and dependent on receiving their medication regularly. Any change in this medication was likely to cause anxiety. The Espranor safety study was un-blinded, and so the patients were sitting in unfamiliar clinical surroundings taking a new product. They also had a health professional asking them repeatedly how they were feeling. The research team felt that all these factors contributed to the incidence of reporting TEAEs for Espranor, and were confident that the first year of full pharmacovigilance data following launch would be a more accurate representation of the true TEAE incidence. The data was peer reviewed and accepted for publication, and was also accepted by the regulatory authorities, as the licence was issued requiring no additional pharmacovigilance measures. Martindale considered that the results of this study, which had been presented in full in the 'Product Overview', provided the prescriber with a clear picture of the safety profile of Espranor and that this did not contradict the overall conclusion of equivalence between the safety profiles of the products presented.

With regards to the appropriate risk minimization measures in this context, the company had extensive discussion with the MHRA for some months about a post-authorization safety study, which involved four questionnaires. In August 2016 the MHRA finally agreed that it would be extremely difficult to gather any useful extra clinical data other than through a good pharmacovigilance system. It was satisfied with all the warnings in the SPC, PIL and Carton. Martindale submitted that the Patient Leaflet was for patients that had been prescribed Espranor and would have been able to read the PIL. The leaflet was purely 'how to administer Espranor', but it also provided details of how to report side-effects.

In response to a request for further information, Martindale submitted that the Espranor risk management plan was approved during the licensing procedure. The Espranor licence was granted on 22 June 2015. At this stage the MHRA requested a commitment to perform a post-authorization safety study. Martindale had extensive discussion with the MHRA about such a study and submitted two different protocols, which involved four questionnaires. By August 2016 the MHRA had sought external advice and finally agreed that it would be extremely difficult to gather any useful additional clinical data, other than through a good pharmacovigilance system. A post-authorization safety study to monitor the risks of overdose and respiratory depression associated with Espranor was not considered feasible at this stage. The MHRA was satisfied with all the warnings in the SPC, PIL and Carton and Martindale was not asked to produce another risk management plan. The email from the MHRA was provided as well as the risk management post-authorization safety study protocol preliminary assessment report.

PANEL RULING

The Panel considered that its general comment above at point 1 about the page numbers applied to the website by the complainant were relevant here. The Panel adopted the page numbering applied by the complainant.

The Panel noted that the first claim at issue was a subheading and read 'Equivalent safety and efficacy to sublingual buprenorphine'. It appeared on page 8 of the Product Overview detail aid which was headed 'Summary of key points' and introduced a section which summarised efficacy and safety data. The first bullet point beneath the claim in question read 'Two Phase II studies confirmed that in the target patient population Espranor and Subutex were comparable in terms of their safety profile and frequency of reported adverse events' and was referenced to the Espranor PAR. The Panel noted that the PAR referred to two Phase II studies including the Espranor safety study (Strang *et al*

2017). The Panel noted Martindale's submission that the key safety concern facing any new formulation of buprenorphine was respiratory depression and the investigation of this safety concern was the aim of the Espranor safety study. The Panel noted that the study results, as reflected in the PAR, stated that whilst administration of Espranor did not result in a higher risk of respiratory depression when compared to the Subutex, a higher number of mild treatment-emergent adverse events (TEAEs) were reported in the Espranor group. Strang *et al* stated that a greater proportion of Espranor subjects experienced at least one AE and similarly for TEAEs (73.0 and 69.6% respectively). The second Phase II study (conducted in India) referred to was described in the PAR as a supportive study only as the treatment practice, patient population, support network, type of addiction etc in India could be different compared to UK. It did state, however, that the safety results were similar to the UK study.

The Panel noted that the 'Product Overview' detail aid included a table of the reported adverse events for both products on page 6. This reproduced data from a closely similar table in the clinical study report and appeared in a section of the detail aid which discussed treatment-emergent adverse events including the statement '56.5% of patients reported mild AEs with Espranor compared with 7.7% of patients taking Subutex'. Possible reasons for the higher number of mild adverse events for Espranor were discussed above the table including the small study size and the small numbers in the competitor arm and that the study was unblinded. The Panel noted that the claim at issue 'Equivalent safety and efficacy to sublingual buprenorphine' appeared on page 8. The Panel considered that the claims and data on page 8 needed to be capable of standing alone in relation to the requirements of the Code and, in this regard, considered that the phrase 'Equivalent safety ...' was not a fair overall reflection of the adverse event data given the difference in the incidence in mild adverse events. The Panel noted that p values were not stated, or referred to, by either party which might be a reflection of the small study size and its power. The claim in question 'Equivalent safety and efficacy to sublingual buprenorphine' was misleading in this regard as alleged. Breaches of Clauses 7.2 and 7.3 were ruled. The claim was incapable of substantiation and did not reflect the available evidence and breaches of Clauses 7.4 and 7.9 were ruled.

The second claim at issue on page 7 of the website read 'Clinical trials show that Espranor is as effective as conventional compressed sublingual forms of buprenorphine at treating opioid dependence with a comparable safety profile' and was referenced to Strang *et al* (2015). There was no further discussion of the products' adverse event profiles. The Panel considered that its comments immediately above about the adverse event data applied here. In addition, the Panel noted that Strang *et al* (2015) stated there were 'more AEs and TEAEs with Espranor (mostly mild with similar proportions for moderate)'. The Panel considered that the claim at issue 'Clinical trials show that Espranor is as effective as conventional compressed sublingual forms of buprenorphine at treating opioid dependence with a comparable safety profile' was not a fair reflection of the adverse event data in relation to mild adverse events. Breaches of Clauses 7.2 and 7.3 were ruled. The claim was incapable of substantiation and did not reflect the available evidence and breaches of Clauses 7.4 and 7.9 were ruled.

The Panel noted Martindale's submission that the Patient Leaflet was for patients that had been prescribed Espranor as a 'how to administer' guide and provided details of how to report side-effects. The patient would also have the Espranor patient information leaflet with the full list of adverse events. The Panel noted that the leaflet must be capable of standing alone with regard to the requirements of the Code. It was headed 'This leaflet is intended for patients that have been prescribed Espranor'. No information about the product was given other than a diagrammatic illustration of its administration and information on how to report side-effects. Given its limited circulation to patients for whom the product had been prescribed and specific purpose, to illustrate administration, the Panel, on balance, did not consider that it was necessary to include safety data as alleged. The Panel did not consider the omission misleading. No breach of Clause 7.2 was ruled.

9 Provision of marked-up references

COMPLAINT

Indivior stated that Martindale's clinical study report was used to reference significant claims in its materials, presumably as the publication (Strang 2017) was not available at the time. Indivior asked Martindale on 1 March 2017 to provide fully marked up references to support the claims and a few times thereafter. Martindale subsequently sent 6 out of at least 123 pages of the study report, which did not support the claims referenced, around 5 weeks later. Indivior was very concerned that some claims were taken from extracts of the preamble of the study report and not from any data itself, eg the claim 'Rapid dissolution reduces the time required for supervised administration' which was substantiated by Martindale with text from the 'Study Rationale' of the study report, which did not refer to, or provide any evidence or data to, support the claim, but was simply an opinion. Indivior was very concerned that other claims supported by the study report would require verification. Indivior had not had sight of the full report at the time of writing this letter and was concerned at the length of time taken to receive final comments from Martindale on 14 June 2017.

Indivior was very concerned at the strength of some claims made, some of which appeared to be based on opinion and summation rather than data or peer-reviewed evidence. Indivior alleged that Martindale was in breach of Clauses 7.2, 7.3, 7.4 and 7.9.

RESPONSE

Martindale submitted that the Code did not require companies requested for substantiation to provide 'marked-up' references as Indivior suggested.

With regard to the supply of the full study report, Martindale provided, in good faith, the relevant pages from the clinical study report, which it considered were sufficient for the issue at hand. Furthermore, the study results were published in March 2017 and a copy of the published study was provided to Indivior. Martindale considered that Indivior had been provided with all the relevant substantiation needed to critically evaluate the claims concerning the Espranor study results.

Martindale submitted that as soon as it received details of the complaint (27 March), it provided all of the relevant references within 5 working days. Before that it had provided a hard copy of the published Espranor study which contained all the data necessary to address those areas that Indivior was querying.

Martindale submitted that it was unreasonable for a competitor to expect to receive a confidential document such as the full clinical study report. The published paper, which was sent to Indivior on 28 March, contained the dissolution data that seemed to be the essence of the complaint.

PANEL RULING

The Panel noted that Clause 7.5 required that substantiation for any information, claim or comparison must be provided as soon as possible, and certainly within ten working days, at the request of members of the health professions or other relevant decision makers. The Panel noted that, whilst relevant, this Clause had not been raised, Martindale had therefore not been asked to comment on it and the Panel could make no rulings in that regard.

The Panel noted Indivior's concern with regard to the strength of some claims which appeared to be based on opinion and summation, rather than data or peer reviewed evidence. The Panel noted that Indivior had not identified the claims at issue and it was not for the Panel to identify the claims. In the Panel's view, it did not have a valid complaint to consider and thus ruled no breach of Clauses 7.2, 7.3, 7.4 and 7.9.

10 Conclusion

COMPLAINT

Overall, Indivior alleged that Martindale had not maintained high standards with regard to the launch campaign for Espranor and was in breach of Clause 9.1, particularly in relation to complaint number 1, 2, 3, 5, 7, 8 and 9.

Indivior alleged that the breaches were overall very serious, and specifically in the case of complaint numbers 1, 2, 3, 5 and 7, brought discredit upon, and reduced confidence in, the pharmaceutical industry in the field of Addiction Medicine. The Addiction Field in the NHS was under significant resource constraints, making it particularly important for the pharmaceutical industry to provide credible evidence based information to prescribers and patients alike about its products. Indivior stated that the behaviour of Martindale constituted a breach of Clause 2.

RESPONSE

Whilst Martindale accepted there were some unavoidable delays in inter-company dialogue, these delays occurred on both sides. A major obstacle to early resolution was a lack of clarity from Indivior regarding specific claims at issue and not accepting that Martindale were unable to provide Indivior with the full Clinical Study Report as it contained commercially sensitive data.

Martindale remained open and prepared for further inter-company dialogue which it considered had been agreed at the face-to-face meeting at the end of May and were disappointed that Indivior did not pursue this course to its resolution.

Martindale submitted that it hoped that the responses provided would serve to address the issues raised by Indivior and would reassure the PMCPA of its commitment to the highest standards in the promotion of its medicines.

Martindale included hard copies of all references and electronic copies of all references except the Clinical Study Report. This contained company confidential information and Martindale requested that it did not get sent to Indivior.

PANEL RULING

The Panel noted Indivior's general allegation that Martindale had failed to maintain high standards particularly in relation to Points 1, 2, 3, 5, 7, 8 and 9. The Panel noted that Indivior had specifically raised Clause 9.1 at Point 5 above and a breach was ruled in that regard. The Panel noted its comments and rulings at Point 1-4 and 6-8 above and considered that Martindale had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted that Indivior alleged a breach of Clause 2 specifically in relation to Points 1, 2, 3, 5 and 7. The Panel noted that Clause 2 had also been raised at Point 5 above and a breach was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. Examples of activities that were likely to be in breach of Clause 2 as set out in its supplementary information included, *inter alia*, prejudicing patient safety and/or public health.

The Panel noted its rulings of breaches and comments at points 1, 2, 3 and 7 above. The Panel noted the vulnerable nature of the patient population and the therapy area. The Panel noted Indivior's reference to the need for evidence-based information and, in this regard, noted the difficulties of undertaking studies in this patient population. The Panel noted the small study size, Espranor n=23 and Subutex n=13 and that it was unblinded. The Panel considered that further information about the study should have been provided in the materials to enable the reader to assess the data. This was particularly so given the strong unqualified nature of some of the claims at issue. In addition, the Panel considered that the cumulative effect of advertising Espranor to the public and encouraging patients to ask for it,

implying that there was absolutely no possibility of diversion, and claims in relation to reduced supervision time due to the instant disintegration of Espranor, which was not so, prejudiced patient safety and a breach of Clause 2 was ruled.

Complaint received **27 June 2017**

Case completed **2 January 2018**
