CASE AUTH/2500/4/12

ANONYMOUS v EISAI

Promotion of Zonegran

An anonymous consultant neurologist alleged that Zonegran (zonisamide) promotional materials, used by a representative of Eisai were misleading. Zonegran was indicated in the treatment of adults with partial seizures. The complainant stated that the materials and discussion with the representative incorrectly inferred that Zonegran could be used in overweight epileptics. The complainant subsequently discovered that weight loss could be a side effect of treatment.

The detailed response from Eisai is given below.

The Panel noted that the complainant was anonymous and non-contactable. A complainant had the burden of proving his/her complaint on the balance of probabilities and all complaints were judged on the evidence provided by the parties. It was impossible to know what the representative had said or what materials he/she had used. The company could not identify the representative in question. The Panel noted that according to Eisai a detail aid was to be used and it thus considered the complainant's allegations solely in relation to that.

The Panel noted that the Zonegran summary of production characteristics (SPC) stated that Zonegran might cause weight loss.

The Panel noted Eisai's submission that as there was similar efficacy between different anti-epileptic medicines other important factors were taken in to account before such medicines were prescribed.

The first page of the Zonegran detail aid gave details of the indication then in larger type the claim 'Think beyond efficacy … When looking for additional seizure control …'. The third page of the detail aid contained four text boxes with the following statements: 'What about side effects?'; 'Will they be able to stay on treatment?'; 'What happens if they forget a dose?' and 'Will it impact on other treatments?'. The detail aid then went on to address these questions. The 'What about side effects?' section listed treatment emergent adverse events reported by ≥10% Zonegran patients. Weight loss was not mentioned. The final section started on page 12 with two pages answering the question 'Will weight gain be an issue?'. This section was separate from that addressing side effects and consisted of the results from Wellmer *et al* (2009) (which looked at the impact of Zonegran on body mass index), details on the issue of weight gain in epileptic patients and the lack of weight gain seen with Zonegran. The fifth and final bullet point was in bold type and stated 'BMI decrease was significant in patients who were overweight prior to Zonegran initiation'.

The Panel noted that the representative briefing document on Wellmer *et al* stated 'In this retrospective study, zonisamide reduced weight in 35% of patients, particularly those who were overweight prior to treatment. This study helps provide some information regarding the variability and extent of weight change under zonisamide treatment in daily practice, however provides no indication of why patients change weight'. This was followed by bold text which read 'Please note that this is a study in epileptic patients on Zonegran & is not advocating the use of Zonegran as a weight loss drug'.

The Panel noted that in describing the study limitations, Wellmer *et al* noted that the retrospective design did not allow controlling variables such as intended weight loss through fasting. It suggested that prospective studies should be carried out. The discussion section noted that weight loss was not restricted to overweight patients and in normal and underweight patients it could be an adverse event. Although weight loss was described as mild to moderate in most cases, in some individuals it reached critical dimensions.

The Panel considered that the detail aid encouraged prescribers to consider factors other than seizure control when deciding which treatment to prescribe. This was not necessarily unacceptable as factors such as side effects would be relevant to the prescribing decision. However the licensed indication should be clear and overall the discussion of factors other than seizure control should be presented in the context of the indication. By separating in the detail aid the weight loss seen with Zonegran from other side effects, the detail aid might imply that Zonegran's indications included weight loss in epileptic patients. This impression was compounded by the fact that there was no mention, other than in the prescribing information, that anorexia was a common side effect. It was not sufficiently clear from the Wellmer *et al* briefing document or the detail aid that the medicine should not be promoted to aid weight loss in epileptic patients. In addition, there was no mention of the study limitations or that it was a retrospective study. There was no briefing material for the detail aid. This was unacceptable.

The Panel considered that, taking all the circumstances into account, the detail aid was misleading with regard to Zonegran's effect on weight loss, and a breach was ruled. The Panel considered that by failing to be clear about Zonegran and weight loss in epilepsy, the detail aid exaggerated the medicine's properties. A breach was ruled. The Panel considered that Eisai had not maintained high standards and a breach was ruled.

The Panel noted its rulings above and considered that, taking all the circumstances into account, they did not warrant a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

The Authority received a complaint from an anonymous consultant neurologist; no contact details were provided. The complaint was about the promotion of Zonegran (zonisamide) by Eisai Limited. Zonegran was indicated in the treatment of adults with partial seizures.

COMPLAINT

The complainant alleged that a representative showed him/her promotional materials which he/she considered were misleading and could endanger patients. The materials and discussion inferred that Zonegran could be used in overweight epileptics. The complainant subsequently discovered that such a suggestion was not evidence based and weight loss could be a side effect of treatment. The complainant noted that a claim could not be made about a side effect as the study was not powered to do this – the study would look at the efficacy of the medicine and an overall safety profile. The complainant alleged that the material and verbal claims were incorrect. The complainant also noted that diarrhoea was a side effect and queried whether he/she should use Zonegran in epileptic patients who were also constipated.

When writing to Eisai, the Authority asked it to respond in relation to Clauses 2, 7.2, 7.10 and 9.1 of the Code.

RESPONSE

Eisai explained that as there was similar efficacy between different anti-epileptic medicines (which was well established for Zonegran which had been on the market for seven years), epileptologists and neurologists considered other important factors such as dosing frequency, interactions with other medicines, tolerability and side effects in order to prescribe an anti-epileptic medicine to match individual patient needs.

With this in mind the detail aid was specifically devised to address questions that might come up during a call with a representative (Eisai provided a copy of the detail aid relevant to the complaint and also the efficacy leavepiece).

The current detail aid was an interactive iPad version, designed such that representatives could bring up specific information, if and when needed, to address prescribers' questions. An identical paper version was used that was replaced with the electronic version in April 2011.

The e-detail addressed a number of prescribers' issues when selecting anti-epileptic medicine treatment such as; frequency of dosing, retention rates on Zonegran, tolerability, reasons for discontinuing treatment with Zonegran, common adverse events with Zonegran, drug-drug interactions with other anti-epileptic medicines or the oral contraceptive pill as well as weight changes with Zonegran. This was a common subject matter as some anti-epileptic medicines might contribute to weight gain whilst others might have minimal effect on weight or a slight weight reduction.

As there were minimal trials published on this matter, the e-detail contained the results from Wellmer *et al* (2009) which looked at the variability and extent of weight change with Zonegran. The result of the study (figure 2 from the published paper) was shown in the e-detail. Thus if a clinician had a question about weight changes on Zonegran, the representative could provide some information about the variability of weight change from a study that investigated this particular topic.

The majority of patients on Zonegran did not experience weight gain, however some patients had weight loss that was reversible following discontinuation of Zonegran and was not related to the dose of Zonegran. This was similar to the result seen in a pivotal Phase III trial (data on file) which was also referenced in the e-detail.

Eisai stated that its representatives had been briefed on each of the studies cited in the e-detail including Wellmer *et al* (a copy of an email and briefing document were provided). The sales team had been clearly told that Wellmer *et al* might explain some of the variability observed with weight changes on Zonegran treatment and that Zonegran must not be promoted as a weight loss agent.

Eisai submitted that there appeared to be a misinterpretation by the complainant who stated that the study should look at efficacy and was not 'powered to detect side effects'. This was not the purpose of the study. The study did not look at efficacy but focused specifically on the impact on weight from observing the effect of Zonegran on 103 epileptic patients.

Eisai stated that the e-detail was intended to clarify issues and present the facts. There was nothing in the material that promoted the use of Zonegran for weight management. Eisai considered that its material was balanced, up-to-date, could be substantiated and did not mislead. The information on the various topics was presented objectively thus the company denied any breaches of Clauses 7.2 and 7.10. In addition, the company denied that the material demonstrated that high standards had not been maintained (Clause 9.1) or that it had reduced confidence in the pharmaceutical industry (Clause 2).

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. A complainant had the burden of proving his/her complaint on the balance of probabilities and all complaints were judged on the evidence provided by the parties. It was impossible to know what the representative had said at the interview and equally impossible to know

what materials he/she had used. The company could not identify the representative in question. The Panel noted that according to Eisai a detail aid was to be used and it thus considered the complainant's allegations solely in relation to the detail aid (ref Zonegran-UK2375a).

The Panel noted that the allegation concerned a discussion about the use of Zonegran for weight loss for epileptic patients who were overweight, when in fact weight loss was a side effect for the medicine, not an indication. The Panel noted Section 4.4, Special warnings and precautions for use, of the Zonegran SPC, stated that Zonegran might cause weight loss. If substantial undesirable weight loss occurred discontinuation of Zonegran should be considered. Section 4.7, Undesirable effects, listed anorexia as very common (≥1/10) and weight decrease as common (≥1/100<1/10). The SPC stated that the most common adverse reactions in controlled adjunctive therapy studies were somnolence, dizziness and anorexia.

The Panel noted Eisai's submission that as there was similar efficacy between different anti-epileptic medicines, epileptologists and neurologists took other important factors into account before prescribing such medicines.

The first page of the detail aid provided by Eisai gave details of the indication then in larger type the claim 'Think beyond efficacy ... When looking for additional seizure control ...'. The brand name 'Zonegran' appeared at the bottom right corner of this page, below which was the strap line 'Beyond efficacy'. The third page of the detail aid contained four text boxes with the following statements: 'What about side effects?'; 'Will they be able to stay on treatment?'; 'What happens if they forget a dose?' and 'Will it impact on other treatments?'. The detail aid then went on to address these questions. The 'What about side effects?' section listed treatment emergent adverse events reported by ≥10% Zonegran patients in Brodie *et al* (2005). Weight loss was not mentioned. The final section started on page 12 with two pages answering the question 'Will weight gain be an issue?'. This section was separate from that addressing side effects and consisted of one page showing the results from Wellmer *et al*, which looked at the impact of Zonegran on body mass index (BMI), and a second page with the sub heading 'The majority of patients treated with Zonegran did not experience weight gain'. This page then had four bullet points detailing the issue of weight gain in epileptic patients and the lack of weight gain seen with Zonegran. The fifth and final bullet point was in bold type and stated 'BMI decrease was significant in patients who were overweight prior to Zonegran initiation'. This was also referenced to Wellmer *et al*.

The Panel noted that the representatives' briefing document on Wellmer *et al* (ref Zonegran-UK2373) had the same title as the paper, 'The impact of zonisamide on weight. A clinical study in 103 patients with epilepsy' and was labelled '(internal use only)'. It covered the objective, design, results and conclusion of the study. Wellmer *et al* did not mention the type of epilepsy and as noted in the briefing material it was possible that some patients were outside the Zonegran indication. The conclusion noted on the briefing document stated 'In this retrospective study, zonisamide reduced weight in 35% of patients, particularly those who were overweight prior to treatment. This study helps provide some information regarding the variability and extent of weight change under zonisamide treatment in daily practice, however provides no indication of why patients change weight'. This was followed by bold text which read 'Please note that this is a study in epileptic patients on Zonegran & is not advocating the use of Zonegran as a weight loss drug'. There was then further bold text in a box which stated 'This article is for your information and is not to be distributed proactively. Should you receive a request for a copy of this article, please contact Medical Information'. There did not appear to be a briefing document for the detail aid.

The Panel noted that in describing the study limitations, Wellmer *et al* noted that the retrospective design did not allow controlling variables such as intended weight loss through fasting. It suggested that prospective studies should be carried out. The discussion section noted that weight loss was not restricted to overweight patients and in normal and underweight patients it could be an adverse event. Although weight loss was described as mild to moderate in most cases, in some individuals it reached critical dimensions. The Phase III study, Zonegran 302c, looked at the safety and efficacy of Zonegran. The extract (dated 2005) provided by Eisai concluded that 'There were no marked changes in mean weight in any of the zonisamide or placebo treatment groups. Slightly larger decreases were seen with zonisamide compared with placebo, although the overall effect on weight loss was considered to be mild. There was no evidence to suggest that the weight loss was associated with the dose of zonisamide'. This also stated that weight loss (less than 10%) was more frequent in treated patients (5%, n=498) than placebo (1.7%, n=350).

The Panel considered that contrary to the complainant's allegation Eisai had some data about weight loss in a study which looked specifically at this aspect.

The Panel considered that the theme of the detail aid encouraged prescribers to consider factors other than seizure control when deciding which treatment to prescribe for patients who needed adjunctive therapy. This was not necessarily unacceptable as factors such as side effects would be relevant to the prescribing decision. However the licensed indication should be clear and overall the discussion of factors other than seizure control should be presented in the context of the indication. By separating in the detail aid the weight loss seen with Zonegran from other side effects, the detail aid might give the impression that Zonegran's indications included weight loss in epileptic patients. This impression was compounded by the fact that there was no mention, other than in the prescribing

information, that anorexia was a common side effect and that the weight gain section was the final one in the detail aid and therefore likely to be the last topic the representative discussed with a health professional before closing the call. Although the statement at the end of the briefing document for Wellmer *et al* emphasised that Zonegran was not a weight loss medicine, it was not sufficiently clear from the Wellmer *et al* briefing document or the detail aid that the medicine should not be promoted to aid weight loss in epileptic patients. Representatives needed very clear, unambiguous guidance in this regard. The Panel was also concerned about the claims in the detail aid referenced to Wellmer *et al*. There was no mention of the study limitations or that it was a retrospective study. There did not appear to be any briefing material for the detail aid. This was unacceptable.

The Panel considered that, taking all the circumstances into account, the detail aid was misleading with regard to Zonegran's effect on weight, and a breach of Clause 7.2 was ruled. The Panel considered that by failing to be clear about Zonegran and weight loss in epilepsy, the detail aid exaggerated the medicine's properties. A breach of Clause 7.10 was ruled. The Panel considered that Eisai had not maintained high standards and a breach of Clause 9.1 was ruled. The Panel noted its rulings above and considered that, taking all the circumstances into account, they did not warrant a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

Complaint received **20 April 2012**

Case completed **20 June 2012**