Appeal ASMI Complaints Panel Determination 02/14

GlaxoSmithKline Consumer Healthcare Australia Pty Ltd

("GSK")

v

Reckitt Benckiser (Australia) Pty Limited ("RB")

Nurofen Zavance "Headache" marketing campaign

Hearing – 20 March 2015

Arbiter's Determination

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Nurofen Zavance "Headache" marketing campaign

1 This is an appeal from a determination by the ASMI Complaints Panel dated 24 December 2014 in relation to an advertising campaign conducted by RB in respect of Nurofen Zavance.

2 The complaint related to:

- three television commercials
- a YouTube advertisement
- a consumer website
- a digital advertising display
- bus shelter advertising
- print advertisement
- a range of point of sale materials (all directed to consumers)
- three items contained in a show bag provided to pharmacy assistants at the Pharmacy Assistant National Conference held on October 16-18, 2014

3 There were a number of complaints in the original complaint which are not pursued on appeal.

4 The relevant claims for the purpose of the appeal are as follows:

(a) Superiority Claim:

- The pharmacy assistant materials contained the following claims relating to the superior efficacy of standard Nurofen over paracetamol in the relief of tension-type headaches (**TTH**);
- Nurofen is superior to paracetamol for treating TTH

- Nurofen has been shown to be significantly more effective than paracetamol at treating TTH ($p<0.01$)
- More people achieve complete relief at 2 hours from TTH with Nurofen than with paracetamol ($p<0.01$)
- Over 95% of people achieved complete relief from TTH with Nurofen
- More people achieve complete relief from TTH with Nurofen than with paracetamol

(b) Fast Acting Claims:

- Effectively these are claims that Nurofen Zavance (i.e. ibuprofen sodium) provides faster pain relief than does standard ibuprofen in the management of TTH

Superiority claim

5 GSK says that RB has advertised that ibuprofen (i.e. Nurofen) is superior to paracetamol (i.e. Panadol) in the treatment of TTH. GSK says these claims are based upon a single 19 year old study, namely Schachtel et al 1996.[1]

6 GSK says that in considering whether the body of scientific evidence supports that claim, it is necessary to take into account an unpublished study NL9701 which was commissioned by RB (UK). Both the Schachtel and NL9701 studies provide data of head-to-head comparisons of ibuprofen 400mg v paracetamol 1000mg in TTH.

7 GSK does not dispute the fact that Schachtel supports the superiority claim. It says, however, that NL9701 does not do so because it found that ibuprofen is not significantly superior to paracetamol in the management of TTH.

8 The Panel found that because the study NL9701 had not been published and was not peer reviewed, it "*should not displace the results of published and peer reviewed studies*" when assessing advertising claims.[2] It accordingly came to the view that the Schachtel study constituted the body of relevant scientific evidence and therefore that there was no breach of the ASMI code or the TGAC in making the claims.

9 On appeal, GSK puts its argument slightly differently. It says that the relevant data from study NL9701 was published within a review conducted by Moore et al 2014.[3] In argument

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[1] Schachtel BP, Furey SA, Thoden WR. Nonprescription ibuprofen and acetaminophen in the treatment of tension-type headache. *J Clin Pharmacol* 1996 December; 36(12):1120-1125.
[2] Para 49 of the Panel's Determination.
[3] Moore RA, Derry S, Wiffen PJ, Straube S, Bendtsen L. Evidence for efficacy of acute treatment of episodic tension-type headache: methodological critique of randomised trials for oral treatments. *Pain* 2014 August 17.

on appeal, GSK referred to this Moore study as Moore 2014A which was attached as reference 11 to its original appeal.

10 According to the argument developed by GSK, the Moore 2014A study was a systematic review which took into account comparisons of both ibuprofen 400mg and paracetamol 1000mg with placebo. The results (presented in table 3 of the paper) show that there was little difference between those two drugs in the treatment of TTH. GSK further submitted that the results of a systematic literature review that consider the entire available body of evidence carried greater weight than do those of a single study and that therefore the Moore 2014A review ought to be preferred.

11 GSK further submitted that the relevant data from study NL9701 are published within the Moore 2014A systematic review and that effectively meant that NL9701 had been independently peer reviewed and published as part of the data set evaluated in the Moore 2014A systematic review. Accordingly, it followed that the relevant data from study NL9701 showing that ibuprofen was not significantly superior to paracetamol in the management of TTH is available in peer reviewed published literature.

12 In answer to GSK's contentions, RB pointed out that Moore 2014A had accepted that the Schachtel study was of high quality and rated it as 5/5 on the Oxford Quality Scale. GSK further submitted that Schachtel was a randomised controlled trial and accordingly provided level 11 evidence of appropriate study design under the NHMRC guidelines.

13 RB further said that whilst NL9701 formed part of the data set within Moore 2014A, that did not mean it became published or peer reviewed. Further, that it was not uncommon for systematic reviews such as Moore 2014A not to be in harmony with findings from large scale high quality single trials such as Schachtel and that reviews should always be carefully weighed against conflicting evidence from high quality sources.

Determination

14 In its original complaint (at page 18), GSK put its argument this way:

(a) the Moore 2014A study included data from 55 trials and the pooled results showed that paracetamol and ibuprofen had similar efficacy for the primary measure of pain free at 2 hours;

(b) of these reports (i.e. the reports relied upon by Moore 2014A) three provided data of head-to-head comparisons between ibuprofen 400mg and paracetamol 1000mg in TTH. These three reports were Packman et al 2000,[4] Schachtel and NL9701;

(c) the Packman study was to be ignored because it evaluated a liquid gel formulation of ibuprofen as opposed to standard ibuprofen;

[4] Packman B, Packman E, Doyle G, Cooper S, Ashraf E, Koronkiewicz K, Jayawardena S. Solubilized ibuprofen: evaluation of onset, relief, and safety of a novel formulation in the treatment of episodic tension-type headache. *Headache* 2000 July;40(7):561-567.

(d) the two remaining reports, i.e. Schachtel and NL9701 therefore constituted "*the body of evidence on this topic as it relates to the claims being made*". GSK then went on to compare the Schachtel and study NL9701 with a view to persuading the Panel to accept the findings of study NL9701 which it claimed clearly demonstrated that Nurofen was not superior to paracetamol for treating TTH.

15 The Panel, in my view, correctly dismissed GSK's original argument on the basis that it is well accepted that published and peer reviewed studies should not be displaced by unpublished unpeer reviewed studies. The only reservation I would make to this approach would be in circumstances in which there was clear evidence to show that an unpublished study was superior to a published study including reasons why it had not been published and had not been peer reviewed.

16 The argument which was submitted by GSK on appeal to the effect that the Moore 2014A study effectively meant that study NL9701 had acquired the status of a published and peer reviewed study by reason of it having been included in Moore 2014A, was not put in that way to the Panel. In my view, the answer to this argument is to be found by looking at the Moore 2014A study. When one does so, one finds that:

(a) Table 3 of the Moore 2014A study refers to three trials which were taken into account in relation to testing the efficacy of ibuprofen 400mg "*pain free at 2 hours*". Those studies are not specifically identified. Assuming for the moment that GSK is correct when it says that the three studies are Schachtel, NL9701 and Packman:

(i) for the reasons given by GSK, the Packman study is not one which should be taken into account;

(ii) the Moore 2014A study rated Schachtel as having five points on the Oxford scale whereas it rated study NL9701 as at 4 points thus indicating that it did not consider NL9701 to be equal to or superior to the Schachtel study;

(iii) there is nothing whatsoever in the Moore 2014A study to indicate that Moore conducted a peer review of the NL9701 study; and

(iv) there is no specific consideration recorded in the Moore 2014A study of the comparative merits of the Schachtel study as opposed to the merits of the NL9701 study, both of which appear to have come to opposite conclusions;

(b) if in fact the three studies were not the ones identified by GSK, then there is even less in the Moore 2014A study to base an argument that study NL9701 has acquired the status of a published and peer reviewed study.

17 GSK's further argument on appeal that Moore 2014A itself should be regarded as a part of the body of evidence and that therefore when weighed with study NL9701 should, when taken together, outweigh the Schachtel 1996 study, also cannot be correct:

(a) firstly, this argument flies in the face of the argument which GSK presented for the Panel in its original complaint which, as I have said above, was to compare Schachtel and NL9701 as being the only relevant studies (para 14 above and page 18 of GSK's original complaint). If, on GSK's own argument, the NL9701 study and the Schachtel study were the only two studies of the three referred to in table 3 of Moore 2014A which should have been taken into account in reaching the conclusions Moore did, then on GSK's own analysis, one cannot elevate Moore 2014A study to the status of a separate study which when added to study NL9701 would be sufficient to displace the findings in Schachtel 1996;

(b) the Moore 2014A study is a review which rests upon the studies which it purports to review. It cannot be given the status of a separate study when, on GSK's analysis it relied upon the NL9701 study and another inappropriate study (i.e. the Packman study) in reaching its conclusions;

(c) even if GSK were incorrect in its suggestion that the three studies taken into account by Moore 2014A were Schachtel, NL9701 and Packman, there would not be sufficient, in my view, in the Moore 2014A review to elevate it to the status of a separate study which would be required to be compared with Schachtel unless the Moore review clearly indicated why its conclusions were to be preferred to that of Schachtel.

18 It follows that I would reject GSK's appeal on this aspect and uphold the decision of the Panel.

Fast Acting Claims

19 In relation to the claims made by RB that Nurofen Zavance (ibuprofen sodium) provides faster pain relief than does standard ibuprofen in the management of TTH, GSK contends that when the entire available body of scientific evidence is taken into account, these claims are invalid because:

(a) the Panel accepted that the studies by Moore et al 2014[5] [Moore 2014B], Schleier P[6] and Norholt SE[7] which were all published and peer reviewed studies as supporting the "*faster*" and "*quick*" relief claims for Nurofen Zavance versus standard Nurofen in headaches (para 33 of the Panel's Determination);

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[5] Moore RA, Derry S, Straube S, Ireson-Paine J, Wiffen PJ. Validating speed of onset as a key component of good analgesic response in acute pain. *Eur J Pain* 2014 May 22. (Moore 2014B – GSK reference 4),

[6] Schleier P, Prochnau A, Schmidt-Westhausen AM, Peters H, Becker J, Latz T, Jackowski J, Peters EU, Romanos GE, Zahn B, Ludemann J, Maares J, Petersen B. Ibuprofen sodium dehydrate, an ibuprofen formulation with improved absorption characteristics, provides faster and greater pain relief than ibuprofen acid. *Int J Clin Pharmacol Ther* 2007 February; 45(2):89-97.

[7] Norholt SE, Hallmer F, Hartlev J, Pallesen L, Blomlof J, Hansen EJ, Fernandes N, Eriksson L, Pinholt EM. Analgesic efficacy with rapidly absorbed ibuprofen sodium dehydrate in postsurgical dental pain: results from the randomized QUIKK trial. *Int J Clin Pharmacol Ther* 2011 December;49(12):722-729.

(b) the Panel did not accept that the results of unpublished and non-peer reviewed studies should displace the results of published and peer reviewed studies in assessing advertising claims (Panel Determination para 34);

(c) the Moore, Schleier and Norholt studies related to dental pain whereas two unpublished studies which are to be found in ClinicalTrials.gov which is a Government funded public database in the United States are the only two studies that specifically evaluate the speed and onset of ibuprofen sodium versus standard ibuprofen in headaches. These studies are NCT01077973[8] and study NCT01362491[9]. Both of these studies dispute the "*faster in headache*" claim.

20 GSK says that the ClinicalTrials.gov results database is a reliable and scientifically valid source of information and says that the results are not made public until a ClinicalTrials.gov's staff member has reviewed them. However, during the hearing of the appeal, GSK admitted that the studies published in ClinicalTrials.gov were not peer reviewed and was unable to provide any information as to the qualifications of the staff member who is supposed to have reviewed the studies which are included in the database.

21 GSK further submitted that the chances of a clinical trial being published are roughly 50% and that databanks such as ClinicalTrials.gov are an accepted alternative form of results dissemination and that there were no reasonable grounds to exclude it as part of an evaluation of the body of scientific literature.

22 GSK further submitted that the Moore 2014B study contained a statement that confidence about its conclusions in relation to third molar extraction studies should not be extrapolated to all acute pain conditions including conditions like TTH (**the Moore Precautionary Statement**). Accordingly, GSK submits that the Moore, Schleier and Norholt studies which are concerned with pain following third molar extraction should not be preferred to the studies NCT01077973 and NCT01362491.

23 In the course of argument in the appeal, GSK agreed that dental pain studies have been used to support efficacy in other pain conditions such as headaches, but sought to distinguish those from studies which studied faster action as opposed to efficacy.

24 GSK went on to argue that Moore 2014B is support for the proposition that the dental pain model is not recognised as a transferrable model for evaluating the **onset** of pain relief in TTH. In my view, this argument overstates the extent of the Moore Precautionary Statement. That study did not relate only to the onset of pain relief but also found that there was better overall pain relief and a lesser need for additional analgesia indicating longer lasting pain relief (see para 4 at page 5). Accordingly, the Moore Precautionary Statement relates to all of these conclusions. On GSK's own admission, it is generally accepted that data from dental pain studies can be used to infer efficacy in other pain

[8] GSK reference 8
[9] GSK reference 9

states[10]. Accordingly the precaution which Moore is suggesting should be applied, would apply to efficacy studies as well.

25 In my view, what Moore is talking about is the degree of confidence that should be applied in relation to the extrapolation of results of studies of third molar extractions to other pain conditions. He is not saying they cannot be applied at all, but that caution should be utilised in extrapolating the results.

26 The question then is whether the two studies upon which GSK wants to rely provide sufficient evidence to invoke the Moore Precautionary Statement to the extent necessary to displace the peer reviewed published studies to the contrary.

27 In its submission, RB says that unpublished and non-peer reviewed studies should not be entirely discounted but consistent with accepted practice in the scientific community, the results of high quality published and peer reviewed studies should take precedence over unpublished and non-peer reviewed publications. I believe this to be an uncontroversial approach to this issue.

28 RB further points out that only one person considers and reviews the data for the purposes of publication on ClinicalTrials.gov. This is a far less rigorous review than would occur in relation to publication.

Determination

29 GSK has not suggested that either the Moore 2014B or the Schleier or Norholt studies are in any way to be doubted insofar as they pertain to dental pain.

30 As I have said above, I do not believe that the Moore Precautionary Statement is sufficient to discredit what appears to be a long standing practice of using dental pain studies to assess efficacy in other pain states. Having regard to the nature of the Moore 2014B study itself, it is clear that the onset of pain is dealt with on the same basis as efficacy in this regard.

31 In relation to the studies published in ClinicalTrials.gov, I believe it is appropriate to refer to GSK's reference to Moore 2014A[11]. In that study, I note that:

(a) Moore identified a clinical trial report with results from ClinicalTrials.gov which was, in fact, NCT01077973[12] and an additional six trials without results identified in ClinicalTrials.gov[13];

(b) it is apparent from figure 1 in the Moore 2014A study, that the report with results from ClinicalTrials.gov was included in the 40 reports included in the review, i.e. NCT01077973 was included in Moore 2014A;

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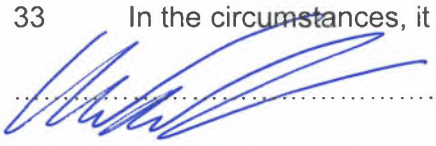
[10] See page 3 of GSK's submission on appeal.
[11] GSK reference 11 to its original complaint.
[12] Reference 53 to Moore 2014A.
[13] Which were included in Appendix 3 to the Moore 2014A study.

(c) at page 6 of the Moore 2014A, he states that few trials conformed to IHS guidance on the conduct of trials in episodic TTH. This is principally because of inadequate outcome reporting but also because of a lack of placebo control. He goes on to say "*disappointingly, ongoing trials found in ClinicalTrials.gov suffer from much the same problems ....*";

(d) if this is a reference NCT01077973, then clearly Moore does not agree with GSK's submission in relation to that particular study. In any event, it would appear to give some support for the proposition that trials included in ClinicalTrials.gov need to be treated with caution.

32 In my view, because the Moore Precautionary Statement does not operate to the extent suggested by GSK, the body of scientific evidence is to be determined by weighing the results in the Moore 2014B study, the Schleier and Norholt studies all of which are published and peer reviewed against the possible credence of the NCT01077973 and NCT01362491 unpublished studies. On that basis, I am satisfied that the body of scientific evidence supports the claim made by RB. In the circumstances, I would dismiss the appeal by GSK in this regard.

33 In the circumstances, it is appropriate that GSK bears ASMI's costs of the appeal.



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Harold Werksman – Arbiter

15 April 2015