CASE AUTH/3508/5/21

GENERAL PRACTITIONER v ADVANZ PHARMA

Macrobid promotional email

A complaint from a general practitioner about a promotional email entitled 'Minimising antimicrobial resistance in lower urinary tract infections', by Advanz Pharma Services (UK) Limited, made to the Medicines and Healthcare products Regulatory Agency (MHRA) was referred to the PMCPA.

Advanz Pharma marketed Macrobid (nitrofurantoin) for the treatment of and prophylaxis against certain lower urinary tract infections or pyelitis.

The complainant alleged that the main evidence had been misinterpreted. The complainant stated that 1 in 3 *E (Escherichia).coli* urinary tract infections (UTIs) showed *in vitro* resistance to trimethoprim, but this did not translate to clinical (in)effectiveness. The complainant stated that if Advanz had correctly referenced NICE it would have said that success rates of five different antibiotics *in vivo* were the same.

The detailed response from Advanz is given below.

The Panel noted that the subject line of the email stated: 'Minimising antimicrobial resistance in lower urinary tract infections'. The body of the email was entitled 'Urinary tract infections (UTI) are one of the most common reasons for antibiotic prescriptions in primary care'. Below this were a number of claims, including the claim in question, 'In the UK, 1 in 3 adults will fail treatment for lower UTI with trimethoprim' which was beneath the subheading 'RESIST THE RESISTANCE' and was referenced to NICE NG109 (2018) and the Scottish One Health antimicrobial use and antimicrobial resistance in 2018 annual report.

The NICE NG109 guideline (2018) which was entitled 'Urinary tract infection (lower): antimicrobial prescribing' stated that for England, resistance of *E.Coli* (the main causative organism of lower UTIs) in laboratory-processed urine specimens to trimethoprim was 30.3% (varied by area from 27.1 to 33.4%) based on Public Health England antimicrobial resistance quarterly surveillance dated March 2018. The Scottish report gave the percentage resistance of *E.Coli* urinary isolates in 2018 in NHS Scotland for trimethoprim as 33.6% (percentage resistance of *E. coli* urinary isolates from 2014 to 2018 for trimethoprim ranged from 33.4% to 34.2%). The Panel noted Advanz's submission that these data indicated that *E.coli* isolates from patient derived urinary specimens were resistant to trimethoprim in approximately 33% of cases. The Panel further noted Advanz's submission that the NICE NG109 guideline stated that resistant bacteria were a particular concern in UTIs and, where possible, any previous urine

culture and susceptibility results, and antibiotic prescribing, should be checked and antibiotics chosen accordingly.

The Panel noted Advanz's submission that there was evidence to suggest that susceptibility results of urinary cultures were not always accurate and there were differences between *in vitro* and *in vivo* effectiveness of antibiotics which was acknowledged within the NICE NG109 guidelines. The Panel further noted Advanz's submission that on re-assessment of the material the company considered that the claim that the resistance rates for trimethoprim referenced from *in vitro* testing 'will' result in treatment failure did not comprehensively reflect potential *in vivo* outcomes.

The Panel considered that the claim 'In the UK, 1 in 3 adults will fail treatment for lower UTI with trimethoprim' was misleading as it implied that clinically, 1 in 3 adults would not respond adequately to trimethoprim for lower UTI which was not supported by clinical data; the misleading impression given by the claim could not be substantiated. The Panel ruled breaches of the Code including that Advanz had failed to maintain high standards.

A complaint was received via the Medicines and Healthcare products Regulatory Agency (MHRA) from a general practitioner about a promotional email entitled 'Minimising antimicrobial resistance in lower urinary tract infections' (ADV/MAB/PM/0263) by Advanz Pharma Services (UK) Limited.

Advanz Pharma marketed Macrobid (nitrofurantoin) for the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures. It was indicated in adults and children over 12 years of age.

COMPLAINT

The complainant alleged that the main evidence within the promotional email had been misinterpreted. The complainant stated that 1 in 3 *E (Escherichia).coli* urinary tract infections (UTIs) showed *in vitro* resistance to trimethoprim, but this did not translate to clinical (in)effectiveness. The complainant stated that if Advanz had correctly referenced NICE it would have said that success rates of five different antibiotics *in vivo* were the same.

The complainant agreed for the MHRA to refer his/her complaint to the PMCPA.

When writing to Advanz, the Authority asked it to consider the requirements of Clauses 7.2, 7.4 and 9.1 of the Code.

RESPONSE

Advanz acknowledged that the claim referred to by the complainant, specifically 'In the UK, 1 in 3 adults will fail treatment for UTI with trimethoprim' might be perceived as not comprehensively reflecting the evidence referenced.

Background to 'Minimising antimicrobial resistance in lower urinary tract infections' promotional email (ADV/MAB/PM/0263)

Advanz submitted that as per the title, the objective of this promotional email was to highlight the relatively low resistance rates observed with Macrobid (nitrofurantoin) as compared with another commonly used antibiotic for urinary tract infections (UTIs), trimethoprim, and thus flag the relative contribution that Macrobid had in reducing antimicrobial resistance (AMR), this being a known significant threat to public health. The references provided by Advanz stated:

'• NICE NG 109: Urinary tract infection (lower): antimicrobial prescribing (October 2018) Nationally for England, resistance of *E. coli* (the main causative organism of lower UTIs) in laboratory-processed urine specimens to the following antibiotics is:
  - nitrofurantoin: 2.5% (varies by area from 2.0 to 3.6%)
  - trimethoprim: 30.3% (varies by area from 27.1 to 33.4%)
  - pivmecillinam: 7.5% (varies by area from 4.1 to 15.7%)
  - cefalexin: 9.9% (varies by area from 8.1 to 11.4%).

  (Public Health England. Antimicrobial resistance quarterly surveillance: March 2018)

- Scottish One Health Antimicrobial Use and Antimicrobial Resistance (SONAAR) Annual Report 2018

  Table 58: Total number and the percentage resistance of *E. coli* urinary isolates from 2014 to 2018 for trimethoprim ranges from 33.4% to 34.3%.'

The references suggested that approximately 1 in 3 *E. coli* urinary isolates were resistant to trimethoprim in both England and Scotland. *E. coli* was the commonest cause of lower UTIs having been isolated in 70-95% of cases (NICE NG109, 2018). Furthermore, NICE guidance (NG109) specifically stated:

> '… the committee agreed that the choice of antibiotic should largely be driven by minimising the risk of resistance. Resistant bacteria are a particular concern in UTIs and, where possible, any previous urine culture and susceptibility results, and antibiotic prescribing, should be checked and antibiotics chosen accordingly.'

Additionally, the following points were taken into consideration when the claim was considered, and due diligence was applied for substantiation:

- Susceptibility testing was common in practice and guided choice of antibiotic.
- The data for the referenced resistance to Trimethoprim were taken from clinical urine specimens which originated from patients. Extrapolation of *in vitro* data to clinical treatment outcomes were relevant in this regard.
- If results indicated resistance to an antibiotic, antibiotics with high sensitivity were chosen if antibiotics had not been commenced or there was no clinical improvement/worsening of symptoms with current antibiotic. Clinical interpretation in these circumstances was 'failure' of resistant antibiotic.
- The NICE report for Antimicrobial stewardship stated: 'The term 'antimicrobial resistance' is defined as the 'loss of effectiveness of any anti-infective medicine' – thus the extrapolation of trimethoprim resistance to 'fail treatment' was made in this context
- Evidence had shown that if an isolate had absolute/high level resistance *in vitro*, then this could not be overcome with *in vivo* treatment, regardless of achievable antibiotic concentrations (Cunha 2016).

Advanz submitted that, in summary, the data indicated that *E. coli* isolates from patient derived urinary specimens were resistant to trimethoprim in approximately 33% of cases. Further, guidance to health professionals in the prescribing of antibiotics was to seek ways to minimise antimicrobial resistance as this led to the loss of effectiveness of a medicine. Considering these factors, Advanz submitted that the claim was appropriately substantiated and complied with the Code.

Upon receipt of this complaint, Advanz re-assessed the claim and acknowledged that whilst the intention was not to mislead or misrepresent the evidence used to substantiate the claim, there was evidence to suggest that susceptibility results of urinary cultures were not always accurate and there were differences between *in vitro and in vivo* effectiveness of antibiotics. This was also acknowledged within the NICE NG109 guidelines. Advanz considered the claim that the resistance rates for trimethoprim referenced from *in vitro* testing 'will' result in treatment failure did not comprehensively reflect potential *in vivo* outcomes. Advanz accepted breaches of Clauses 7.2 and 7.4 and it had initiated withdrawal of materials using this claim.

In accepting these breaches, Advanz highlighted that this was the first Code complaint received since 2018. Advanz stated that it had a robust process to review and approve promotional materials in accordance with the Code requirements. As highlighted in the background to the material, several independent data sources were carefully considered when substantiating the claim, demonstrating the intention to be accurate, fair and balanced and to maintain standards in keeping with the spirit of the Code. The extrapolation of *in vitro* data in this circumstance was of direct relevance as the originating samples were from patients and significance of these data were reflected by their inclusion in NICE guidance.

Advanz requested that these points be taken into consideration when considering Clause 9.1.

PANEL RULING

The Panel noted that the subject line of the promotional email in question stated: 'Minimising antimicrobial resistance in lower urinary tract infections'. The body of the email was entitled 'Urinary tract infections (UTI) are one of the most common reasons for antibiotic prescriptions in primary care'. Below this were a number of claims, including the claim in question, 'In the UK, 1 in 3 adults will fail treatment for lower UTI with trimethoprim' which was beneath the subheading 'RESIST THE RESISTANCE' and was referenced to NICE NG109 (2018) and the Scottish One Health antimicrobial use and antimicrobial resistance in 2018 annual report.

The Panel noted that the NICE NG109 guideline (2018) which was entitled 'Urinary tract infection (lower): antimicrobial prescribing' stated that for England, resistance of *E.Coli* (the main causative organism of lower UTIs) in laboratory-processed urine specimens to trimethoprim was 30.3% (varied by area from 27.1 to 33.4%) based on Public Health England antimicrobial resistance quarterly surveillance dated March 2018. The Panel further noted that the Scottish report gave the percentage resistance of *E.Coli* urinary isolates in 2018 in NHS Scotland for trimethoprim as 33.6% (percentage resistance of *E. coli* urinary isolates from 2014 to 2018 for trimethoprim ranged from 33.4% to 34.2%). The Panel noted Advanz's submission that these data indicated that *E.coli* isolates from patient derived urinary specimens were resistant to trimethoprim in approximately 33% of cases. The Panel further noted Advanz's submission that the NICE NG109 guideline stated that resistant bacteria were a particular concern in UTIs and, where possible, any previous urine culture and susceptibility results, and antibiotic prescribing, should be checked and antibiotics chosen accordingly.

Clause 7.2 of the 2019 Code stated that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The supplementary information to this clause stated that care must be taken with the use of data derived from *in-vitro* studies so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it is of direct relevance and significance.

The Panel noted Advanz's submission that there was evidence to suggest that susceptibility results of urinary cultures were not always accurate and there were differences between *in vitro* and *in vivo* effectiveness of antibiotics which was acknowledged within the NICE NG109 guidelines. The Panel further noted Advanz's submission that on re-assessment of the material the company considered that the claim that the resistance rates for trimethoprim referenced from *in vitro* testing 'will' result in treatment failure did not comprehensively reflect potential *in vivo* outcomes.

The Panel considered that the claim 'In the UK, 1 in 3 adults will fail treatment for lower UTI with trimethoprim' was misleading as it implied that clinically, 1 in 3 adults would not respond adequately to trimethoprim for lower UTI which was not supported by clinical data; the misleading impression given by the claim could not be substantiated. The Panel ruled breaches of Clauses 7.2 and 7.4 as acknowledged by Advanz. The Panel considered that Advanz had failed to maintain high standards in this regard and a breach of Clause 9.1 was ruled.

Complaint received **7 May 2021**

Case completed **20 December 2021**