

GALEN v IVAX

Promotion of Mucodyne

Galen complained about the promotion of Mucodyne (carbocysteine) by Ivax alleging that it was inappropriate to cite Allegra *et al* (2006) in support of several claims for the product. Allegra *et al* studied Fluifort, a once daily oral dose of 2700mg of carbocysteine lysine salt monohydrate (equivalent to 1409mg of carbocysteine) for the prevention of acute exacerbations of chronic obstructive bronchitis. Mucodyne (carbocysteine), however, was licensed for oral administration in a dose of 2250mg, reducing to 1500mg, daily in divided doses. The dose of carbocysteine administered as Fluifort was thus not the same as that derived from the recommended doses of Mucodyne. Consequently, it was unacceptable to rely on clinical efficacy data generated on once daily doses of Fluifort to claim efficacy for multiple daily doses of Mucodyne.

In an advertisement headed 'Appearances can be deceiving' Allegra *et al* was cited as evidence that 'Mucodyne reduces the hypersecretion and viscosity of mucus, thereby making it easier for the patient to clear mucus from the bronchial tree through expectoration', 'Use of Mucodyne results in: Carbocysteine vs placebo n=441, 43% reduction in days with acute illness p< 0.01, 40% reduction in antibiotic consumption p< 0.02, 51% (over two months) increase in delay to first exacerbation p=0.028' and Mucodyne 'Clears mucus to reduce COPD exacerbations'.

Galen alleged the absence of bridging pharmacokinetic, bioequivalence or clinical efficacy data rendered the claims misleading and in breach of the Code. Claiming an equivalent therapeutic response of Mucodyne to Fluifort in Allegra *et al*, exaggerated the risk/benefit ratio.

The Panel considered that Allegra *et al* studied a product which was in a different form, given in a different dose and with a different dosage schedule from Mucodyne. No data had been provided to show similarity between the product used in Allegra *et al* and Mucodyne. Thus in the Panel's view it was misleading to imply that Mucodyne would produce the results reported in Allegra *et al*.

The Panel considered it misleading to cite Allegra *et al* in support of the claim 'Mucodyne reduces the hypersecretion and viscosity of mucus thereby making it easier for the patient to clear mucus from the bronchial tree through expectoration'. Thus the Panel ruled a breach of the Code. The Panel did not consider that the reference to Allegra *et al* necessarily meant that the claim was not capable of substantiation or that the properties of Mucodyne had been exaggerated. No breaches of the Code were ruled.

The Panel noted the use of data from Allegra *et al* and considered that the advertisement implied that Allegra *et al* had shown that treatment with Mucodyne led to a 43% reduction in days with acute illness, a 40% decrease in antibiotic consumption and a 51% increase in delay to first exacerbation. This was not so. No data on Mucodyne had been provided. The Panel ruled breaches of the Code.

The Panel noted the claim that Mucodyne 'Clears mucus to reduce COPD exacerbations' and considered that it was misleading to cite Allegra *et al* in support of the claim which

was specifically for Mucodyne. Thus the Panel ruled breaches of the Code. The Panel considered that its ruling also applied to two advertisements and the detail aid which also included the claim.

Galen Limited complained about the promotion of Mucodyne (carbocysteine) by Ivax Pharmaceuticals UK Limited. The items at issue were three journal advertisements (refs IV/MD/ADV1/01/06, IV/MD/ADV2/01/06 ad IV/MD/AD/11/05) and a leaflet (ref IV/MD/DETAIL/LP/08/05).

COMPLAINT

Galen alleged that it was inappropriate to cite Allegra *et al* (2006) in support of several claims for Mucodyne because:

- Allegra *et al* studied the effectiveness of Fluifort (carbocysteine lysine salt monohydrate) (available in Italy) in the prevention of acute exacerbations of chronic obstructive bronchitis. Fluifort was given as a once daily oral dose of 2700mg. An English translation of the Fluifort summary of product characteristics (SPC) was provided.
- Mucodyne contained carbocysteine, not the lysine salt monohydrate, and was licensed for oral administration in a dose of 2250mg, reducing to 1500mg, daily in divided doses.
- The relative molecular weight of carbocysteine was 179.20, that of carbocysteine lysine was 343.39. Consequently, a dose of 2700mg of carbocysteine lysine monohydrate was equivalent to 1409mg of carbocysteine.
- It was evident that taking the equivalent of 1409mg of carbocysteine once a day was not identical to taking 2250mg daily in divided doses or 1500mg daily in divided doses. Consequently, it was unacceptable to rely on clinical efficacy data generated on once daily doses of 1409mg of carbocysteine in order to claim efficacy for multiple daily doses totalling 2250mg or 1500mg of carbocysteine.
- Despite repeated requests, Ivax had not provided bridging pharmacokinetic, bioequivalence or clinical efficacy data to demonstrate that once daily dosing of 1409mg carbocysteine was identical to multiple daily dosing totalling 2250mg / 1500mg carbocysteine.

As the basis of its complaint, Galen noted that an advertisement headed 'Appearances can be deceiving' (ref IV/MD/ADV1/01/06) featured a number of claims referenced to Allegra *et al*:

(a) 'Mucodyne reduces the hypersecretion and viscosity of mucus, thereby making it easier for the patient to clear mucus from the bronchial tree through expectoration.'

(b) 'Use of Mucodyne results in: Carbocysteine vs placebo n=441, 43% reduction in days with acute illness p< 0.01, 40% reduction in antibiotic consumption p< 0.02, 51% (over two months) increase in delay to first exacerbation p=0.028.'

(c) Mucodyne 'Clears mucus to reduce COPD exacerbations'. (This claim was also featured in an advertisement headed 'Not everything needs to be this difficult' (ref IV/MD/ADV2/01/06), advertisement headed 'A clear way ahead in COPD' (ref IV/MD/AD/11/05), and detail aid (ref IV/MD/DETAIL/LP/03/06)

Galen alleged the claims breached Clause 7.2 of the Code. The absence of bridging pharmacokinetic, bioequivalence or clinical efficacy data to demonstrate once daily dosing of 1409mg carbocysteine was identical to multiple daily dosing totalling 2250mg/1500mg carbocysteine was viewed by Galen as sufficient grounds for this breach.

In addition, the claims did not comply with Clause 7.4. This would be rectified through provision of the relevant bridging data mentioned above.

By claiming an equivalent therapeutic response of Mucodyne to Fluifort in the Allegra *et al* paper, Clause 7.10 was contravened as the risk/benefit ratio had been exaggerated by adopting the claims of Fluifort.

In conclusion, Galen believed that the claims were inadequately supported by an unsuitable single source (Allegra *et al*) which formed the basis of several statements that were scientifically unjustifiable. Ivax had not provided bridging pharmacokinetic, bioequivalence or clinical efficacy data to demonstrate that once daily dosing of 1409mg carbocysteine was identical to multiple daily dosing totalling 2250mg/1500mg carbocysteine. Galen alleged that the material was inaccurate, unsubstantiated and misleading, in breach of Clauses 7.2, 7.4 and 7.10. Ivax had failed to substantiate its claims and had also refused to withdraw these items.

RESPONSE

Ivax noted that Galen had stated that Allegra *et al* had used the Italian product, Fluifort, and that the SPC had been provided. This was incorrect as Allegra *et al* used a granulated product and not the commercialised syrup formulation from the SPC provided. The valid SPC had not been provided but Ivax noted that the SPC that it received stated that there was no difference between different dose forms.

Ivax noted that the statement from Galen that 'Mucodyne contains carbocysteine, not the lysine salt monohydrate and is licensed for oral administration in a dose of 2250mg, reducing to 1500mg, daily in divided doses', was correct as it related to Mucodyne but the SPC was incomplete as the sections relating to dosage were omitted. A complete Mucodyne SPC was provided.

Ivax noted that Galen had calculated the weight of carbocysteine in the carbocysteine lysine monohydrate Italian granulated product by simply using the molecular weight and the presumed weight of active in the sachet. Ivax believed that this was

misleading as it ignored the excipient content; Allegra *et al* did not make it clear if the 2700mg referred to weight of the active or the overall weight of the sachet. In general, granular lysine salts had significant excipient content to make them stable. Ivax therefore could not confirm or refute this particular Galen statement but Ivax already presented this concern to Galen in writing.

Ivax noted Galen's statement that 'It is evident that taking the equivalent of 1409mg of carbocysteine lysine once a day was not identical to taking 2250mg daily in divided doses, or 1500mg daily in divided doses. Consequently, it was unacceptable to rely on clinical efficacy data generated on once daily doses of 1409mg of carbocysteine lysine in order to claim efficacy for multiple daily doses totalling 2250mg or 1500mg of Mucodyne (carbocysteine)'. This statement claimed that it was evident that the compounds were different. Ivax believed this to be misleading, because when medicines were compared, it was clear in the UK regulations that only relevant comparisons must be made and this had to take into account the absorption process and the active compound found in the plasma.

Lysine had been used for many years to increase the solubility and absorption of molecules and to reduce the gastrointestinal side effects for molecules such as aspirin. In the absorption process, the lysine was cleaved either at the site of absorption or in the plasma soon after absorption. In the case of lysine salts of carbocysteine, the molecule was well absorbed with or without lysine and as with other lysine derivatives, the lysine was inevitably cleaved leaving active carbocysteine in the plasma. This was clearly indicated on the Fluifort Syrup SPC supplied by Galen, which stated in section 5.2 that:

'Carbocysteine lysine is rapidly absorbed after the oral administration of a dose of 2.7g. The plasma peak is obtained after 1.5-2hrs, with a C_{max} of 11.2mcg/ml. The AUC is 43.3mcg/ml/hr. The pharmacokinetic curve of carbocysteine lysine is described by an open one compartment model. The volume of distribution is 60.4 litres.

The active substance has particular tropism for human pulmonary tissues, with a C_{max} and a $T_{1/2}$ in the mucus of 3.5mcg/ml and 1.8 hours respectively (dose at 2gm/day). A proportion of the active substance is also present in measurable concentrations in the mucus of the paranasal sinuses and ear for up to 8 hours after administration.

Carbocysteine lysine is eliminated with a plasma half life of about 1.5 hours.

The active substance and its metabolites are essentially eliminated via the kidneys. About 30-60% of the administered dose is excreted unchanged in the urine and the remainder is excreted in the form of various metabolites.

The bioavailability of carbocysteine lysine does not vary from one pharmaceutical form to another.'

The Fluifort SPC clearly stated that the lysine salt was absorbed, and that carbocysteine was the active form and that the bioavailability of carbocysteine was the same for different pharmaceutical forms.

Ivax submitted that Galen's statement that Ivax had not provided bridging pharmacokinetic, bioequivalence or clinical efficacy data to demonstrate that once daily dosing of 1409mg carbocysteine lysine was identical to multiple daily dosing totalling 2250mg/1500mg Mucodyne (carbocysteine) was not true. Ivax had provided a detailed response to each of the Galen letters and in Ivax's letter of 4 August, a summary of the pharmacokinetic data was presented on the two SPC documents. Galen requested additional data, but this was included in the documents it had submitted in its complaint to the Authority.

As these data were the SPC and thus formed part of the licence documentation, Ivax was confident that the data were correct and in the absence of the SPC for the granulate product, Ivax assumed that the syrup had a similar pharmacokinetic profile as demonstrated in the Fluifort SPC.

When Ivax compared the pharmacokinetic profile of Mucodyne and carbocysteine lysine, it was seen that the profiles were virtually identical with a significant inter-individual variability. Ivax referred to a comparative table which provided evidence that 2.7g of carbocysteine lysine provided the same drug exposure as defined by area under the curve (AUC) as Mucodyne (carbocysteine). This was refuted in a letter from Galen on 21 September but in Ivax's response of 10 October, a full response was provided as the papers that were quoted were misrepresented.

When making a comparison, it was also important to compare the clinical efficacy in clinical studies. On 4 August, Ivax gave Galen details of a systematic meta-analysis review published in 2006 by the Cochrane collaboration that supported the conclusion of Poole and Black (1996). In this review, all clinical trials that met the selection criteria were discussed. In the results of this analysis, it was clearly demonstrated that whichever end point was reviewed, there was a consistent benefit from carbocysteine and that no additional efficacy was provided by any of the formulations of either N-acetylcysteine, carbocysteine lysine or Mucodyne carbocysteine.

Ivax submitted that the data included above clearly demonstrated that:

- Carbocysteine was the active compound in the plasma from both carbocysteine lysine and Mucodyne.
- Both products had similar drug exposure from doses of 750mg of Mucodyne (carbocysteine) and 2.7g of carbocysteine lysine.
- There were three formulations marketed of carbocysteine and they had been demonstrated to provide the same efficacy with no additional benefit conferred by any one formulation over the other by the Cochrane meta-analysis.
- The different carbocysteine formulations were regarded as synonyms as stated in the National Institute for Health and Clinical Excellence (NICE) handbook for general practitioners.
- The data required to support this position had already been provided to Galen.

Ivax therefore believed that its representation of the data in the material in question was appropriate and was supported by published data.

To provide a fair and accurate assessment, the exact wording of the Galen complaint and Ivax's detailed comments were listed, followed by a conclusion for each item.

1 Advertisement headed 'Appearances can be deceiving'

Galen alleged that Allegra *et al* was cited as proof that Mucodyne (carbocysteine) reduced the hypersecretion and viscosity of mucus from the bronchial tree through expectoration.

In this advertorial, the references for each paragraph were provided at the end, so as not to interrupt the text flow and to ensure the reference numbers were clearly visible. In its complaint, Galen omitted the complete text from this section of the advertisement, which was:

'Mucodyne is a class of treatment called mucolytics and is used for the treatment of respiratory tract disorders, which are characterised by excess mucus. Mucodyne reduces the hypersecretion and viscosity of mucus, thereby making it easier for patients to clear mucus from the bronchial tree through expectoration.'

This advertisement was written in the style where references were provided at the end of each paragraph so as not to interrupt the text. The paragraph in question was clearly supported by two references and not one as suggested by Galen.

The first reference was Allegra *et al* which was used to support the statement relating to mucolytics and their action. The specific comments relating to Mucodyne (carbocysteine) were supported by the Mucodyne SPC. Additionally, the prescribing information was also included.

Ivax therefore believed that this paragraph was appropriately referenced and was true and accurate. It did not believe it was in breach of the Code.

Galen stated that use of Mucodyne in accordance with the terms of the SPC and in particular the licensed posology would result in a 43% reduction in days with acute illness, a 40% reduction in antibiotic consumption and a 51% increase, over 2 months, in delay to first exacerbation.

Ivax believed that this statement was incorrect. The diagram described was clearly labelled Carbocysteine vs placebo with the Allegra *et al* reference. This statement was correct and true as carbocysteine was the active compound as stated on the Fluifort SPC.

The diagram was clearly labelled, as indicating that the study compared the effect of carbocysteine vs placebo. Ivax had already demonstrated that according to the SPC for carbocysteine lysine, the active ingredient in the plasma was carbocysteine and that the AUC for the dose used of 2.7g provided a similar AUC to carbocysteine derived from Mucodyne at a dose of 750mg.

As AUC was accepted as a measure of drug exposure, Ivax concluded that the two formulations would

provide a similar clinical effect. This was supported by the conclusions of the Cochrane Review that studied all forms of carbocysteine and no benefit in either efficacy response or dose response was seen for any of the formulations.

Ivax therefore concluded that this statement in the advertisement was written appropriately and was supported by references and it did not believe that it was in breach of the Code.

In relation to the claim that Mucodyne (carbocysteine) 'Clears mucus to reduce COPD exacerbations', Ivax stated that immediately above this statement was the Mucodyne logo and the indication that it contained carbocysteine which was clearly stated by Allegra *et al* paper to have these effects.

In view of the content of this advertisement and full data provided, Ivax believed that the data were provided in a balanced manner, were fully referenced and adequate data was provided for the health professional to be able to determine their own conclusion. In view of the comparative pharmacokinetics provided in the SPC, Ivax did not believe that this was a breach of the Code.

2 Advertisement headed 'Not everything needs to be this difficult'

The complaint failed to take into account the complete text from the advertisement and was taken out of context. It was also presented in a manner that failed to present the data in an accurate manner.

Allegra *et al* was used on three occasions in the advertorial.

The statement 'Mucodyne is a mucolytic agent and affects mucus-producing cells to reduce hypersecretion and viscosity of secretions, aiding elimination of mucus from the bronchial tree' was supported by two references. The Mucodyne SPC to support the Mucodyne element and Allegra *et al* to support the additional statements relating to mucolytics.

The statement 'Patients with excessive mucus production need to receive a higher starting dose of Mucodyne. The treatment is reviewed after a satisfactory response has been achieved (e.g. 4-6 weeks) after which a lower maintenance dose of Mucodyne can be taken for the duration of the troublesome symptoms' was clearly in agreement with the Mucodyne SPC and thus was consistent with the licence. As this advertorial contained prescribing information and was in compliance with the licence, Ivax did not add the SPC reference to all lines of text as this was unnecessary.

Allegra *et al* was used as it contained carbocysteine that produced a similar AUC to Mucodyne (carbocysteine) and the study demonstrated that treatment should be assessed after a 4-6 week period.

The statement Mucodyne (carbocysteine) 'Clears mucus to reduce COPD exacerbations' included the Mucodyne logo and was in accordance with the Mucodyne licence, therefore as above the SPC was not required to be referenced as API was included. The reference to Allegra *et al* was included to ensure

consistency as it studied the effect of carbocysteine in patients with COPD.

When the text was reviewed in its entirety and the balance of the advertisement was taken into account, Ivax did not believe that the material breached the Code. All statements were consistent with both the Mucodyne SPC and Allegra *et al* and thus Ivax concluded it was appropriately discussed.

Ivax was also concerned that Galen continually referred to an assumed carbocysteine content even when no confirmatory data was available and when the documents it had provided clearly demonstrated that the dose used by Allegra *et al* provided the AUC and hence drug exposure equivalent to Mucodyne (carbocysteine).

3 Advertisement headed 'A clear way ahead in COPD'

This complaint was as the previous one as it contained prescribing information and statements made agreed with the Mucodyne SPC and Allegra *et al* and therefore would not be discussed separately.

4 Detail aid

The detail aid had never been amongst the list of items on which Galen based its complaint. This complaint was the first indication that Galen wished to make a complaint against this item, however, Ivax's response was the same as the 'Appearances can be deceiving' advertisement and the 'A clear way ahead in COPD' advertisement.

PANEL RULING

The Panel noted that Allegra *et al* reported the results of a placebo controlled trial designed to assess the prevention of acute exacerbations of COPD with carbocysteine lysine salt monohydrate. The active treatment consisted of a granular formulation of carbocysteine lysine salt monohydrate plus excipients, which was dissolved in about 50ml of water before intake once a day in the morning. Patients were not given the ready made syrup formulation described in the Fluifort SPC provided by Galen. This SPC stated that 'the bioavailability of carbocysteine does not vary from one pharmaceutical form to another'. The Panel considered that this statement might apply to carbocysteine lysine salt monohydrate. There was no similar statement in the Mucodyne SPC. The Panel considered that Allegra *et al* studied a product which was in a different form, given in a different dose and with a different dosage schedule from Mucodyne. No data had been provided to show similarity between the product used in Allegra *et al* and Mucodyne. Thus in the Panel's view it was misleading to imply that Mucodyne would produce the results reported in Allegra *et al*.

The Panel considered each of the items as follows.

1 Advertisement headed 'Appearances can be deceiving'

a) As noted above the Panel considered it misleading to cite Allegra *et al* in support of the claim 'Mucodyne reduces the hypersecretion and viscosity of mucus

thereby making it easier for the patient to clear mucus from the bronchial tree through expectoration'. Thus the Panel ruled a breach of Clause 7.2 of the Code. The Panel did not consider that the reference to Allegra *et al* necessarily meant that the claim was not capable of substantiation nor that the properties of Mucodyne had been exaggerated. No breach of Clauses 7.4 and 7.10 of the Code was ruled.

b) Use of data from Allegra *et al*

The Panel considered that the advertisement gave the impression that Allegra *et al* had shown that treatment with Mucodyne led to a 43% reduction in days with acute illness, a 40% decrease in antibiotic consumption and a 51% increase in delay to first exacerbation. This was not so. No data on Mucodyne had been provided. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10.

c) Claim that Mucodyne 'Clears mucus to reduce COPD exacerbations'

The Panel considered that it was misleading to cite Allegra *et al* in support of the claim which was specifically for Mucodyne. Thus the Panel ruled breaches of Clauses 7.2, 7.4 and 7.10.

2 Advertisements and detail aid including the claim 'Clears mucus to reduce COPD exacerbations'

The Panel considered that its ruling at 1(c) above applied to the two advertisements and the detail aid.

Complaint received 2 November 2006

Case completed 10 January 2007