CASE AUTH/2796/9/15

HEALTH PROFESSIONAL v BAUSCH & LOMB

Pulse Quick Guide

A general practitioner (GP) who was a GP trainer with an interest in allergy complained about an article published in Pulse as a Pulse Quick Guide. The article was entitled 'New approaches in management and treatment of anaphylaxis' and discussed adrenaline auto injectors (AAI) in relation to administration needle length, skin to muscle depth, and dosage cost. The named author was a consultant allergist who had been commissioned to write the article. An advertisement for Emerade (adrenaline) marketed by Bausch & Lomb appeared on the reverse.

Emerade was indicated for the emergency treatment of severe acute allergic reactions (anaphylaxis) triggered by allergens in foods, medicines, insect stings or bites, and other allergens as well as for exercise-induced or idiopathic anaphylaxis.

The complainant noted that the item was presented as a Pulse article on anaphylaxis; whereas it was obviously promotional. The complainant was unaware that any 'New guidelines' were presented. The Emerade device had been in the UK for over 2 years. Many of the suggestions appeared to be unscientific and poorly referenced, with very broad assumptions presented as fact.

The complainant queried the claim '68% of the allergy population has a STMD [skin-to-muscle depth] greater than the most common AAI [adrenaline autoinjectors]' and if this was really so including children. Just giving the STMD did not allow for the compression of fat/skin when a needle was pressed into the thigh. He/she understood that the European Medicines Agency (EMA) recently (June 2015) gave a Committee for Medicinal Products for Human Use report on AAIs. It suggested that further data should be generated but that until then, proper educational material should be given to patients and carers.

The statement that the British National Formulary (BNF) recommended a 500mcg dose was not correct, unless the new anticipated BNF had changed this recommendation.

The dosage suggestions of the UK Resuscitation Council were for professionals, not for patients' self-administration. The complainant also queried what 'for some patients' actually meant in the bullet-point 'For some patients, The UK Resuscitation Council also recommends 500mcg of adrenaline and makes specific needle length recommendations for intramuscular delivery'. The complainant alleged that it was unclear and misleading. 'Some patients' might equally be overdosing on the 500mcg dose. The complainant found it hard to believe this was an error in the article and believed it was included as a deliberate attempt to confuse doctors.

The referenced article on accuracy in use of AAIs was written in part by a non-clinical psychologist and was funded in part by the UK distributor of Emerade. 100% success with their sponsor's device, was astonishing, at the very least.

The cost per annum savings were made on the assumption that the AAIs were not used at all. The complainant understood that the published shelf lives were not relevant to the actual surviving shelf life when the devices were actually dispensed.

The detailed response from Bausch & Lomb is given below.

The Panel noted that the Pulse Quick Guide was supplied with Pulse as an A4 laminated loose insert, a full page Emerade advertisement appeared on the reverse. The comparison of shelf life at production, cost to the NHS and cost per annum were included in a table comparing Emerade, EpiPen and Jext. The table also included doses and exposed needle length.

The Panel noted the origin of the Pulse Guide and Bausch & Lomb's submission that the Pulse Quick Guide was clearly identified as being 'Initiated, developed, and funded by Bausch & Lomb' as stated in the top right hand corner of the article. The Panel noted that it appeared adjacent to the heading 'Pulse Quick Guide'. However, it was in a very small font size compared to the heading and subheading, in a black type face and was not emboldened. In the Panel's view, this would be missed by many readers. The Panel did not consider that the statement was prominent enough to ensure awareness of the company's role at the outset. The Panel also noted that 'see reverse for prescribing information' appeared at the bottom of the article in black, unemboldened font and appeared, at first glance, to be part of the article itself. The Panel considered that the nature of the material and role of the company was not clear. This misleading impression was compounded by the prominence of the Pulse and Nursing in Practice logos. Some readers might assume that the article was independent editorial matter. The material was disguised in that regard and a breach of the Code was ruled.

The Panel noted that the Quick Guide referred to new approaches rather than new guidelines as alleged by the complainant. Whilst the Panel noted that Emerade was first authorized in January 2013 it queried whether there were in fact new approaches in the management of treatment of anaphylaxis considering the length of time Emerade had been available. However, the allegations related to 'new guidelines' and as neither this phrase nor a closely similar phrase had been used or implied, the Panel ruled no breach of the Code on this narrow ground.

With regard to the claim '… 68% of the allergy population having a STMD greater than the most common AAI …' the Panel noted that Johnstone *et*

***al* reported STMDs >15mm in 68% of adults. The two other references quoted lower percentages in children, namely 60% and 30%. The Panel considered that the claim implied that 68% of the entire allergy population had an STMD greater than that of the most common AAIs. This was not so. The Panel considered that the statement was misleading and could not be substantiated. Breaches of the Code were ruled.**

In the Panel's view the reference to the BNF dose in the Guide was misleading. The Guide did not refer to severe anaphylaxis as mentioned in the BNF and neither the Guide nor the BNF reflected the dose recommended in the summary of product characteristics (SPC). A breach of the Code was ruled.

The Panel considered that it would be helpful if the Guide was clear that the UK Resuscitation Council guidelines were for health professionals considering that elsewhere the Guide was concerned with self administration. However, it did not consider that in the circumstances it was misleading and on this narrow ground ruled no breach of the Code. In the Panel's view, the Guide should be clearer about both the licensed dose of Emerade and the patients for whom 500mcg adrenaline was recommended. The SPC stated that 500mcg was not recommended for use in children. The UK Resuscitation Council guidelines recommended 500mcg for patients aged 12 and over except for those that were small or prepubertal. The Panel considered that the Guide was not sufficiently clear regarding the licensed doses. There was a possibility that it might lead to some patients being inappropriately prescribed a dose of 500mcg. This was clearly contraindicated in children. The Panel considered that the Guide was misleading and did not promote the rational use of the medicine. Breaches of the Code were ruled. Such material could potentially have an impact on patient safety. The Panel ruled a breach of the Code as high standards had not been maintained. The Panel noted that prejudicing patient safety was an activity likely to be ruled in breach of Clause 2. The Panel noted that there was no evidence to show that patient safety had been adversely affected but considered that to provide misleading information about licensed doses was a serious matter particularly given that the 500mcg dose was contraindicated in children and on balance a breach of Clause 2 was ruled.

With regard to the allegation about cost per annum savings, the Panel noted Bausch & Lomb's submission that as the bulk of all AAI's in circulation were never used, a longer shelf life was a beneficial factor as the requirement to replace the pen would be less frequent. The Panel noted that Emerade had a shelf life at production of 30 months compared to EpiPen and Jext with 18 months each. The Panel examined the table comparing the products. The costs were given and the final column gave the cost per annum; the cheapest being Emerade at £10.78 (150 and 300mcg). The column detailing shelf-life was headed 'Shelf life at production (months)'. In addition the bullet point in the conclusion read 'Emerade reduces cost, with the longest shelf life at production (30 months) compared to Jext /EpiPen (18 months). The Panel considered that it was clear that the longer shelf life referred to the maximum shelf life from the date of production. Whilst the supply chain was relevant the Panel considered that the Guide was sufficiently clear that it was referring to the shelf life at production. The Panel did not consider that readers would be misled in this regard and ruled no breach of the Code. The Panel considered that neither the table nor the bullet point 'Emerade reduces cost with the longest shelf-life at production …' were incapable of substantiation on this point and no breach of the Code was ruled.

A general practitioner (GP) and GP trainer with an interest in the allergy field complained about an article (ref EME-UK-1507-04, prepared July 2015) published in Pulse entitled 'New approaches in management and treatment of anaphylaxis'. The article discussed adrenaline auto injectors (AAI) in relation to administration needle length, skin to muscle depth, and dosage cost. The named author was a consultant allergist who had been commissioned to write the article.

Bausch & Lomb's product Emerade (adrenaline) was indicated for the emergency treatment of severe acute allergic reactions (anaphylaxis) triggered by allergens in foods, medicines, insect stings or bites, and other allergens as well as for exercise-induced or idiopathic anaphylaxis.

COMPLAINT

The complainant stated that the article was published as a laminated A4 sheet and was presented as a 'Pulse Quick Guide'.

The complainant's concerns were as follows:

1 The item was presented as a Pulse article on anaphylaxis; whereas it was obviously promotional. The complainant planned to write to Pulse about this and believed it should also take some responsibility, as it had a reputation to uphold.

2 The complainant was unaware that any 'New guidelines' were presented. The Emerade device had been in the UK for over 2 years.

3 Many of the suggestions appeared to be unscientific and poorly referenced, with very broad assumptions being made and presented as fact. For example:

   a) '68% of the allergy population has a STMD [skin-to-muscle depth] greater than the most common AAI [adrenaline autoinjectors]'. The complainant queried if this was really the case including children and alleged that just giving the STMD did not allow for the compression of fat/skin when a needle was pressed into the thigh. He understood that the European Medicines Agency (EMA) recently (June 2015) gave a Committee for Medicinal Products for Human Use report on AAIs. It suggested that further data should be generated but that until then, proper educational material should be given to patients and carers.

b) The statement that the BNF recommended a 500mcg dose was not correct, unless the new anticipated BNF had changed this recommendation; the complainant did not have this yet but noticed the article was prepared in July.

c) The dosage suggestions of the UK Resuscitation Council were for professionals, not for patients' self-administration. The complainant also queried what 'for some patients' actually meant when extracted into the presented bullet-point 'For some patients, The UK Resuscitation Council also recommends 500mcg of adrenaline and makes specific needle length recommendations for intramuscular delivery'. The complainant alleged that it was very unclear and misleading. 'Some patients' might equally be overdosing on the 500mcg dose. The complainant found it hard to believe this was an error in this article and believed it was included as a deliberate attempt to confuse doctors.

d) The referenced article on accuracy in use of AAIs was written in part by a non-clinical psychologist and was funded in part by the UK distributor of Emerade. 100% success with their sponsor's device, was astonishing, at the very least.

4 The cost per annum savings were made on the assumption that the AAIs were not used at all. The complainant understood that the published shelf lives were not relevant to the actual surviving shelf life when the devices were actually dispensed.

When writing to Bausch & Lomb, the Authority asked it to consider the requirements of Clauses 2, 7.2, 7.4, 7.10, 7.11, 9.1 and 12.1 of the Code.

RESPONSE

Bausch & Lomb stated that as members of the ABPI it took compliance with the Code seriously. It responded to each of the complainant's points in turn.

1 Bausch & Lomb submitted that the Pulse Quick Guide was clearly identified as being 'Initiated, developed, and funded by Bausch & Lomb' as stated in the top right hand corner of the article. No attempt was made to hide this information from the reader and was thereby in compliance with Clauses 9.10 and 12.1. Bausch & Lomb provided further detail on these types of articles published by Pulse.

2 Bausch & Lomb submitted that the article did not state 'new guidelines' anywhere in the copy but use of the term 'new approaches' was with reference to emerging data cited in the article on the need for skin to muscle depth assessment at the injection site to ensure that the prescribed adrenaline auto-injector would be able to deliver an intra-muscular injection. So in that context the word 'new' was entirely appropriate and accurate.

3 With regard to the accusation that many of the suggestions were 'unscientific', Bausch & Lomb submitted that the references were from allergy experts, published in peer reviewed journals or presented at international allergy symposia and to that end had scientific credibility.

a) Bausch & Lomb accepted, that the author could have said 'up to 68%'. However, three references were offered to support the statement - Johnstone *et al*, 2015 reported STMDs >15mm in 68% of adults. The others quoted lower percentages in children, namely 60% in Bewick *et al*, 2013 and 30% in Stetcher *et al*, 2009. Bausch & Lomb did not regard it in anyway being misleading or misrepresentative of the current situation given the references stated covering both the adult and child allergy population.

With regard to the anatomy of subcutaneous tissue and its relationship with muscle and the deep fascia, when pressure was applied to the skin, the muscle compartment was compressed and displaced by the subcutaneous tissue – not the other way round. A needle pressed into the flesh, would perhaps progress an additional 2mm towards the muscle compartment, beyond its physical length. Bewick *et al*, 2013 specifically investigated compression, to counter the common misunderstanding that pressing hard on the skin could help push the needle nearer the muscle:

'… skin surface-to-muscle depth was measured in a subgroup of 7 children ages 5 to 14 years (median, 8 years), after applying enough pressure with a trainer EpiPen and an adjacently placed ultrasound probe positioned on the outer mid-thigh to trigger the device. The EpiPen trainer is a reasonable surrogate for the medicinal device because it has previously been shown to require equivalent force for activation. The median compression was 0.5 mm (interquartile range, 0.0 -1.2 mm). In 3 children younger than 7 years old there was little or no change in skin surface-to-muscle depth after compression. In the overall cohort, the skin-to-muscle depth at the mid-thigh was 2.4 mm (0.8 - 3.2 mm) greater than the needle length, which suggests that compression of tissues when firing autoinjectors would not alter the proportion of children whose injection was subcutaneous rather than intramuscular. There was no significant correlation between BMI or age and change in depth with compression'.

b) The current edition of the BNF Section 3.4.3 Adrenaline, Intramuscular Injection for self-injection, Emerade, included 'Dose by intramuscular injection, Adult and Child over 12 years at risk of severe anaphylaxis, 500 micrograms repeated after 5 -15 minutes as necessary'. This was amended in September 2014. Bausch & Lomb provided a screen shot of the relevant on-line version, to support the statement in the article.

c) Bausch & Lomb submitted that the audience for Pulse was health professionals who would be aware that the UK Resuscitation Guidelines were not for self-administration. The fact that these guidelines supported the use of a 500mcg dose and that Emerade was currently the only auto-injector was relevant and important to convey to the audience. Bausch & Lomb submitted that it would expect health professionals to refer to the prescribing information prior to any usage and to that end the advice on which product was suitable for which patient would be clear. The statement was correct in that it stated 'some' not 'all' patients, which would be misleading.

d) Bausch & Lomb submitted that it was common practice for the pharmaceutical industry and in this case the 'distributor' to financially support NHS facilities and staff to assess the value of medicines. For the complainant to infer that it invalidated the outcome of any of such studies or questions the integrity of the investigators and authors was a concerning development. The author of the guide was a healthcare psychologist, who should have the right to respond in their own right to the allegations.

In response to a request for further information Bausch & Lomb stated that the 'cost per annum' savings were made on the basis that the AAI was not used. The bulk of all AAIs in circulation were never used in the management of anaphylaxis and a longer shelf life was a cost beneficial factor in that case as the requirement to replace the pen would be less frequent.

Bausch & Lomb confirmed that it did not take up the additional option of 'online' publication of the 'Quick Guide' and no additional laminated copies were supplied and therefore were not circulated by Bausch & Lomb sales teams.

PANEL RULING

The Panel noted Bausch & Lomb's comments about the study author. It was for Bausch & Lomb to include any comments in its submission if it so wished. It was not the role of the Panel to contact third parties for views.

The Panel noted that the Pulse Quick Guide was supplied with Pulse as an A4 laminated loose insert, a full page Emerade advertisement appeared on the reverse. The comparison of shelf life at production, cost to the NHS and cost per annum were included in a table comparing Emerade, EpiPen and Jext. The table also included doses and exposed needle length.

The Panel noted that the Pulse Guide article was tendered amongst a range of options during a meeting between Bausch & Lomb and Pulse in April 2015; the content would be collaboratively determined between them. Subsequent to the manuscript being submitted by the author, Bausch & Lomb reviewed it to ensure factual accuracy rather than having editorial control. The Panel noted Bausch & Lomb's submission that the Pulse Quick Guide was clearly identified as being 'Initiated, developed, and funded by Bausch & Lomb' as stated in the top right hand corner of the article. The Panel noted that it appeared adjacent to the heading 'Pulse Quick Guide'. However, it was in a very small font size compared to the heading and subheading, in a black type face and was not emboldened. In the Panel's view, this would be missed by many readers. The Panel did not consider that the statement was prominent enough to ensure that readers would be aware of the company's role at the outset. The Panel also noted that 'see reverse for prescribing information' appeared at the bottom of the article in black, unemboldened font and appeared, at first glance, to be part of the article itself. The Panel noted the requirements of Clause 12.1 and its supplementary information that when a company paid for, or otherwise secured or arranged the publication of promotional material in journals such material must not resemble independent editorial matter. The Panel noted that the overall impression given to readers was the most relevant factor. The Panel noted its comments above and considered that the nature of the material and role of the company was not clear. This misleading impression was compounded by the prominence of the Pulse and Nursing in Practice logos at the very bottom of the Guide. Some readers might assume that the article was independent editorial matter. The material was disguised in that regard. A breach of Clause 12.1 was ruled.

The Panel noted the complainant's allegation that the Emerade device had been available in the UK for over 2 years and the complainant was unaware that any 'New guidelines' were presented. Clause 7.11 stated that the word 'new' must not be used to describe any product or presentation which had been generally available or any therapeutic indication which had been promoted, for more than twelve months in the UK. In the Panel's view it was not necessarily unreasonable to assume that this timeframe should similarly apply when referring to guidelines and the like. The Panel noted that the Quick Guide was entitled 'New approaches in the management and treatment of anaphylaxis' as submitted by Bausch & Lomb; the Quick Guide referred to new approaches rather than new guidelines as alleged by the complainant. Whilst the Panel noted that Emerade was first authorized in January 2013 it queried whether there were in fact new approaches in the management of treatment of anaphylaxis considering the length of time Emerade had been available. However, the allegations related to 'new guidelines' and as neither this phrase nor a closely similar phrase had been used or implied, the Panel ruled no breach of Clause 7.11 on this narrow ground.

The Panel noted the complainant's allegation that the claim '…68% of the allergy population having a STMD greater than the most common AAI …' was unscientific and poorly referenced. The complainant queried if this was really the case including in children. The Panel noted that Johnstone *et al* reported STMDs >15mm in 68% of adults. The two other references quoted lower percentages in children, namely 60% and 30%. The Panel considered that the claim in question implied that 68% of the entire allergy population had an STMD greater than that of the most common AAIs. This was not so. The

Panel considered that the statement was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that the Guide stated that 'the BNF now includes a recommendation that adults at risk of anaphylaxis should receive 500mcg AAI dose by intramuscular injection for self-administration, adrenaline 1mg/l (1 in 1000) repeated after 5-15 minutes if necessary'. The screenshot of the BNF, from November 2014, provided by Bausch & Lomb stated 'Dose by intramuscular injection, ADULT and CHILD over 12 years at risk of severe anaphylaxis, 500 micrograms repeated after 5-15 minutes as necessary. The Panel noted that the BNF referred to severe anaphylaxis while the Guide did not make a distinction. The Emerade summary of product characteristics (SPC) recommended an initial dose of 300 to 500mcg for use in adolescents and adults. It also stated that in some cases one dose was not sufficient to revoke the effects of a severe allergic reaction and a second injection with Emerade might be necessary after 5-15 minutes. In the Panel's view the reference to the BNF dose in the Guide was misleading. The Guide did not refer to severe anaphylaxis as mentioned in the BNF and neither the Guide nor the BNF reflected the dose recommended in the SPC. A breach of Clause 7.2 was ruled.

The Panel noted the complainant's allegation that the dosage suggestions of the UK Resuscitation Council were for professionals, not for patients for self-administration. The complainant also queried what 'for some' patients actually meant. The Panel considered that it would be helpful if the Guide was clear that the UK Resuscitation Council guidelines were for health professionals considering that elsewhere the Guide was concerned with self administration. However, it did not consider that in the circumstances it was misleading and on this narrow ground ruled no breach of Clause 7.2. In the Panel's view, the Guide should be clearer about both the licensed dose of Emerade and the patients for whom 500mcg adrenaline was recommended. The SPC stated that 500mcg was not recommended for use in children. The UK Resuscitation Council guidelines recommended 500mcg for patients aged 12 and over except for those that were small or prepubertal. The Panel considered that the Guide was not sufficiently clear regarding the licensed doses. There was a possibility that it might lead to some patients being inappropriately prescribed a dose of 500mcg. This was clearly contraindicated in children. The Panel considered that the Guide was misleading and did not promote the rational use of the medicine. Breaches of Clauses 7.2 and 7.10 were ruled. The Panel noted its ruling that the licensed doses in the Guide were misleading. In the Panel's view such material could potentially have an impact on patient safety. The Panel ruled a breach of Clause 9.1 as high standards had not been maintained. The Panel noted that prejudicing patient safety was an activity likely to be ruled in breach of Clause 2. The Panel noted that there was no evidence to show that patient safety had been adversely affected but considered that to provide misleading information about licensed doses was a serious matter particularly given that the 500mcg dose was contraindicated in children and on balance a breach of Clause 2 was ruled.

With regard to the allegation that the cost per annum savings were on the basis that the AAI was not used, the Panel noted Bausch & Lomb's submission that as the bulk of all AAI's in circulation were never used, a longer shelf life was a beneficial factor as the requirement to replace the pen would be less frequent. The Panel noted that Emerade had a shelf life at production of 30 months compared to EpiPen and Jext with 18 months each. The Panel examined the table comparing the products. Emerade cost £26.94 for the 150 and 300mcg dose and £28.74 for the 500mcg dose. EpiPen cost £26.45 for both doses (150 and 300mcg), and Jext cost £23.99 for both doses. The final column gave the cost per annum; the cheapest being Emerade at £10.78 (150 and 300mcg). The column detailing shelf-life was headed 'Shelf life at production (months)'. In addition the bullet point in the conclusion read 'Emerade reduces cost, with the longest shelf life at production (30 months) compared to Jext /EpiPen (18 months). The Panel considered that it was clear that the longer shelf life referred to the maximum shelf life from the date of production. Whilst the supply chain was relevant the Panel considered that the Guide was sufficiently clear that it was referring to the shelf life at production. The Panel did not consider that readers would be misled in this regard and ruled no breach of Clause 7.2. The Panel considered that neither the table nor the bullet point 'Emerade reduces cost with the longest shelf-life at production …' were incapable of substantiation on this point and no breach of Clause 7.4 was ruled.

Complaint received **24 September 2015**

Case completed **11 December 2015**