CASE AUTH/3135/12/18

COMPLAINANT v ASTELLAS

Promotion of Betmiga

A contactable complainant who described him/herself as a concerned health professional complained about a Betmiga (mirabegron) advertisement issued by Astellas Pharmaceuticals.

Betmiga was indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence in adults with overactive bladder (OAB) syndrome.

The complainant stated that the headline 'More OAB patients stay on treatment with BETMIGA than with antimuscarinics' was interesting since antimuscarinics were often unpopular due to side effects.

The complainant stated that it was very poor to have Chapple *et al* (2017) as the sole reference. This stated, 'Limitations include the retrospective design, use of prescription records to estimate outcomes, and inability to capture reasons for discontinuation'. These 'massive caveats' were not mentioned in the advertisement and it was also not clear whether the treatment was used in patients who were contra-indicted, such as uncontrolled hypertension, or other at-risk groups such as limited liver or kidney function.

The complainant stated that the Betmiga summary of product characteristics (SPC) mentioned nothing about being better than antimuscarinics and as far as he/she could see there was no prospective study that had been undertaken against all antimuscarinics.

The complainant alleged that this was extremely misleading and used very weak data which could easily lead to inappropriate use of Betmiga.

The detailed response from Astellas is given below.

The Panel noted that the advertisement depicted two men and a woman walking together in a field, with the woman walking on a highlighted path. A dotted line pointed to the woman with the boxed statement 'Her 6th hike since the day she started BETMIGA'. At the top of the page in a box, in larger font, was the headline claim, 'More OAB patients stay on treatment with BETMIGA than with antimuscarinics', referenced to Chapple *et al* (2017). In the bottom right-hand corner of the picture was the Betmiga logo with the statement 'Treatment they can keep taking is treatment that can keep working'. Below the picture was the text:

> **'When an antimuscarinic fails because of side effects or poor efficacy, prescribing another may be of minimal benefit [referenced to Chancellor *et al* (2016)]. So why not take a different path? BETMIGA is in another class, relaxing the bladder via ß3-adrenoreceptors [referenced to the Betmiga SPC]. It can be just as effective as an antimuscarinic but it doesn't have the same side-effect profile [referenced to Maman *et al* (2014)]. The result: more patients still taking their treatment at the 12 month mark' [referenced to Chapple *et al* (2017)].**

The Panel noted that the Code did not prohibit the use of retrospective observational studies that utilised prescription records to estimate outcomes as a means of substantiating a claim provided that the claim complied with the requirements of the Code. Context was important.

The Panel noted the text below the picture and within the advertisement as set out above, including, *inter alia*, the use of the connector 'The result' and considered that it implied that the reason more Betmiga patients were still taking their treatment at 12 months was because it had a favourable side-effect profile compared to antimuscarinics. This, in the Panel's view, was not evident from Chapple *et al* which was unable to examine the reasons for discontinuation as these data were not contained in the database. The Panel noted the caution expressed by the study authors, 'Mirabegron provides an alternative treatment option for OAB with the potential to increase treatment persistence'. The Panel noted the limitations of the study including, *inter alia*, the use of prescription-event rather than patient-derived data to estimate outcomes. The Panel noted that the claim in question was unqualified and thus did not fairly reflect the study.

The Panel considered that insufficient information about the study had been provided in the advertisement to enable the reader to meaningfully assess the claim in question and form their own opinion of the therapeutic value of the medicine in relation to treatment persistence. The Panel considered that the claim was misleading, exaggerated and not capable of substantiation. Breaches of the Code were ruled.

A contactable complainant who described him/herself as a concerned health professional complained about a Betmiga (mirabegron) advertisement (ref BET18035UKa) issued by Astellas Pharmaceuticals Limited and published in the December 2018 edition of Pulse magazine.

Betmiga was indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence in adults with overactive bladder (OAB) syndrome.

COMPLAINT

The complainant stated that the headline 'More OAB patients stay on treatment with BETMIGA than with antimuscarinics' was interesting since antimuscarinics were often unpopular due to side effects.

The complainant stated that it was very poor to have Chapple *et al* (2017) as the sole reference. It stated, 'Limitations include the retrospective design, use of prescription records to estimate outcomes, and inability to capture reasons for discontinuation'. These 'massive caveats' were not mentioned in the advertisement and it was also not clear whether the treatment was used in patients who were contra-indicted, such as uncontrolled hypertension, or other at-risk groups such as limited liver or kidney function.

The complainant stated that this might be OK if all the other evidence said the same but the Betmiga summary of product characteristics (SPC) mentioned nothing about being better than antimuscarinics and as far as he/she could see there was no prospective study that had been undertaken against all antimuscarinics.

The complainant alleged that this was extremely misleading and used very weak data which could easily lead to inappropriate use of Betmiga. He/she thought that this fell below the standards the MHRA required let alone the ABPI.

In writing to Astellas attention was drawn to the requirements of Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Astellas stated that it took very seriously all allegations of non-compliance with any regulations, including the Code, and had conducted a comprehensive investigation in order to address all points raised by the complainant.

Astellas disagreed that the claim 'More OAB patients stay on treatment with Betmiga than with antimuscarinics' was misleading and could not be substantiated. Astellas also denied that the reference used to substantiate the claim was poor.

Chapple CR *et al* (2017) was a retrospective, longitudinal, observational study of anonymised data from the UK Clinical Practice Research Datalink (CPRD) GOLD database. The objective of the study was to compare persistence and adherence with mirabegron versus tolterodine extended release (ER) and other antimuscarinics in routine clinical practice over a 12-month period. The primary end point was persistence (time to discontinuation); secondary endpoints included 12-month persistence rates and adherence.

CPRD was a real-world research service supporting retrospective and prospective public health and clinical studies. CPRD was jointly sponsored by the Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR), as part of the Department of Health and Social Care. CPRD collected de-identified patient data from a network of GP practices across the UK. Primary care data were linked to a range of other health related data to provide a longitudinal, representative UK population health dataset. The data encompassed over 35 million patient lives, including 10 million currently registered patients.

Astellas submitted that for more than 30 years, research using CPRD data and services had informed clinical guidance and best practice, resulting in over 2,000 peer-reviewed publications investigating drug safety, use of medicines, effectiveness of health policy, health care delivery and disease risk factors. The CPRD primary care database was thus a rich source of health data for research, including data on demographics, symptoms, tests, diagnoses, therapies, health-related behaviours and referrals to secondary care.

Chapple *et al*, included 21,966 patients, and was published in a peer-reviewed journal, European Urology, the official journal of the European Association of Urology (EAU) which was currently read by more than 20,000 urologists globally. Impact factors were used to measure the credibility of a journal by calculating the number of times selected articles were cited within the last few years; the higher the impact factor, the more highly ranked the journal. Only 1.7% of journals had an impact factor greater than 10. European Urology had an impact factor of 17.581. In addition, Chapple *et al* had been cited in other scientific articles 35 times, many of which were published in international journals.

Chapple *et al* concluded that 'Persistence and adherence were statistically significantly greater with mirabegron than with tolterodine ER and other antimuscarinics prescribed for OAB in the UK'.

With the above in mind, Astellas submitted that the claim at issue was an unambiguous statement of fact, substantiated by Chapple *et al*, a publication of research data from a comprehensive database, published in a highly reputable journal. The claim was therefore consistent with the requirements of Clauses 7.2 and 7.4. The claim did not in any way exaggerate the qualities of the medicine and was thus not in breach of Clause 7.10.

Clarity of Study Limitations

Astellas stated it was important to note that the advertisement was about patients' persistence with treatment. Retrospective database investigations were universally accepted to be the best way to assess a patient's persistence with a treatment. Any prospective study would change compliance rates; it was human nature to behave differently when being observed. In addition, the ABPI guidance Demonstrating Value with Real World Data recognised the value of retrospective data in that regard.

Given this, Astellas submitted it was not necessary to include the limitations of the study in the advertisement itself. Astellas did not consider that

omitting this information rendered the advertisement misleading and disagreed that the advertisement was in breach of Clause 7.2 in that regard.

Inference that Betmiga is 'Better' than Antimuscarinics

With regard to the complainant's statement that there was nothing in the Betmiga summary of product characteristics (SPC) about Betmiga being 'better' than antimuscarinics, Astellas did not consider that there was any direct or implied claim in the advertisement at issue of superior efficacy for Betmiga vs antimuscarinic medicines. The advertisement was about persistence in, and adherence by, patients in their treatment and this was reflected in:

- The headline claim ('More OAB patients stay on treatment with Betmiga than with antimuscarinics');
- The imagery of a patient being able to conduct normal activities such as going on a hike;
- The text underneath the image which referred to taking a different path with Betmiga if a patient discontinued an antimuscarinic ('**It can be just as effective** as an antimuscarinic, but it doesn't have the same side-effect profile'; emphasis added by Astellas).

Astellas therefore disagreed that there were any claims of superior efficacy and denied a breach of Clauses 7.2 and 7.4. There was no claim or other information about Betmiga that could be considered exaggerated in this regard and Astellas denied a breach of Clause 7.10.

Inappropriate Use of Betmiga

With regard to the allegation that the advertisement might lead to clinicians using Betmiga inappropriately, Astellas noted that no further explanation was provided by the complainant. The advertisement evidently and prominently stated the indication for Betmiga, and the contraindications and warnings were clearly laid out in the prescribing information. Astellas therefore denied a breach of Clause 7.10 in this regard.

MHRA Standards

With regard to the allegation that the advertisement fell below the standards of the MHRA, Astellas submitted it was important to highlight that the claim at issue, supported by Chapple *et al*, had been vetted by the MHRA which had no comments on the claim. Astellas recognised that the Code reflected and extended beyond the law. Astellas submitted that the fact that this vetting had occurred should help to reassure the complainant.

PANEL RULING

The Panel noted the complainant's allegation that the advertisement fell below standards that the MHRA required. The Panel noted Astellas' submission that the claim at issue, supported by Chapple *et al* (2017), had been vetted by the MHRA. The Panel was unclear if the advertisement at issue had been vetted by the MHRA or just the claim 'More OAB patients stay on treatment with Betmiga than with antimuscarinics'. Astellas made no submission in that regard but referred to vetting of the claim. The Panel could only consider the matter under the Code.

The Panel noted from the approval certificate that the advertisement in question was intended as a double page spread in Pulse. It depicted two men and a woman walking together in a field, with the woman walking on a highlighted path. A dotted line pointed to the woman with the boxed statement 'Her 6th hike since the day she started BETMIGA'. At the top of the page in a box, in larger font, was the headline claim, 'More OAB patients stay on treatment with BETMIGA than with antimuscarinics', referenced to Chapple *et al* (2017). In the bottom right-hand corner of the picture was the Betmiga logo with the statement 'Treatment they can keep taking is treatment that can keep working'. Below the picture was the text:

'When an antimuscarinic fails because of side effects or poor efficacy, prescribing another may be of minimal benefit [referenced to Chancellor *et al* (2016)]. So why not take a different path? BETMIGA is in another class, relaxing the bladder via ß3-adrenoreceptors [referenced to the Betmiga SPC]. It can be just as effective as an antimuscarinic but it doesn't have the same side-effect profile [referenced to Maman *et al* (2014)]. The result: more patients still taking their treatment at the 12 month mark' [referenced to Chapple *et al* (2017)].

The Panel noted the complainant's allegation that it was poor for Chapple *et al* to be the sole reference for the headline claim and he/she referred to the limitations of the study as described in the paper which were not mentioned in the advertisement. The Panel further noted the complainant's statement that the Betmiga SPC did not mention that it was 'better' than antimuscarinics and there had been no prospective studies against all antimuscarinics.

The Panel noted Astellas' submission that Chapple *et al* was a retrospective, longitudinal, observational study of anonymised data from a recognised UK database, included 21,966 patients, was published in a peer-reviewed journal and had been cited in other scientific articles. The Panel noted Astellas' submission that Chapple *et al* concluded, 'Persistence and adherence were statistically significantly greater with mirabegron than with tolterodine ER and other antimuscarinics prescribed for OAB in the UK'. The Panel further noted Astellas' submission that there was no direct or implied claim of superior efficacy for Betmiga versus antimuscarinic medicines in the advertisement at issue.

In the Panel's view, the acceptability of the headline claim 'More OAB patients stay on treatment with BETMIGA than with antimuscarinics' should be considered within the context of the advertisement.

The Panel did not agree that it was not necessary to have the limitations of the study in the advertisement because, in Astellas' view, retrospective database

investigations were universally accepted to be the best way to assess a patient's persistence with treatment. The Panel noted that the Code did not prohibit the use of retrospective observational studies that utilised prescription records to estimate outcomes as a means of substantiating a claim provided that the claim complied with the requirements of the Code including Clauses 7.2 and 7.4. Context was important.

The Panel noted the text below the picture and within the advertisement as set out above, including, *inter alia*, the use of the connector 'The result' and considered that it implied that the reason more Betmiga patients were still taking their treatment at 12 months was because it had a favourable side-effect profile compared to antimuscarinics. This, in the Panel's view, was not evident from Chapple *et al* which was unable to examine the reasons for discontinuation as these data were not contained in the database. The Panel noted the caution expressed by the study authors, 'Mirabegron provides an alternative treatment option for OAB with the **potential** to increase treatment persistence' (emphasis added). The Panel noted the limitations of the study including, *inter alia*, the use of prescription-event rather than patient-derived data to estimate outcomes. The Panel noted that the claim in question was unqualified and thus did not fairly reflect the study.

The Panel noted its comments above and considered that insufficient information about the study had been provided in the advertisement to enable the reader to meaningfully assess the claim in question and form their own opinion of the therapeutic value of the medicine in relation to treatment persistence. The Panel considered that the claim was misleading in this regard and a breach of Clause 7.2 was ruled.

The Panel noted that Clause 7.4 stated any information, claim or comparison must be capable of substantiation. The Panel noted its comments above and considered that the misleading implication that the difference in treatment persistence between Betmiga and antimuscarinics was as a result of their different side-effect profiles was not capable of substantiation and thus ruled a breach of Clause 7.4.

In the Panel's view, the claim in question within the context of the advertisement, and on the balance of probabilities, exaggerated Betmiga's properties in relation to treatment persistence and side effects and therefore did not encourage the rational use of Betmiga and a breach of Clause 7.10 was ruled.

Complaint received **18 December 2018**

Case completed **3 April 2019**