CASE AUTH/2131/6/08

COMMUNITY PHARMACIST v GRÜNENTHAL

Promotion of Versatis

A community pharmacist complained that a representative from Grünenthal had told her that a study showed that Versatis (lidocaine medicated plaster) had roughly equivalent efficacy to gabapentin, with a much lower incidence of interactions and side-effects. The complainant asked for further information and was told it was still being worked on, and was not due out until September. The representative did not offer to supply information in September. The complainant did not make notes at the time, and it was possible that the representative had referred to a study against pregabalin.

The detailed responses from Grünenthal are set out below.

The Panel noted that the complainant referred to a comparison with gabapentin although she observed that it was possible she was referring to a study against pregabalin. Grünenthal's responses related to both products. Further comments from the complainant referred to pregabalin.

It appeared that the complaint referred to the use of interim data in the detail aid to support a claim 'Versatis is comparable to pregabalin in patient response at four weeks'. It appeared that the complainant had asked for the substantiating data and was told it would not be available until September. Grünenthal submitted that the complainant had asked to see the data when the study was completed, not the interim data.

On the basis of the parties' submissions, the Panel did not consider that there was sufficient evidence to show that on the balance of probabilities the complainant had asked for the interim data. With regard to the failure to supply the interim data the Panel ruled no breach of the Code.

The Panel then considered the use of interim data to support the claim made by the representative that Versatis had approximately equal efficacy to pregabalin and similar claims in the detail aid. Page 4 of the detail aid was headed 'First comparative study in PHN' [post herpetic neuralgia] and featured the claim 'Versatis is comparable to pregabalin in patient response at 4 weeks' referenced to data on file. Beneath the heading the claim 'Statistically shown to be at least comparable in efficacy to pregabalin (interim analysis p=0.0083)' appeared. The page included a bar chart of response rate after 4 weeks and other details.

Page 5 was referenced to the same interim analysis. It had the headline claim 'Versatis is comparable to pregabalin in reducing pain intensity at 4 weeks'. This was followed by the claim 'Interim efficacy parameters reported how many patients had 30% and 50% reductions in pain intensity'. The data was shown in a bar chart.

The Panel noted the data for pregabalin in Hempenstall *et al* (2005). The meta-analysis of published studies compared current therapies and calculated NNT to reach a 50% pain reduction. This was neither shown nor referenced on pages 4 and 5 of the detail aid. Hempenstall *et al* was not a direct clinical comparison of Versatis and pregabalin and nor was the data limited to the response with either medicine at 4 weeks.

The interim data provided by Grünenthal to substantiate the 4 week claims for Versatis (n=27) vs pregabalin (n=24) consisted of one page; page 53 of 418. No details of the inclusion criteria, study design and its intended length etc were provided. The page provided stated that the study was a non-inferiority study. The Panel considered there was a difference between showing non-inferiority to showing comparability. The Panel considered that on the basis of the interim data provided the claims for comparable efficacy for Versatis and pregabalin had not been substantiated and were misleading in that regard. Breaches of the Code were ruled.

Page 8 of the detail aid featured a comparison between Versatis and pregabalin for adverse events. The claims referred to fewer patients in the Versatis group having drug-related adverse events at week 4 compared with the pregabalin group. The associated bar chart was adapted from data on file. No information from the data on file with regard adverse events had been supplied by Grünenthal. The company had made a brief submission in relation to the content of the summary of product characteristics (SPC). The Panel considered, however, that the SPC provided general data regarding adverse events and as such could not be used to substantiate the very specific four week claims in the detail aid. The Panel considered that its comments above regarding the use of interim data for efficacy also applied to the use of interim data for the adverse events. Breaches of the Code were ruled.

A community pharmacist complained about the promotion of Versatis (lidocaine medicated plaster) by a representative from Grünenthal Ltd.

COMPLAINT

The complainant stated that in June a

representative from Grünenthal called at her pharmacy to discuss Versatis.

During the discussion the representative told the complainant that a study showed that Versatis had roughly equivalent efficacy to gabapentin, with a much lower incidence of interactions and side-effects. The complainant asked for further information and was told it was still being worked on, and was not due out until September. The representative did not offer to supply information in September. The complainant did not make notes at the time, and it was possible that the representative had referred to a study against pregabalin.

When writing to Grünenthal, the Authority asked it to respond in relation to Clauses 7.2, 7.4 and 7.5 of the Code.

RESPONSE

Grünenthal explained that with a high level of local prescribing of Versatis, the representative in question made a courtesy call on this pharmacist; the pharmacist was very busy and there was no more than a three minute discussion. The pharmacist was interested in the Versatis vs pregabalin interim data and stated that she would like to see the data when the study was completed. In response to the pharmacist's question, the representative said that she could not give the complete trial data now as it was not finished, but would call back with it when it was available – probably in September. The representative left her card and asked if there was anything else she could help with to which the pharmacist answered 'no'.

Where the pharmacist cited 'further information' in her complaint, it therefore referred to the full trial data that she said she would like to see. The representative was correct in that the final results of the whole trial would be available later, once fully analysed. The representative's electronic call notes, made just after the call, corroborated the discussion; a copy was provided. The representative specifically noted that the pharmacist wanted the data when complete and that this was the 'Next Objective' with this customer. The intention was, therefore, to comply with the pharmacist's request for the further data as available in September. The call entry recorded the fact that the pharmacist raised no further questions. Hence, there was no breach of Clause 7.5.

The detail aid the representative used with the pharmacist compared the efficacy of gabapentin and pregabalin in post herpetic neuralgia (PHN) – as adapted from Hempenstall *et al* (2005) – and supported the representative's comment about efficacy. Therefore, there was no breach of Clause 7.2.

The representative's comments about efficacy and side-effects were also supported from the interim data in the detail aid and were not in breach of Clause 7.2.

In terms of the representative's comments about drug interactions, the Versatis summary of product characteristics (SPC) stated: 'No interaction studies have been performed. No clinically relevant interactions have been observed in clinical studies with the plaster. Since the maximum lidocaine plasma concentrations observed in clinical trials with the plaster were low (see section 5.2), a clinically relevant pharmacokinetic interaction is unlikely'.

Hence, on balance, the representative's comments about drug interactions were reasonable, could be substantiated and, therefore, did not breach Clauses 7.2 or 7.4.

It seemed, therefore, that a simple misunderstanding had arisen with regard to what the pharmacist had asked for. When retail pharmacists were busy, it was possible that time constraints here had created inadvertent misunderstandings. Grünenthal would never intend to mislead customers.

COMMENTS FROM THE COMPLAINANT

Having given preliminary consideration to the matter, the Panel decided that it would be helpful to have the complainant's comments on Grünenthal's response with regard to exactly what information she had asked the representative for.

The complainant submitted that the representative did not initially state that the data to which she referred was interim only. She talked about how the study showed that Versatis had approximately equal efficacy to pregabalin, with a lower incidence of side-effects. It was only when the complainant asked if she could see a copy of the data that she learned it was incomplete, and might be available in September.

It was correct that she wished to see the data from the full trial, when complete, and the complainant emphasized that she had not disputed any findings from that trial, when complete. It was quite feasible that the representative's comments would be supported by the full results, but the complainant felt strongly that interim results should not be referred to as if they were finalised.

The complainant stated that she had raised no further questions at the time because she was so taken aback at what appeared to be a breach of the Code – the first apparent breach she had ever encountered. Grünenthal referred to misunderstandings three times in its letter.

FURTHER COMMENTS FROM THE RESPONDENT

In response to the complainant's comments Grünenthal referred to Hempenstall *et al* – the only published meta-analysis to date, investigating the comparative efficacy of current therapies available

for the treatment of PHN. This was a robust, peer reviewed journal publication produced by world experts in the field of pain management. It used the validated technique of number needed to treat (NNT) to define the treatment-specific effect of an intervention. This in turn ensured a fair and effective comparison of efficacy across different therapies. It was also important to note that Hempenstall *et al* used the strictest inclusion criteria to ensure that papers included were of the highest scientific standard.

Hempenstall *et al* reported that, the NNT to reach a pre-ordained 50% pain reduction for gabapentin was 4.39 (3.34 - 6.07), compared with 2 (1.43 - 3.31) for Versatis. In clinically meaningful terms, 2 patients needed to be treated with Versatis for one to find a clinical effect (in this case a 50% reduction in pain) and 4 with gabapentin for one to reach a similar clinical effect.

In terms of drug interactions, the Versatis SPC stated:

> 'No interaction studies have been performed. No clinically relevant interactions have been observed in clinical studies with the plaster. Since the maximum lidocaine plasma concentrations observed in clinical trials with the plaster were low (see section 5.2), a clinically relevant pharmacokinetic interaction is unlikely. Although normally the absorption of lidocaine from the skin is low, the plaster must be used with caution in patients receiving Class 1 antiarrhythmic drugs (eg tocainide, mexiletine) and other local anaesthetics since the risk of additive systemic effects cannot be excluded.'

With reference to <u>likely</u> interactions, part of the equivalent SPC data for gabapentin [Pfizer's product Neurontin, to be taken orally] stated that:

> 'In a study involving healthy volunteers (N=12), when 60mg controlled-release morphine capsule was administered 2 hours prior to a 600mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.
>
> Coadministration of gabapentin with antacids containing aluminium and magnesium reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.
>
> A slight decrease in renal excretion of gabapentin that is observed when it is coadministered with cimetidine is not expected to be of clinical importance.'

The fact that topically applied Versatis had been shown to generate limited systemic levels of lidocaine supported the claim that there were fewer interactions to be expected in this type of application.

In conclusion, it was clear from the SPC that there was a reduced potential for interactions for Versatis when compared with gabapentin.

In relation to adverse events Grünenthal referred to the latest SPCs for gabapentin and Versatis. It was evident that the adverse events reported for Versatis were mild to moderate in nature and mainly related to application site reactions. However, it was clear from the gabapentin SPC that there were a significant number of serious adverse events reported, many of which were very common (≥1/100, <1/10).

Grünenthal noted that section 4.8 of the Versatis SPC stated: 'Approximately 16% of patients can be expected to experience adverse reactions. These are localised reactions due to the nature of the medicinal product. The most commonly reported adverse reactions were administration site reactions including erythema, rash, application site pruritus, application site burning, application site dermatitis, application site erythema, application site vesicles, dermatitis, skin irritation, and pruritus.'

The SPC stated that adverse reactions reported in PHN studies were predominantly of mild and moderate intensity and less than 5% led to treatment discontinuation. Systemic adverse reactions following the appropriate use of the plaster were unlikely since the systemic concentration of lidocaine was very low. Systemic adverse reactions to lidocaine were similar in nature to those observed with other amide local anaesthetics.

The gabapentin adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain were provided in a single list in the SPC by class and frequency. Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported. Within each frequency grouping, undesirable effects were presented in order of decreasing seriousness.

Grünenthal submitted that it was clear from SPC comparisons that significantly more frequent adverse events had been reported for gabapentin compared with Versatis. This would be expected given the nature of comparing a systemic anti-convulsant with a peripherally acting analgesic plaster that generated low levels of systemic lidocaine.

Grünenthal submitted that these data and evidence substantiated the claim that 'Versatis has roughly equivalent efficacy to gabapentin with a much lower incidence of interactions and side- effects'.

FURTHER INFORMATION FROM THE RESPONDENT

The Panel considered that it needed further

information from the respondent in relation to a comparison with pregabalin.

Grünenthal submitted that the interim data was never referred to as finalised. The detail aid clearly marked the results as 'interim analysis' next to the p value. Grünenthal had confirmed this with the representative involved, who made it clear these data were interim.

The complainant did not question the validity of data presented at the time. Also, an opportunity was given at the end of the meeting where the representative specifically checked if she could do anything else to help before the complainant ended the discussion.

The relevant page of the detail aid was based on the planned statistical interim analysis of the data, of which the complainant requested the full data set when available in September. In an internal report from the statistician, 'A test of non-inferiority in the PHN strata results in a p-value of 0.0083, strongly suggesting that lidocaine 5% medicated plaster is non-inferior to pregabalin in PHN subjects alone'. This was not something Grünenthal had claimed. However, it was statistically correct to view the efficacy of Versatis as comparable to pregabalin at this interim stage.

Further substantiation of the comparison of Versatis with pregabalin was given in Hempenstall *et al*. It was the only published meta-analysis to have investigated the comparative efficacy of current therapies available for the treatment of post herpetic neuralgia (PHN). To reiterate, this paper was a robust, peer reviewed journal publication produced by world experts in the field of pain management. It used the validated technique of number needed to treat (NNT) to define the treatment-specific effect of an intervention. This in turn enabled an effective comparison of efficacy across different therapies. It was also important to note that Hempenstall *et al* used the strictest inclusion criteria to ensure that papers included were of the highest scientific standard.

As could be seen from this review, the NNT to reach a pre-ordained 50% pain reduction for pregabalin was 4.93 (3.66 - 7.58), compared with an NNT for Versatis of 2 (1.43 - 3.31).

In clinically meaningful terms, two patients needed to be treated with Versatis for one patient to receive a clinical effect (in this case a 50% reduction in pain) compared with five patients with pregabalin for one to receive a clinical effect. Hence, from this comprehensive analysis of the data comparing these two products, one could conclude that Versatis had a comparable efficacy to that of pregabalin.

PANEL RULING

The Panel noted that the complainant referred to a comparison with gabapentin in her complaint although she noted that it was possible she was referring to a study against pregabalin. Grünenthal's response related to both products. The further comments from the complainant referred to pregabalin. The further comments from Grünenthal referred to both products.

The Panel noted that the representative had used the detail aid with the complainant. It appeared from the complainant's comments that the complaint referred to the use of interim data to support claims. The detail aid used interim data to support a claim 'Versatis is comparable to pregabalin in patient response at four weeks'. It appeared that the complainant had asked for data to substantiate this claim and was told it would not be available until September. Grünenthal submitted that the complainant had asked to see the data when the study was completed not the interim data.

The Panel noted the parties' accounts of the request differed. It was difficult in such cases to know what had transpired. A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually necessary on the part of the individual before he or she was moved to actually submit a complaint.

On the basis of the parties' submissions, the Panel did not consider that there was sufficient evidence to show that on the balance of probabilities the complainant had asked for the interim data. With regard to the failure to supply the interim data the Panel ruled no breach of Clause 7.5.

The Panel then went on to consider the acceptability of using interim data to support the claim made by the representative that Versatis had approximately equal efficacy to pregabalin and similar claims in the detail aid. Page 4 of the detail aid was headed 'First comparative study in PHN' and featured the headline claim 'Versatis is comparable to pregabalin in patient response at 4 weeks' referenced to data on file. Beneath the heading the claim 'Statistically shown to be at least comparable in efficacy to pregabalin (interim analysis p=0.0083)' appeared. The page included a bar chart of response rate after 4 weeks and other details.

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The Panel noted the data for pregabalin in Hempenstall *et al*. The meta-analysis of published studies compared current therapies and calculated NNT to reach a 50% pain reduction. This was neither shown nor referenced on pages 4 and 5 of the detail aid. Hempenstall *et al* was not a direct clinical comparison of Versatis and pregabalin and nor was the data limited to the response with either medicine at 4 weeks.

The interim data provided by Grünenthal to substantiate the 4 week claims for Versatis (n=27) vs pregabalin (n=24) consisted of one page; page 53 of 418. No details of the inclusion criteria, study design and its intended length etc were provided. The page provided stated that the study was a non-inferiority study. The Panel considered there was a difference between showing non-inferiority to showing comparability. The Panel considered that on the basis of the interim data provided the claims for comparable efficacy for Versatis and pregabalin had not been substantiated and were misleading in that regard. Breaches of Clauses 7.2 and 7.4 were ruled.

Page 8 of the detail aid featured a comparison between Versatis and pregabalin for adverse events. The claims referred to fewer patients in the Versatis group having drug-related adverse events at week 4 compared with the pregabalin group. The associated bar chart was adapted from data on file. No information from the data on file with regard adverse events had been supplied by Grünenthal. The company had made a brief submission in relation to the content of the SPC. The Panel considered, however, that the SPC provided general data regarding adverse events and as such could not be used to substantiate the very specific four week claims in the detail aid. The Panel considered that its comments above regarding the use of interim data for efficacy also applied to the use of interim data for the adverse events. Breaches of Clauses 7.2 and 7.4 were ruled.

During its consideration of this case the Panel had some concerns as to whether the meta-analysis by Hempenstall *et al* was sufficient to substantiate the comparative claims for Versatis and other therapies including pregabalin and gabapentin. The study concluded that the evidence base supported the use of gabapentin and pregabalin for PHN and also supported lidocaine patches. The discussion stated that data extracted from small and/or single unreplicated studies needed to be viewed with a particular degree of caution. This applied to lidocaine patches (1 study, 64 patients). The data for gabapentin was from 3 studies, (n=559) and three studies had also been used for pregabalin (n=411). The difference in size of the three data sets was not reported in the detail aid. Hempenstall *et al* stated that the dichotomous data for adverse events needed to be viewed with caution for a number of reasons. The Panel requested its concerns regarding the use of the meta-analysis be drawn to Grünenthal's attention.

Complaint received **10 June 2008**

Case completed **29 August 2008**