CONSULTANT NEUROLOGIST v BEACON

Episenta mailing

A consultant neurologist complained that a mailing from Beacon promoting Episenta (prolonged release sodium valproate) included claims that Episenta was bioequivalent to Epilim (sodium valproate; marketed by Sanofi-Aventis) and was interchangeable with it including the modified release formulations (Epilim Chrono). The modified release formulations were not interchangeable for epilepsy and the majority of authorities, including the Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Clinical Excellence (NICE) and various epilepsy guidelines, suggested patients with controlled epilepsy should be prescribed a branded formulation preparation (either named generic or branded) and should not change preparations. A forthcoming article in Drugs and Therapeutics Bulletin was likely to support this view.

The complainant considered that the mailing contradicted the advice that the majority of neurologists currently gave to patients and to GPs about maintaining a named brand supply for patients with epilepsy.

The complainant provided a copy of an article on the relevance of generic prescribing to antiepileptic medicines.

The detailed response from Beacon is given below.

The Panel noted that the Episenta summary of product characteristics (SPC) advised that when changing from sodium valproate enteric coated tablets to Episenta to keep the same daily dose. There was no other advice in the SPC with regard to changing from one anti-epileptic medicine to Episenta.

The Panel noted Beacon's submission that the MHRA had evaluated all the data and concluded that Episenta was bioequivalent to Epilim Chrono.

The Panel noted from the article provided by the complainant that there were concerns about generic prescribing of anti-epileptic medicines.

The Panel noted that two studies by Wangemann compared the bioequivalence of Orfiril 300mg [Episenta] with that of Ergenyl Chrono 300 [Epilim Chrono] in healthy volunteers. Both the single dose study and the five day study concluded [Episenta] met the commonly accepted range of bioequivalence of 80-125% compared with the reference formulation [Epilim Chrono].

The Epilim Chrono SPC stated that it was interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis *in patients where adequate control had been achieved* (emphasis added). The Epilim SPC included similar advice.

It appeared to the Panel that 'interchangeable' in the Epilim SPC meant changing from one product to another for a reason and not the random switching of patients from one brand to another and back again.

Based on the data before it the Panel considered that it was not unreasonable to refer to Episenta and Epilim Chrono being interchangeable as alleged. No breach of the Code was ruled.

A consultant neurologist complained about two letters from Beacon Pharmaceuticals Ltd promoting Episenta (prolonged release valproate).

The mailing at issue had been sent to neurologists and paediatric neurologists. It consisted of a letter (ref 20091021) and a four page leaflet (ref 20091021). The letter included a question 'Would it be useful if [a sodium valproate product] was bioequivalent to, and thus interchangeable with, Epilim or Epilim Chrono?' Followed by a statement that Episenta 'can help achieve these outcomes'. The leaflet included the claims 'Episenta is bioequivalent to Epilim Chrono' and 'Episenta is interchangeable with other conventional or prolonged release formulations of valproate on an equivalent daily dosage basis'.

Sanofi-Aventis marketed Epilim and Epilim Chrono (controlled release sodium valproate).

COMPLAINT

The complainant noted that the letters stated that Episenta was bioequivalent to Epilim and was interchangeable with it including the modified release formulations. The modified release formulations were not interchangeable for epilepsy and the majority of authorities, including the Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Clinical Excellence (NICE) and various epilepsy guidelines, suggested patients with controlled epilepsy should be prescribed a branded formulation preparation (either named generic or branded) and should not change preparations. A forthcoming article in Drugs and Therapeutics Bulletin was likely to support this view.

The complainant considered that the letters contradicted the advice that the majority of neurologists currently gave to patients and to GPs

about maintaining a named brand supply for patients with epilepsy.

The complainant provided a copy of an article on the relevance of generic prescribing to antiepileptic medicines.

When writing to Beacon, the Authority asked it to respond in relation to Clause 7.2 of the Code.

RESPONSE

Beacon noted that the complainant referred to two letters it had sent and provided a copy of one of them. Beacon had sent several mailings in 2009 to all neurologists or paediatric neurologists involved in the management of epilepsy. Despite the wide distribution of these mailings Beacon had received no other enquiries or complaints related to this issue. The statement at issue was:

> **'Episenta is bioequivalent to Epilim Chrono**
> Episenta is interchangeable with other conventional or prolonged release formulations of valproate on an equivalent daily dosage basis.'

Beacon could justify this statement in a number of ways but one of the most relevant was Section 4.2 of the Epilim Chrono summary of product characteristics (SPC), which stated:

'In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.'

Thus the Epilim Chrono SPC supported the view that presentations might be interchangeable. Beacon had discussed various claims which it wanted to make with Sanofi-Aventis in May 2009 and Sanofi-Aventis did not object to the statement above.

Bioequivalence was a key point. Pharmaceuticals in the UK were rigorously assessed by the Medicines and Healthcare products Regulatory Agency (MHRA). In order to gain a marketing authorization for Episenta, Beacon had to establish that it was 'essentially similar' to a reference brand product. One key aspect of essential similarity was bioequivalence.

Two studies were undertaken by Wangemann (1998); one compared the pharmacokinetics of single dose Episenta and Epilim Chrono and the other evaluated steady state kinetics after 5 days' dosing. The author concluded that the presentations did not differ with respect to the rate or extent of absorption.

The MHRA had evaluated all of the available pharmacokinetic data for Episenta capsules and sachets and concluded that it was bioequivalent with Epilim Chrono. The Episenta marketing authorization was granted on the grounds that it was 'essentially similar' to and thus interchangeable with Epilim Chrono.

The complainant mentioned the NICE guidelines. The relevant guideline was Clinical Guideline 20, October 2004, and there were few references made to the point of debate.

Section 4.8.8 of the full guide stated:

> 'Changing the formulation or brand of AED [anti-epileptic drug] is not recommended because different preparations may vary in bioavailability or have different pharmacokinetic profiles and, thus, increased potential for reduced effect or excessive side effects.'

This statement carried the lowest D grade recommendation and so was based directly on level 4 evidence or extrapolated from levels 1, 2, or 3.

Beacon submitted that the issue of generic prescribing was not evaluated by NICE as summarised in the following section:

> '11.1.6 Generic prescribing
> This was not a key clinical question, and therefore no evidence review was undertaken. This is an important issue in the prescribing of AEDs, and the prescriber is advised to consult the BNF [British National Formulary] for specific advice for different AEDs. For example, for carbamazepine, the BNF states that 'different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing the formulation'; for phenytoin, that 'on the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients'.'

Comments in the BNF on the variable bioavailability of AEDs were restricted to just two products, carbamazepine and phenytoin. The BNF entries were as follows:

> Carbamazepine
> 'Different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing the formulation'.
>
> Phenytoin Non Proprietary
> 'On the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients'.

Beacon had not found substantive evidence to support variable bioavailability that was relevant to

products in the UK, even for carbamazepine or phenytoin. The article provided by the complainant supported the view that most evidence was either anecdotal or from uncontrolled studies. Notwithstanding this Beacon supported the view that branded products should be prescribed for patients with epilepsy, particularly where this might affect concordance. Beacon believed this was an important issue for these patients as non-adherence could have serious consequences. Thus, Beacon believed it agreed with the complainant and the main sentiment within the article provided by the complainant.

Beacon emphasised that it did not advocate random switching of patients from one brand of sodium valproate to another, and nor was this stated in its materials. However, a physician might consider changing a patient from another brand of sodium valproate to Episenta where poor adherence might be contributing to poor symptom control. This was the clear message within Beacon's mailing. The simple once daily, night time dose of Episenta coupled with its easy to swallow presentation might be useful attributes in engendering concordance.

Stefan (2006) switched patients from either Epilim or Epilim Chrono to Episenta and concluded:

'It is notable that the number of seizures in more than 90% of patients who were already treated with sustained release valproate (BD) was reduced even further by the switch to the evening dosage regimen. This is presumably due to better compliance.'

The claim regarding bioequivalence was entirely in line with the marketing authorization and therefore complied with the Code.

PANEL RULING

The Panel noted that the Episenta SPC advised that when changing from sodium valproate enteric coated tablets to Episenta to keep the same daily dose. There was no other advice in the SPC with regard to changing from one anti-epileptic medicine to Episenta.

The Panel noted Beacon's submission that the MHRA had evaluated all the data and concluded that Episenta was bioequivalent to Epilim Chrono.

The Panel noted from the article provided by the complainant that there were concerns about generic prescribing of anti-epileptic medicines.

The Panel noted that both Wangemann studies compared the bioequivalence of Orfiril 300mg [Episenta] with that of Ergenyl Chrono 300 [Epilim Chrono] in healthy volunteers. Both the single dose study and the five day study concluded [Episenta] met the commonly accepted range of bioequivalence of 80-125% compared with the reference formulation [Epilim Chrono].

The Epilim Chrono SPC stated that it was interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis **in patients where adequate control had been achieved** (emphasis added). The Epilim SPC included similar advice.

It appeared to the Panel that 'interchangeable' in the Epilim SPC meant changing from one product to another for a reason and not the random switching of patients from one brand to another and back again.

Based on the data before it the Panel considered that it was not unreasonable to refer to Episenta and Epilim Chrono being interchangeable as alleged. No breach of Clause 7.2 was ruled.

During its consideration of this case the Panel noted that the claim in the material that Episenta was interchangeable with other conventional or prolonged release formulation was referenced to the Epilim SPC. The Panel was concerned that the claim implied that the Epilim SPC specifically referred to Episenta which was not so. Further, the Epilim SPC statement referred only to interchangeability in patients who were adequately controlled; the claim in the Episenta promotional material did not refer to adequately controlled patients. The Panel requested that Beacon be advised of its concerns.

Complaint received **8 December 2009**

Case completed **8 February 2010**