CASE AUTH/2727/8/14

PHARMACIST v PIERRE FABRE

Promotion of Navelbine

A pharmacist complained about a letter sent by Pierre Fabre regarding Navelbine (vinorelbine) oral dosing to oncology pharmacists.

Navelbine was licensed as a single agent or in combination for the first line treatment of stage 3 or 4 non small cell lung cancer (NSCLC) and the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The letter was headed 'Under-dosing of Navelbine Oral' and stated that the only recommended dose of single agent Navelbine in advanced breast cancer was 80mg/m^2 weekly (following three doses at 60mg/m^2). The letter stated that efficacy was clearly associated with appropriate dosing and explained the consequences of under-dosing. It encouraged checks of local protocols to ensure that Navelbine oral was being used at the appropriate dose and included a bar chart.

The complainant referred in detail to missing information and noted that no prescribing information was provided.

The complainant pointed out that the indication in the letter was simply listed as 'Advanced Breast Cancer' rather than the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The complainant stated that the dosage information in the letter, which was the key point of the letter, did not reflect a number of exclusions to dose escalation in the summary of product characteristics (SPC) related to full blood count. The letter stated that 'a blood test' was required for each dose when increasing frequency of dose but did not specify which tests were needed and did not highlight that that blood tests would define if dose escalation was appropriate.

The complainant noted that the approved name appeared directly below the most prominent display of the brand name, it did not appear with the same area as the brand name. There was no statement regarding reporting adverse events.

The complainant alleged that while the statement 'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefit for patients' should have been accompanied by an evidence base relevant to the use of anti-cancer agents in Stage 3 or 4 breast cancer, where the primary treatment objective was not always survival. The complainant was aware of very little evidence to substantiate the statement in this setting and none for vinorelbine dosing.

The complainant stated that the graph included in the letter used an example dose for a 1.7m^2 patient and while that was an appropriate example the need to round to available capsule sizes meant that some adjustment of final dose given occurred. It was hard to be convinced that those values were not selected to make the difference as numerically large as possible.

The complainant alleged that there had been an attempt to make the communication appear like a safety letter rather than promotional material. A clinician following the advice would use 50% more of the medicine and the complainant could not see how this had not resulted in promotion.

The complainant used the SPC schedule but frequently did not dose escalate due to full blood count or due to other toxicity/response profiles. The complainant was concerned that clinicians would half read the letter and feel they should be dose escalating rather than optimising patient benefit with toxicity.

The detailed response from Pierre Fabre is given below.

The Panel noted Pierre Fabre's submission that the letter was a safety letter to health professionals to highlight the under-dosing of Navelbine in advanced breast cancer. Pierre Fabre submitted that market research indicated that health professionals in the UK routinely under-dosed Navelbine patients and it had been asked by health professionals to send a reminder. In Pierre Fabre's view the provision of prescribing information might have implied that the communication was predominantly promotional in nature, whilst in its view the converse was true.

The Panel noted that the exemptions to the Code did not refer to 'safety letters'. The letter in question did not appear to meet any of the listed exemptions to the definition of promotion. Overall, the Panel considered that the letter in question was promotional. Its aim, according to Pierre Fabre, was to ensure the dosage regimen of single agent oral Navelbine was in accordance with its licence and that this was reflected in trust protocols. In the Panel's view the potential safety consequences of under-dosing were not such that they rendered the letter in question non promotional given the very broad definition of promotion in the Code. Doses lower than 80mg/m^2 weekly were recommended in certain circumstances. Prescribing information should have been included and a statement that adverse events should be reported. The Panel ruled breaches of the Code as these requirements had not been met.

The Panel considered that the size requirement in the Code for the non proprietary name was satisfied and no breach was ruled.

The Panel considered that the reference to 'advanced breast cancer' in the letter in question was not sufficiently qualified such that it was not a fair reflection of Navelbine's licensed indication for advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen and was inconsistent with the particulars listed in its SPC. A breach of the Code was ruled.

The Panel considered that the letter did not give sufficient weight to the importance of blood tests nor did it reflect the SPC requirement. Blood tests were not simply required when increasing the frequency of dosing as stated in the letter but on the day of each new administration. A breach of the Code was ruled. The Panel was very concerned about the failure to make the monitoring requirements clear and the potential impact on patient safety. It considered that this was a serious matter, particularly given Pierre Fabre's submission that the letter was a safety letter.
The Panel noted Pierre Fabre's submission that the use of 'may', within the claim, 'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefits for patients' made it clear that not all patients might suffer from lack of efficacy due to under-dosing. It was, of course, perfectly reasonable for a company to promote its licensed dose. However, within the context of the letter the claim 'Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefit for patients' implied that there was data directly relevant to the use of Navelbine and the treatment of stage 3 and 4 advanced breast cancer relapsing or refractory to an anthracycline containing regimen and that was not so. Pierre Fabre provided data in patients with early stage breast cancer and non Hodgkin's Lymphoma. The word 'may' was insufficient to negate the primary impression. The claim was misleading and not capable of substantiation as alleged. Breaches of the Code were ruled.

With regard to calculations used in the bar chart headed 'Navelbine Oral dose and dose intensity' with the subheading 'Dose delivered per cycle (3 wks). Patient BSA 1.7m^2, capsules 80/30/20mg'. The Panel noted Pierre Fabre's submission that the complainant's example could not be delivered in practice and it did not take into account actual capsule strengths. Pierre Fabre had based the dose delivered on the amount of medicine that could practically be prescribed at each dose. The complainant and respondent agreed the example patient (1.7m^2) was appropriate. The Panel considered that the approach taken by Pierre Fabre was not unreasonable. Although a body surface area of 1.6m^2 gave a smaller dose delivered, on the narrow grounds alleged, the graph was not misleading. No breach of the Code was ruled.

The Panel noted its ruling that the letter was promotional and did not consider it was disguised in this regard. No breach of the Code was ruled.

A pharmacist complained about a letter sent by Pierre Fabre Limited regarding Navelbine (vinorelbine) oral dosing to oncology pharmacists practising within his service.

Navelbine was licensed as a single agent or in combination for the first line treatment of stage 3 or 4 non small cell lung cancer (NSCLC) and the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The letter dated 5 August was headed 'Under-dosing of Navelbine Oral' and stated that the only recommended dose of single agent Navelbine in advanced breast cancer was 80mg/m^2 weekly (following three doses at 60mg/m^2). The letter stated that efficacy was clearly associated with appropriate dosing and explained the consequences of under-dosing. It encouraged checks of local protocols to ensure that Navelbine oral was being used at the appropriate dose and included a bar chart.

COMPLAINT

The complainant explained that the letter was a direct mailing, which claimed to make 'factual, accurate, informative announcements and reference material concerning licensed medicines', however, it did not do so without making 'product claims'. The complainant stated that had the letter stated 'We would like to draw your attention to the dosing in the summary of product characteristics (SPC) and we have no evidence that other schedules are as effective' it would have achieved the same effect.

The complainant alleged a number of breaches of the Code.

1 Clause 4.1

The complainant stated that the letter could not be classed as an abbreviated advertisement because it was an A4 page with a surface area of 623sqcm exceeding the limit of 420sqcm. No prescribing information was provided other than the content of the letter provided.

The complainant noted that there was no information provided about:

- a succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the SPC, together with a statement that prescribers should consult the SPC in relation to other adverse reactions
- the cost (excluding VAT) of either a specified package of the medicine to which the advertisement related, or a specified quantity or recommended daily dose, calculated by reference to any specified package of the product, except in the case of advertisements in journals printed in the UK which have more than 15 per cent of their circulation outside the UK and audiovisual

advertisements and prescribing information provided in association with them
- the legal classification of the product
- the number of the relevant marketing authorization and the name and address of the holder of the authorization or the name and address of the part of the business responsible for its sale or supply
- the date the prescribing information was drawn up or last revised.

In addition, the information provided in the letter for the following sections was weak:

- at least one authorized indication for use consistent with the summary of product characteristics
- a succinct statement of the information in the SPC relating to the dosage and method of use relevant to the indications quoted in the advertisement and, where not otherwise obvious, the route of administration.

The complainant pointed out that the indication in the letter was simply listed as 'Advanced Breast Cancer'; the marketing authorization was for the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The complainant stated that the dosage information in the letter, which was the key point of the letter, referred to 80mg/m^2 weekly, following three doses of 60mg/m^2. There were a number of exclusions to dose escalation in the SPC related to full blood count, which were not listed in the letter. The letter stated that 'a blood test' was required for each dose when increasing frequency from doses 1 and 8 to doses 1, 8 and 15 but did not specify which tests were needed and did not highlight that that blood tests would define if dose escalation was appropriate.

The complainant referred to Clause 4.3 and stated that it was a relatively minor issue, however the approved name appeared directly below the most prominent display of the brand name, it did not appear with the same area as the brand name. The complainant referred to Clause 4.3 that 'All promotional material must include the prominent statement 'Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to [relevant pharmaceutical company]'.

No such statement appeared in the letter.

The complainant stated that while he/she did not believe the letter could be classified as abbreviated prescribing information, had it been it would have been required to contain the following statement: 'Information about this product, including adverse reactions, precautions, contra-indications and method of use can be found at [the address of the website referred to below] and state that prescribers are recommended to consult the summary of product characteristics before prescribing'. Given that the author was writing to highlight that prescribers were not following the SPC it might have been useful to direct prescribers to the SPC as well as medical information.

2 Clause 7

The complainant alleged that while Clause 7 did not specify that claims could not be made to the effect that a licensed dose was superior to an unlicensed dose of the same product without providing evidence, to make such a claim required evidence. The statement 'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefit for patients' should have been accompanied by an evidence base, relevant to the use of anti-cancer agents in Stage 3 or 4 breast cancer, where the primary treatment objective was not always survival. The complainant was aware of very little evidence that substantiated that statement in this setting and none for vinorelbine dosing.

The complainant referred to Clause 7.8 and stated that the graph included in the letter used an example dose for a 1.7m^2 patient and whilst that was an appropriate example dose, the need to round to available capsule sizes meant that some adjustment of final dose given occurred. Had the graph compared 60mg/m^2 on days 1 and 8 it would have shown a 120mg/m^2 dose over the 21 day time frame in comparison to 80mg/m^2 on days 1, 8, 15 of 240mg/m^2. The difference would have been smaller both numerically and in proportion (120 to 240 was a 100% increase, 200 to 420 was a 110% increase). It was hard to be convinced that those values were not selected to make the difference as numerically large as possible. Had a 1.6m2 patient been selected for comparison, the comparison would have been 200mg vs 390mg.

3 Clause 12

The complainant referred to Clause 12.1 and alleged that the author had attempted to make the communication appear like a safety letter rather than promotional material. A clinician following the advice would use 50% more of the medicine and the complainant could not see how this had not resulted in promotion.

The complainant stated that his/her service used the SPC schedule but frequently did not dose escalate due to full blood count or due to other toxicity/ response profiles. The complainant was concerned that his/her clinicians would half read the letter and feel they should be dose escalating rather than optimising patient benefit with toxicity.

When writing to Pierre Fabre, the Authority asked it to respond in relation to Clauses 4.1, 4.3, 4.10, 7.8, and 12.1 of the Code as cited by the complainant. In addition, Pierre Fabre was also asked to consider Clauses 3.2, with regard to the indication stated in the letter in question, and Clauses 7.2 and 7.4 with regard to the evidence base to support the claim

'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefits for patients'.

RESPONSE

Pierre Fabre stated that it did not agree with the complainant's view that the letter in question was a promotional item. It was a safety letter sent via the medical department directly to health professionals in oncology to highlight the under-dosing of Navelbine in advanced breast cancer.

Pierre Fabre submitted that it had conducted market research, which showed that around 90% of patients were on an unlicensed low dose schedule, 60mg/m^2 on day 1 and day 8 every three weeks, vs a recommended dose of 80mg/m^2 every week (explained further below). The other 10% of patients were reported to receive a weekly dose of 60mg/m^2; which still fell short of the recommended 80mg/m^2 weekly schedule.

Pierre Fabre submitted that it had also been asked by health professionals to send a reminder on the appropriate dosing of Navelbine (details could be supplied if necessary), for patients with advanced breast cancer.

Pierre Fabre submitted that if it had included prescribing information along with the safety letter, it might have given the impression that the communication was predominately promotional in nature, while the converse was true. Moreover, Pierre Fabre did not want the nature of the safety letter to be classified as a promotional 'Dear Doctor' letter. The content was non-promotional, based on facts, which could be substantiated. Any product branding was also deliberately removed to ensure that the letter was seen as a non-promotional item. Given that the nature and the intent of the letter was non-promotional, Pierre Fabre contested the additional concerns of the complainant in relation to the provision of the information listed in Clause 4.2 ie in summary a legal classification, the number of the relevant marketing authorization and the name and address of the holder of the authorization, the date the prescribing information was drawn up or last revised, at least one authorized indication for use and succinct statement of the information in the summary of product characteristics (SPC) relating to the dosage and method of use.

Pierre Fabre believed that the safety letter was non-promotional and thus excluded it from the requirement to include prescribing information that would typically accompany a promotional item. Pierre Fabre denied a breach of Clause 4.1.

Similarly, Pierre Fabre submitted that Clauses 4.3 and 4.10 did not apply and it thus denied a breach of those clauses.

Pierre Fabre stated that although its products were provided with the SPC, the market research data indicated that under-dosing was prevalent. Pierre Fabre acknowledged that inclusion of the SPC would enable quicker referencing by the recipient, and so it would include SPCs in future safety communication.

With regard to Clause 3.2, Pierre Fabre reiterated that in its view the letter was not promotional. Moreover, it had not strayed outside Navelbine's marketing authorization. The safety letter focused on the under-dosing of Navelbine, within its licenced indication for advanced breast cancer. Thus, Pierre Fabre denied a breach of Clause 3.2.

Pierre Fabre stated that efficacy of cancer chemotherapy was generally established on the basis of randomised controlled clinical trials evaluating a particular medicine or combination using a specific dose and schedule. This was not only specific for advanced breast cancer, but could be clearly demonstrated in other forms of other malignancies.

Navelbine oral was authorised as a single agent for the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen. The first three administrations were approximated to 60mg/m^2 once weekly, after which consequent doses were approximated to 80mg/m^2 once weekly. This titration should be routinely carried out, except in patients for whom the neutrophil count dropped below 500/mm^3 or more than once between 500 and 1000/mm^3 during the first three administrations of 60mg/m^2. Pierre Fabre noted that it had clearly stated in the letter that blood tests should be carried out prior to escalation of dose, to ensure the wellbeing of patients.

The optimal dose of Navelbine oral was investigated in a dose-finding phase I study (Bonneterre *et al* 2001). The recommended dose of oral vinorelbine for further trials was defined at 80 mg/m^2/week. The study had three respective arms, 60mg/m^2, 80mg/m^2 and 100mg/m^2 dosing regimens. The results indicated that 80mg/m^2 was the most appropriate dose, with 4 tumour responses. 60mg/m^2 was considered ineffective in comparison to 80mg/m^2, as it did not yield any responses, while the 100mg/m^2 arm had 2 tumour responses. Therefore, the 80mg/m^2 weekly was the more efficacious dose (after the initial dose loading of 60mg/m^2) for patients with advanced breast cancer. This was the recommend dose for patients with stable neutrophil counts.

Pierre Fabre stated that there existed compelling preclinical and clinical evidence to indicate that reduction in standard dose intensity might compromise disease-free and overall survival in the curative setting in patients with cancer (Lyman *et al*, Budman *et al*, 1998, Lepage *et al* 1993). Pierre Fabre also referred to a figure and table in Gurney (2002).

Pierre Fabre submitted that the impact of inadvertent under-dosing on adjuvant chemotherapy for stage 2 breast cancer could be summarised by the following:

- Halving the dose of CAF (cyclophosphamide, doxorubicin, and fluorouracil) caused a reduction in the 5-year survival from 79 to 72% (absolute reduction=7%) (Budman *et al*).

Assuming that (conservatively) 30% of patients who

received CAF for stage 2 breast cancer were under dosed because of conventional dosing, absolute reduction in 5-year survival might be 30 of 7% = 2.1%, which was a 17.5% relative reduction in survival (Gurney).

Pierre Fabre stated that if it were to focus on the delivered dose intensity (total dose delivered over time to complete chemotherapy) and the relative dose intensity (ratio of delivered dose intensity to standard dose intensity and could be expressed as a percentage); there had been a clearly demonstrable relationship between survival and relative dose intensity (RDI) in a number of retrospective studies in patients with early stage breast cancer and Non-Hodgkin's Lymphoma (NHL). Details were provided.

Pierre Fabre submitted that the claim 'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit the potential survival benefits for patients' had clearly been demonstrated by the evidence provided and was not misleading. Moreover, 'may' indicated that not all patients might suffer from lack of efficacy due to under-dosing. It was accurate, balanced, fair and capable of substantiation, thus Pierre Fabre denied a breach of Clauses 7.2 and 7.4.

With regard the graph included in the letter and the requirements of Clause 7.8, Pierre Fabre stated that it had used an average surface area of a patient as 1.7m^2 to calculate the doses in the safety letter as below:

Calculation used in safety letter (based on available capsule strength 20mg, 30mg & 80mg)

	60mg/m^2 d1, d8	**80mg/m^2 d1, d8**	**60mg/m^2 weekly**	**80mg/m^2 weekly**
Intended dose (1.7m2 x dose)	102mg d1,d8	136mg d1,d8	102mg d1,d8,d15	136mg/d1,d8,d15
Rounded dose (based on 20mg, 30mg and 80mg capsules	100mg d1,d8	140mg d1,d8	100mg d1,d8,d15	140mg d1,d8,d15
Rounded dose per cycle	200mg	280mg	300mg	420mg

d = day

This represented a 110% difference between the extremes of dose. While the complaint suggested that Pierre Fabre could have represented the doses in the following manner:

	60mg/m^2 d1, d8	**80mg/m^2 weekly**
Intended dose per cycle	120mg/m2	240mg/m2

This would represent a 100% difference between the extremes of dose. However, this calculation did not take into account the actual capsule strengths and could not be delivered in practice. If the cycle doses were converted to actual doses, then the same rounding up and down needed to be carried out in order to arrive at a delivered dose.

	60mg/m^2 d1, d8	**80mg/m^2 weekly**
Intended dose per cycle	120mg/m2	240mg/m2
Intended dose per cycle for patient (1.7m2)	204mg	408mg
Individual doses	102mg on d1 and d8	136mg on d1,d8,d15
Practically delivered doses	100mg (80mg and 20mg caps) on d1 and d8 = **200mg**	140mg (80mg and 2x30mg) on d1,d8 d15 = **420mg**

The dosing schedule, as demonstrated by the complainant, was focused on amount of medicine per cycle, while Pierre Fabre had chosen to base the dose delivered on the amount of medicine that could be practically prescribed at each dose.

Pierre Fabre submitted that it had kept within the spirit of the Code and had provided readers with a clear, fair, balanced view of the dose delivered per cycle. The company thus denied a breach Clause 7.8.

Pierre Fabre did not accept that the safety letter was disguised promotion; it was sent by the medical department to health professionals. The complaint conceded that it '… appear(s) as a safety letter than promotional material …'.

Pierre Fabre stated that the communication was a safety letter. As an ethical and patient focused company, it decided to send the safety letter after obtaining evidence that the majority of patients with advanced breast cancer that received oral

vinorelbine, were under-dosed. The company had not stated that all patients that were under-dosed 'would' and 'definitely' had their survival benefits curtained, it had merely stated that if patients were not receiving the most efficacious dose as per the SPC, they might limit their potential survival benefit. The letter did not make any exaggerated claims of improvement of survival benefit/outcomes – but instead focused on data that had been collected from Pierre Fabre's own studies and other health professionals (on different malignancies as well as breast cancer).

Pierre Fabre thus did not accept that it had disguised a safety letter as a promotional mailing, and denied a breach of Clause 12.1.

PANEL RULING

The Panel noted Pierre Fabre's submission that the letter in question was a safety letter meant for health professionals to highlight the under-dosing of Navelbine in advanced breast cancer. The letter was signed by the medical manager and sent to health professionals that worked in oncology. Pierre Fabre submitted that its market research had indicated that health professionals in the UK routinely under-dosed Navelbine patients and it had also been asked by health professionals to send a reminder on the appropriate dosing of Navelbine for patients with advanced breast cancer. In Pierre Fabre's view the provision of prescribing information might have implied that the communication was predominantly promotional in nature, whilst in its view the converse was true.

The Panel noted that the exemptions to the Code did not refer to 'safety letters'. The letter in question did not appear to meet any of the listed exemptions to the definition of promotion. The Panel further noted that the letter in question had not been sent at the request of the MHRA nor had it been triggered as a result of a safety report to the company or analysis of patient safety data. The Panel was concerned that the very limited market research supplied did not appear to support the company's position about suboptimal dosing. In addition, no supporting material had been supplied in relation to the statement in the letter that many trust protocols specified a regimen that Pierre Fabre only recommended when Navelbine was used in combination with other anti-cancer agents rather than that licensed for single agent use. Whilst noting its concerns about the market research, the Panel nonetheless considered that suboptimal dosing was an important issue but any communication in this regard had to comply with the Code. The Panel noted that discussing safety matters or adverse events did not *ipso facto* mean that a communication was non promotional. Each case had to be decided on its individual circumstances. The Panel noted the broad definition of promotion in Clause 1.2 ie any activity which promoted the administration, consumption, prescription, purchase, recommendation, sale, supply or use of a company's medicine. Overall, the Panel considered that the letter in question was promotional. Its aim, according to Pierre Fabre, was to ensure the dosage regimen of single agent oral Navelbine was in accordance with its licence and that this was reflected in trust protocols. The letter in question referred to the brand name seven times. In the Panel's view the potential safety consequences of under-dosing were not such that they rendered the letter in question non promotional given the very broad definition of promotion in Clause 1.2 of the Code. Doses lower than 80mg/m^2 weekly were recommended in certain circumstances. The Panel considered that the promotional nature of the letter triggered the requirement to provide prescribing information, as listed in Clause 4.2; the letter should also have included a statement that adverse events should be reported. The Panel noted that these requirements had not been met and ruled breaches of Clauses 4.1 and 4.10.

With regard to the allegation that while the approved name appeared directly below the most prominent display of the brand name, it did not appear with the same area as the brand name the Panel noted the most prominent display of the brand name was within the heading 'Under-dosing of Navelbine Oral' with the non-proprietary name in smaller font size appearing on the line below 'Navelbine® Oral (vinorelbine soft capsules)'. Both the brand name and non proprietary name were in bold type. The Panel noted the requirements of Clause 4.3 that the size of the non proprietary name or the list of active ingredients should occupy a total area no less than that taken up by the brand name or in type of a size such that the lower case 'x' was no less than 2mm in height. The Panel noted that whilst the total size occupied by the non proprietary name appeared to be less than that of the brand name the font size was such that lower case letters were not less than 2mm in height. The Panel considered that the size requirement for the non proprietary name was thus satisfied and no breach of Clause 4.3 was ruled.

The Panel noted that beneath the heading 'Under-dosing of Navelbine Oral' the first paragraph stated 'The only recommended dose of single agent Navelbine Oral in advanced breast cancer is 80mg/m^2 weekly (following three doses at 60mg/m^2)'. Navelbine Oral was indicated as a single agent or in combination for, *inter alia*, the treatment of advanced breast cancer, stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen. The Panel considered that the reference to 'advanced breast cancer' in the letter in question was not sufficiently qualified such that it was not a fair reflection of Navelbine's licensed indication for advanced breast cancer and was inconsistent with the particulars listed in its SPC. A breach of Clause 3.2 was ruled.

With regard to the final paragraph of the letter which began 'When increasing the frequency of dosing please be aware that a blood test is recommended before each dose', the Panel noted Section 4.4 of the Navelbine SPC, Special warnings, stated, *inter alia*, 'Close haematological monitoring must be undertaken during treatment (determination of haemoglobin level and the leucocyte, neutrophil and platelet counts on the day of each new administration). Dosing should be determined by

haematological status ...'. In addition, Section 4.2 of the Navelbine SPC, Posology and method of administration, stated, *inter alia*, that 'Beyond the third administration, it is recommended to increase the dose of Navelbine to 80mg/m^2 once weekly except in those patients for whom the neutrophil count dropped once below 500/mm^3 or more than once between 500 and 1000/mm^3 during the first three administrations at 60mg/m^2'. The Panel considered that the letter was misleading as alleged. It did not give sufficient weight to the importance of blood tests nor did it reflect the SPC requirement. Blood tests were not simply required when increasing the frequency of dosing as stated in the letter but on the day of each new administration. A breach of Clause 7.2 was ruled. The Panel was very concerned about the failure to make the monitoring requirements clear and the potential impact on patient safety. It considered that this was a serious matter, particularly given Pierre Fabre's submission that the letter was a safety letter.

The Panel noted Pierre Fabre's submission that the use of 'may', within the claim, 'Efficacy of anticancer agents is clearly associated with appropriate dosing. Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefits for patients' made it clear that not all patients might suffer from lack of efficacy due to under-dosing. The Panel noted that the data submitted by Pierre Fabre indicated that in certain patient populations the dose of cytotoxic treatments was important in relation to disease free survival and overall survival. Bonneterre *et al*, a phase 1 and pharmacokinetic study of oral vinorelbine in first and second line patients with locally advanced or metastatic breast cancer found that no response was observed, in the six evaluable patients treated, with 60mg/m^2/week. The SPC referred to 60mg/m^2 dose, whether that be as an initial dose for three administrations or following certain neutrophil counts or patients with liver insufficiency. It was, of course, perfectly reasonable for a company to promote its licensed dose. However, nonetheless, the Panel considered that within the context of a letter which discussed the recommended dose of single agent Navelbine oral in advanced breast cancer the claim 'Under-dosing may restrict the efficacy of Navelbine Oral and limit potential survival benefit for patients' implied that there was data directly relevant to the use of Navelbine and the treatment of stage 3 and 4 advanced breast cancer relapsing or refractory to an anthracycline containing regimen and that was not so. Pierre Fabre provided data in patients with early stage breast cancer and non Hodgkin's Lymphoma. The Panel also considered that the word 'may' was insufficient to negate the primary impression. The claim was misleading and not capable of substantiation as alleged. A breach of Clauses 7.2 and 7.4 was ruled.

With regard to calculations used in the bar chart headed 'Navelbine Oral dose and dose intensity' with the subheading 'Dose delivered per cycle (3 wks). Patient BSA 1.7m^2, capsules 80/30/20mg'. The bar chart showed four bars. The first two were data for 60mg/m^2 and 80mg/m^2 administered on d1 d8 and q21 and the third and fourth bar showed data for 60mg/m^2 weekly and 80mg/m^2 administered weekly. The 80mg/m^2 weekly bar was labelled 'Recommended dose'. An asterix to each 80mg/m^2 dose read 'First cycle/3weeks at 60mg/m^2'. In relation to this graph, the complainant alleged that use of a 1.7m^2 patient required a greater dose per cycle than if a 1.6m^2 patient had been used. The Panel noted Pierre Fabre's submission that the example chosen by the complainant could not be delivered in practice and it did not take into account actual capsule strengths. Pierre Fabre had based the dose delivered on the amount of medicine that could practically be prescribed at each dose. The complainant and respondent agreed the example patient (1.7m^2) was appropriate. The Panel considered that the approach taken by Pierre Fabre was not unreasonable, the example dose for a patient with a body surface area of 1.7m^2 was appropriate. Although a body surface area of 1.6m^2 gave a smaller dose delivered, on the narrow grounds alleged, the graph was not misleading. No breach of Clause 7.8 was ruled.

The Panel noted it's ruling that the letter was promotional and did not consider it was disguised in this regard. No breach of Clause 12.1 was ruled.

During its consideration of this case the Panel was concerned about a number of matters as follows.

Firstly, the Panel was concerned that the market research data provided did not indicate that health professionals in the UK routinely under-dosed their patients with single agent Navelbine oral, in advanced breast cancer, which was Pierre Fabre's rationale for the letter in question. The Panel did not have a complete copy of the market research and it was unclear which country the data applied to. The data did not segment patients receiving the first three administrations of Navelbine oral, those receiving subsequent administrations and those in whom the dose could not be escalated due to a reduced neutrophil count. In the Panel's view the average dose administered in accordance with the licensed indication could not be established from the market research data provided. In addition, the data did not appear to support the submission that patients were being under-dosed. The Panel queried whether the claim for under-dosing was capable of substantiation.

Secondly, the Panel was concerned about the graph as the doses of 60mg/m^2 and 80mg/m^2 at d1, d8, and q21 appeared to be inconsistent with the single agent licensed regimen of the first three administrations at 60mg/m^2 once weekly and the recommended increase in dose to 80mg/m^2 in certain patients. The Panel noted its comments above regarding the material to support Pierre Fabre's position regarding sub optimal dosing and that the requirement for monitoring prior to each new administration was not sufficiently clear, the Panel considered that it was not clear from the graph that the appropriate dose would depend on patient

experience, tolerability and stage of treatment. The Panel also noted that the inclusion of 'recommended dose', under 80mg/m^2 weekly drew attention to that dose regimen; which would not be appropriate for all patients.

The Panel requested Pierre Fabre be advised of its concerns on the two points outlined above.

Complaint received **16 August 2014**

Case completed **30 October 2014**
