CASE AUTH/2367/10/10

GENERAL PRACTICTIONER AND GP PRESCRIBING LEAD v TAKEDA

Use of inverted black triangle

A general practitioner and GP prescribing lead, complained about a two page advertisement for Amias (candesartan), issued by Takeda, which had appeared in 'Guidelines in Practice', October 2010. The advertisement featured a table of data comparing clinical aspects of the use of candesartan, losartan and valsartan. One of the aspects compared was whether the medicines were subject to special reporting requirements with regard to adverse events ie were they 'black triangle' medicines? The table showed that both losartan and valsartan were black triangle medicines whereas candesartan was not.

The complainant stated that the first page of the advertisement was misleading. The advertisement placed a black triangle next to the generic name losartan. Generic losartan did not carry a black triangle warning in the BNF while Cozaar, the branded product did. The reference clarifying that the triangle related to the branded product was on the second page of the advertisement. The complainant alleged that the advertisement was misleading as it suggested that losartan was a black triangle medicine which was not so.

The detailed response from Takeda is given below.

The Panel noted that the advertisement was headed 'The Facts: ARBs [angiotensin receptor blockers] in Chronic Heart Failure'. The Panel noted Takeda's submission that a black triangle had been reinstated on Cozaar when it was approved for use in patients with chronic heart failure.

The Panel noted from the electronic medicines compendium (www.medicines.org.uk) that generic forms of losartan were now available. The summary of product characteristics (SPCs) for these generics stated that they were indicated for chronic heart failure but did not indicate that they were black triangle medicines.

The Panel considered that the position was confusing. The list included in the MHRA's list of new drugs under intensive surveillance, October 2010, was not clear as to whether the black triangle for losartan applied to the generic form or only to the brand ie Cozaar. If the black triangle had been reinstated on Cozaar when it was approved for use in chronic heart failure then it would seem logical to expect all forms of losartan so indicated to also carry the black triangle. In a publication from the MHRA, 'New drugs and vaccines under intensive surveillance' the Agency requested emails from companies if they held marketing authorizations for a medicine that had had a black triangle reinstated. The Panel had no way of knowing if the manufacturers of generic losartan had emailed the MHRA and the outcome of such communication. By whatever means it appeared that the generic losartans, although approved for use in heart failure, were not black triangle medicines. Conversely, however, the advertisement implied that all forms of losartan were black triangle medicines. An asterisk beside the symbol referred the reader to a list of references which appeared overleaf and which made it clear that the black triangle related to the Cozaar SPC. The Panel noted that the claims could not be qualified by the use of a footnote or the like. The Panel thus considered that the implication that all forms of losartan were black triangle medicines was misleading and in that regard it ruled a breach of the Code.

Upon appeal by Takeda the Appeal Board noted that the first page of the two page advertisement featured a table in which six clinical attributes of the use of candesartan, losartan and valsartan in heart failure were compared. For the most part, ticks were shown for candesartan and crosses for losartan and valsartan. The seventh and final attribute to be compared was 'Black triangle drug' for which candesartan received a cross and losartan and valsartan each received a tick. In the column headings to the table, losartan and valsartan each had a black triangle next to their name. In the Appeal Board's view, Takeda had chosen to highlight the possession, or otherwise, of a black triangle as a means to differentiate the products. The Appeal Board noted that the Code did not require companies to display the black triangle against the names of competitor products. If, however, they chose to do so it must be in a manner which complied with the Code. The Appeal Board considered that the overall aim of the advertisement was to encourage the prescription of Amias, not the reporting of adverse events with losartan or valsartan. By highlighting the black triangle status of the three medicines, prescribers might be inclined to favour candesartan because it was not subject to enhanced surveillance and in that regard might be perceived by some to have patient safety benefits.

The Appeal Board noted that the black triangle status of generic losartan was confusing and appeared illogical given that branded losartan (Cozaar) was subject to enhanced surveillance. The Appeal Board noted Takeda's submission that as the black triangle could now be reinstated for well established medicines which received a new

indication, there was a possibility that such reinstatement could still be in place when generic versions became available. Takeda accepted that there was an inconsistency in the labelling of generic losartan. The complainant had pointed out that generic losartan did not carry a black triangle warning in the BNF whereas Cozaar did.

The Appeal Board was concerned about patient safety but considered that its role was to consider the matter in relation to the Code which required information and claims in advertisements to be accurate. Contrary to the impression given by the advertisement at issue not all formulations of losartan were officially designated as black triangle medicines. Although the black triangle next to losartan in the table heading was referenced to the Cozaar SPC, the Appeal Board noted that claims could not be qualified by footnotes and the like. The Appeal Board considered that the advertisement was misleading as alleged and upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful.

The Panel noted that the Code required that where the pages of a two page advertisement were not facing, neither must be false or misleading when read in isolation. The Panel noted that the reference to the Cozaar SPC was overleaf from the table of data in question and further noted its comments above about the use of footnotes to qualify claims. However, given its ruling of a breach of the Code in relation to page 1 of the advertisement, the Panel did not consider that this meant that it was false or misleading when read in isolation. No breach of the Code was ruled.

The Panel noted that the advertisement in question was not an abbreviated advertisement and thus no breach of the requirements of the Code in that regard was ruled.

The Panel noted that prescribing information was an integral part of the advertisement and was included on the second page. No breach of the Code was ruled.

A general practitioner and GP prescribing lead, complained about a two page advertisement (ref TA101054) for Amias (candesartan), issued by Takeda UK Ltd, which had appeared in 'Guidelines in Practice', October 2010. The advertisement featured a table of data comparing clinical aspects of the use of candesartan, losartan and valsartan. One of the aspects compared was whether the medicines were subject to special reporting requirements with regard to adverse events ie were they 'black triangle' medicines? The table showed that both losartan and valsartan were black triangle medicines whereas candesartan was not.

COMPLAINT

The complainant stated that the first page of the advertisement was misleading and breached Clauses 6.1, 7.2, and possibly 5.7, of the Code.

The advertisement placed a black triangle next to the generic name losartan. Generic losartan did not carry a black triangle warning in the BNF while Cozaar, the branded product did. The reference clarifying that the triangle related to the branded product was on the second page of the advertisement.

The complainant alleged that the advertisement was misleading as it suggested that losartan was a black triangle medicine which was not so.

When writing to Takeda, the Authority asked it to respond in relation to Clause 4.1 of the Code in addition to the clauses cited by the complainant.

RESPONSE

Takeda stated that it was concerned that a health professional considered that the advertisement was misleading and it took this allegation very seriously. It was not Takeda's intention for any of its materials to be misleading and it had thoroughly reviewed the advertisement at issue with particular focus on Clauses 7.2, 6.1 and 5.7. The Authority requested that Takeda also consider the requirements of Clause 4.1. As the complaint was about the use of the black triangle symbol, Takeda wondered if this was a typographical error and should be Clause 4.11. Takeda therefore responded in relation to both Clauses 4.1 and 4.11.

The advertisement in question was a double-sided insert within Guidelines in Practice. On the first page of the advertisement there was a table which included information on the three angiotensin receptor blockers licensed for chronic heart failure (candesartan, losartan and valsartan). A black triangle had been placed beside losartan and valsartan. The complainant had stated that only the Cozaar brand of losartan (Merck Sharp and Dohme) was a black triangle medicine and that the generic versions did not have black triangle status. The information in the table was supported by a reference to the summary of product characteristics (SPC) for Cozaar although in line with Clauses 7.4 and 7.6 there was no absolute requirement to include a reference as the information was not from a published study and therefore Takeda would just be required to substantiate the information if requested.

Takeda stated that for several reasons, it did not agree that only the branded (Cozaar) version of losartan was a black triangle medicine whilst the generic versions were not:

- Within the information provided by the Medicines and Healthcare products Regulatory Agency (MHRA) on black triangle medicines it was clear that it related to an *'active substance'* and not any particular brand or preparation.

- A black triangle could be reinstated to a previously licensed active substance if it had a significant new indication which altered the

established risk/benefit profile or it was approved for use in a new patient population. For losartan (and valsartan), the black triangle was reinstated following the approval of its use in chronic heart failure. The MHRA even included losartan (Cozaar) as an example when explaining about the reinstatement of the black triangle in established medicines. When the black triangle was reinstated for losartan, it was still under patent protection and therefore only available as Cozaar. The patent for Cozaar had since expired, however the MHRA could not be expected to track and follow the patent status for all branded medicines and thus the availability of generic versions. As it was clear that the black triangle related to the *active substance*, rather than a particular brand or preparation, the fact that the MHRA referred to Cozaar was irrelevant.

- The MHRA published a monthly list of all black triangle medicines by trade name and by generic name. As the generic versions did not have a brand name, only Cozaar was listed under trade name.

- The MHRA clearly requested to be emailed by *any* company that held the marketing authorization for a medicine that had the black triangle reinstated due to the product being approved for use in a significantly new indication. This would apply to all companies (including generic companies) that held a marketing authorization for losartan. If a generic company had not done this (and therefore did not show the black triangle on its SPC) it did not negate the fact that the active medicine, losartan, had a black triangle and was subject to enhanced surveillance.

- Importantly, when a generic company applied for a marketing authorization for a generic version of a branded medicine it did so by demonstrating that the generic version was equivalent to the branded version. Once bioequivalence had been demonstrated the company could bridge all the clinical data for the branded version and apply it to the generic version. It would seem only appropriate that any enhanced safety requirements also applied to these bioequivalent generic versions.

- Takeda noted that the purpose of the black triangle being reinstated to an established medicine was to confirm the risk/benefit profile when used in a new indication. This was to ensure patient safety. When GPs prescribed any medicine they generally did so by writing the generic name for that medicine (rather than a brand name). GPs would not know which version of losartan (Cozaar or one of the generics) was actually dispensed to the patient at the pharmacy. It was therefore important that all suspected adverse reactions associated with the use of losartan (generic or branded) in heart failure were reported.

Takeda thus did not believe the advertisement was misleading and in breach of Clauses 6.1, 7.2 and 4.11 as alleged. Furthermore, as this advertisement was not an abbreviated advertisement and prescribing information (which was clear and legible) was provided Takeda did not believe it to be in breach of Clauses 5.7 or 4.1.

PANEL RULING

The Panel noted that the advertisement was headed 'The Facts: ARBs [angiotensin receptor blockers] in Chronic Heart Failure'. The Panel noted Takeda's submission that a black triangle had been reinstated on Cozaar when it was approved for use in patients with chronic heart failure. The Cozaar summary of product characteristics (SPC) stated that the usual initial dose of losartan in heart failure was 12.5mg once daily. The dose should generally be titrated at weekly intervals (ie 12.5mg daily, 25mg daily, 50mg daily) to the usual maintenance dose of 50mg once daily, as tolerated by the patient. Cozaar was available in tablets of 12.5mg, 25mg, 50mg and 100mg.

The Panel noted from the electronic medicines compendium (www.medicines.org.uk) that generic forms of losartan were now available. From a practical point of view some of these could not be used to initiate treatment in chronic heart failure given that generic tablets of 12.5mg were not available. The SPCs for these generics, however, did state that they were indicated for chronic heart failure but did not indicate that they were black triangle medicines.

The Panel considered that the position was confusing. The list included in the MHRA's list of new drugs under intensive surveillance, October 2010, was not clear as to whether the black triangle for losartan applied to the generic form or only to the brand ie Cozaar. If the black triangle had been reinstated on Cozaar when it was approved for use in chronic heart failure then it would seem logical to expect all forms of losartan so indicated to also carry the black triangle. In a publication from the MHRA, 'New drugs and vaccines under intensive surveillance' the Agency requested emails from companies if they held marketing authorizations for a medicine that had had a black triangle reinstated. The Panel had no way of knowing if the manufacturers of generic losartan had emailed the MHRA and the outcome of such communication. By whatever means it appeared that the generic losartans, although approved for use in heart failure, were not black triangle medicines. Conversely, however, the advertisement implied that all forms of losartan were black triangle medicines. An asterisk beside the symbol referred the reader to a list of references which appeared overleaf and which made it clear that the black triangle related to the Cozaar SPC. The Panel noted that the claims could not be qualified by the use of a footnote or the like. The Panel thus considered that the implication that all forms of losartan were black triangle medicines was misleading and in that regard it ruled a breach of Clause 7.2. This ruling was appealed.

The Panel noted that Clause 6.1 required that where the pages of a two page advertisement were not facing, neither must be false or misleading when read in isolation. The Panel noted that the reference to the Cozaar SPC was overleaf from the table of data in question and further noted its comments above about the use of footnotes to qualify claims. However, given its ruling of a breach of Clause 7.2 in relation to page 1 of the advertisement, the Panel did not consider that this meant that it was false or misleading when read in isolation. No breach of Clause 6.1 was ruled. This ruling was not appealed.

Clause 5.7 related to abbreviated advertisements and required companies to display the black triangle when medicines were subject to special reporting in relation to adverse reactions. The advertisement in question was not an abbreviated advertisement and thus Clause 5 did not apply and so no breach of Clause 5.7 was ruled. This ruling was not appealed. A black triangle had been displayed and so the material met the requirements of Clause 4.11 but the Panel made no ruling on this point as the company had not been asked to respond to it either by the complainant or by the Authority.

The Panel noted that prescribing information was an integral part of the advertisement and was included on the second page. No breach of Clause 4.1 was ruled. This ruling was not appealed.

APPEAL BY TAKEDA

Takeda noted that the Panel had noted that generic forms of losartan were now available (from information obtained from www.medicines.org.uk), but that some of these could not be used to initiate treatment in chronic heart failure given that generic tablets of 12.5mg were not available. The Panel acknowledged that the SPCs for these generics did, however, state that they were indicated for chronic heart failure although they did not indicate that they were black triangle medicines.

Takeda noted that the electronic medicines compendium did not contain the SPCs of all generic forms of losartan available in the UK. On review of the MHRA website there were documents relating to marketing authorizations of at least 13 generic forms of losartan 25mg, many of which did not appear on www.medicines.org.uk. Many of the available generic 25mg tablets had a score line that the tablet could be broken in half ie two 12.5mg doses. When a physician prescribed the initiation dose of losartan for heart failure (12.5mg) the prescription would only be filled with a version of losartan that fulfilled this dosing requirement. This could be with either divisible losartan 25mg tablets or 12.5mg tablets. Takeda further noted that the 12.5mg dose was only a titration dose and should only be given for a week. The dose should then be up-titrated to 25mg once daily for a further week and then to the target maintenance dose of 50mg once daily. All generic forms of losartan were available as tablets of 50mg.

Takeda submitted that as stated by the Panel, there did seem to be some confusion regarding this matter. It was absolutely not clear from the MHRA website whether the black triangle applied only to branded versions of an active substance. Furthermore, the SPC for one of the generic losartans (Dexcel Pharma) referred to the intensive monitoring in relation to the heart failure indication (as per the SPC for Cozaar). Takeda never thought to consider that the requirement of the enhanced safety reporting associated with a black triangle did not extend to all forms of an active substance (ie branded and generic versions of a medicine). If it was clear that a black triangle applied only to a branded product then Takeda would not have included it in the advertisement or alternatively the company would have made specific reference to Cozaar only.

Takeda submitted that when the black triangle was introduced, it was intended to cover the first few years following the introduction of a new active substance onto the UK market (ie a period when there would not be any generic versions available). As the black triangle could now be reinstated for medicines which received a significant new indication, there was the possibility (and as was the case with losartan) where a black triangle was still in place when generic versions became available. This was a new situation however and with more and more mature products receiving indications in new patient populations (eg paediatric licence extensions) close to their patient expiry this was going to become a more common occurrence.

Takeda submitted that the final and most fundamental reason for appealing the ruling was patient safety. The purpose of the black triangle in this instance was to ensure enhanced adverse event reporting requirements when losartan was used in patients with heart failure. This was a newly licensed patient population and the purpose of the black triangle was to collect further important safety data when losartan was used in this patient cohort in clinical practice. A health professional should be encouraged to report all adverse events in this population irrespective of which company manufactured the losartan. Generic versions were required to be equivalent medicines in order to obtain a marketing authorization, and for this reason and the fact that they were lower in price, when a branded product lost its patent protection generics become the most widely dispensed form of a medicine. In November 2010, only 4.5% of the total volume of losartan was branded Cozaar and so if only adverse events related to Cozaar were subject to enhanced reporting then the vast majority of patient safety information that would have been reported under these enhanced requirements would go unreported.

Takeda submitted that within clinical practice, a prescriber would not know what form of losartan (Cozaar or a generic) was going to be dispensed at the local pharmacy. Unless the patient brought their tablets with them the physician would not know whether the enhanced safety reporting requirements

applied to any adverse events experienced by that patient. Therefore, the most stringent safety requirements should apply.

For the reasons stated above, Takeda submitted that it was not misleading to include a black triangle next to the 'losartan' in the advertisement at issue. Takeda submitted that if the Panel's ruling of a breach of Clause 7.2 was upheld it would have a significant impact on the effectiveness of the enhanced safety reporting requirements that related to the inclusion of the black triangle symbol, ultimately impacting patient safety.

COMMENTS FROM THE COMPLAINANT

The complainant reiterated that to label generic losartan as a black triangle medicine was, at best, misleading and clearly in breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted that the first page of the two page advertisement featured a table in which six clinical attributes of the use of candesartan, losartan and valsartan in heart failure were compared. For the most part, ticks were shown for candesartan and crosses for losartan and valsartan. The seventh and final attribute to be compared was 'Black triangle drug' for which candesartan received a cross and losartan and valsartan each received a tick. In the column headings to the table, losartan and valsartan each had a black triangle next to their name. In the Appeal Board's view, Takeda had chosen to highlight the possession, or otherwise, of a black triangle as a means to differentiate the products. The Appeal Board noted that the Code did not require companies to display the black triangle against the names of competitor products. If, however, they chose to do so it must be in a manner which complied with the Code. The Appeal Board considered that the overall aim of the advertisement was to encourage the prescription of Amias, not the reporting of adverse events with losartan or valsartan. By highlighting the black triangle status of the three medicines, prescribers might be inclined to favour candesartan because it was not subject to enhanced surveillance and in that regard might be perceived by some to have patient safety benefits.

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The Appeal Board was concerned about patient safety but considered that its role was to consider the matter in relation to the Code which required information and claims in advertisements to be accurate. Contrary to the impression given by the advertisement at issue not all formulations of losartan were officially designated as black triangle medicines. Although the black triangle next to losartan in the table heading was referenced to the Cozaar SPC, the Appeal Board noted that claims could not be qualified by footnotes and the like. The Appeal Board considered that the advertisement was misleading as alleged and upheld the Panel's ruling of a breach of Clause 7.2. The appeal was thus unsuccessful.

During its consideration of the above the Appeal Board expressed some sympathy for Takeda's position and noted the important role that the black triangle played in the maintenance and monitoring of patient safety. Given its concerns in that regard, the Appeal Board requested that the PMCPA inform the MHRA and the ABPI regulatory expert network about the issues raised in this case and ask the MHRA to clarify the position with some urgency.

Complaint received **27 October 2010**

Case completed **6 April 2011**