CASE AUTH/3271/10/19

COMPLAINANT v NAPP

Website

A complainant who described him/herself as a concerned UK health professional, complained about Napp Pharmaceutical's Invokana (canagliflozin) website. Invokana was indicated for use alone or in combination therapy in patients with type 2 diabetes.

The complainant noted that the landing page of the website had two sections identified – one to take UK health professionals to the Invokana health professional website and another to take patients or members of the public to patient information pages. The complainant alleged that the section for patients and members of the public listed facets of Invokana and therefore promoted the medicine to members of the public.

The complainant stated that of more concern, was that the prescribing information on the health professionals' part of the website did not refer to necrotising fasciitis of the perineum (Fournier's gangrene). This was a very serious addition to the summary of product characteristics (SPC) that Napp appeared not to have updated. The complainant alleged that Fournier's gangrene was also not listed in the safety section of the Invokana website. The complainant submitted that this was an issue of patient safety; mention of Fournier's gangrene should be on all other materials and communicated to representatives. The complainant noted that the missing text on gangrene was very different to gangrene of the extremities.

The detailed response from Napp is given below.

The Panel noted that the opening page of the section of the website that was displayed after the reader selected that they were a patient or a member of the general public stated 'Welcome to this website which aims to provide you with more information about your condition and the medicine your doctor or nurse has prescribed. It is also very important that you read the Patient Information Leaflet for Invokana'. The Panel noted that this section of the website included five sections including information on how Invokana worked and how it should be taken The Panel noted that whilst the section providing promotional information to health professionals was clearly labelled and was separated from the section containing information for patients/members of the public, it was clear that the latter was aimed specifically at patients who had been prescribed Invokana and there was thus no information for the general public as required by the Code and a breach was ruled.

With regard to the information for patients and the public, the Panel noted that under the heading of 'What else do you need to know about Invokana?', it was stated that although the medicine was not for weight management nor for the management of high blood pressure, Invokana might result in some weight loss when first taken (2 – 4kg) and that it could also lower blood pressure. The Panel considered that such claims for the product

effectively promoted Invokana to the public and a breach of the Code was ruled. The Panel noted that the prescribing information dated January 2019, which was available on the website when the complaint was submitted, included necrotising fasciitis of the perineum (Fournier's gangrene) in the special warnings and precautions section. The Panel therefore ruled no breach of the Code.

The Panel noted Napp's submission that, although an oversight meant that updated information on Fournier's gangrene was not included within the Safety and Tolerability section of the health professional section of the website, the updated prescribing information and a link to the Invokana SPC on the eMC website containing such information was provided. The Panel noted that Fournier's gangrene was a rare but serious and potentially life-threatening infection that required urgent medical attention. The Panel further noted that marketing authorisation holders of products containing SGLT2 inhibitors were specifically required to notify health professionals with regards to this condition. In the Panel's view, it should therefore have been included in the safety and tolerability section rather than relying on its inclusion in other documents (the SPC and the prescribing information) to which the reader was referred. Failure to specifically refer to Fournier's gangrene within the Safety and Tolerability section of the website was misleading and meant that the information given did not reflect available evidence. Breaches of the Code were ruled including that high standards had not been maintained. As no information had been given, there could be no breach of Clause 7.4 which required any information, claim or comparison to be capable of substantiation. No breach of the Code was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its rulings and comments above but decided, on balance, that the circumstances of this case did not merit a ruling of a breach of Clause 2. No breach was ruled.

A complainant who described him/herself as a concerned UK health professional, complained about Napp Pharmaceutical's Invokana (canagliflozin) website. Invokana was indicated for use alone or in combination therapy in patients with type 2 diabetes.

COMPLAINT

The complainant noted that the landing page of the website had two sections identified – one to take UK health professionals to the Invokana health professional website and another to take patients or members of the public to patient information pages. The complainant alleged that the section for patients and members of the public listed facets of Invokana and therefore promoted the medicine to members of the public.

The complainant stated that of more concern, was that the prescribing information on the health professionals' part of the website did not refer to necrotising fasciitis of the perineum (Fournier's gangrene). This was a very serious addition to the summary of product characteristics (SPC) that Napp appeared not to have updated. The complainant queried whether the website was a simple oversight in this regard or whether other materials were also affected. The complainant alleged that Fournier's gangrene was also not listed in the safety section of the Invokana website.

The complainant submitted that this was an issue of patient safety; mention of Fournier's gangrene should be on all other materials and communicated to representatives.

The complainant noted that the missing text on gangrene was very different to gangrene of the extremities.

In his/her complaint, the complainant provided a link to what appeared to be Invokana prescribing information dated November 2018, however the document downloaded from that link, and sent to Napp with the complaint by the case preparation manager, was dated January 2019.

When writing to Napp, the Authority asked it to consider the requirements of Clauses 2, 4.1, 4.2, 7.2, 7.4, 7.9, 9.1, 26.1 and 28.1 of the Code.

RESPONSE

Napp explained that it marketed Invokana in the UK on behalf of the marketing authorisation holder, Janssen-Cilag International NV. Napp noted that Clause 26.1 stated that 'Prescription only medicines must not be advertised to the public.' and Clause 28.1 stated that 'Promotional material about prescription only medicines directed to a UK audience which is provided on the Internet must comply with all relevant requirements of the Code'. Napp stated that the landing page of the Invokana website (screenshot provided by the complainant) had clear statements and separation of the sections including the section containing promotional content via the red health professional 'button', and the section containing patient or general public information pages via a blue 'button'. This approach fulfilled Clause 28.1 supplementary information Access, which stated that the 'sections for each target audience [are] clearly separated and the intended audience identified.' Also, because health professional access was not password restricted or the like, then as per Clause 28.1 supplementary information, Napp had provided information for the public as well as promotion to health professionals with the sections for each target audience clearly separated and the intended audience identified.

Napp noted the Panel's rulings in Case AUTH/2444/10/11 concerning a similar complaint about access to materials intended for health professionals and clear separation of information to patients/public to a Pradaxa website such that the intended audience was made clear. Napp believed that it had also made this clear on the landing page of the Invokana website.

Napp also noted that in Case AUTH/3107/10/18 there was a similar complaint about promotion to the public. The Panel stated 'The supplementary information stated that unless access to promotional material about prescription only medicines was limited to health professionals and other relevant decision makers, a pharmaceutical company website or a company sponsored website must provide information for the public as well as promotion to health professionals with the sections for each target audience clearly separated and the intended audience identified. This was to avoid the public needing to access material for health professionals unless they chose to…'. Napp submitted that this was exactly what it had done.

The non-promotional information provided about Invokana to patients and the general public was via the blue button. The opening paragraph on the webpage for the public section under 'Welcome to this website' stated 'which aims to provide you with more information about your condition and the medicine your doctor or nurse has prescribed. It is also very important that you read the Patient Information Leaflet for Invokana'.

Although the case preparation manager had not raised Clause 26.2 and its accompanying supplementary information, Napp considered that this was pertinent as it had followed the guidance that information made available to the public had to be factual, presented in a balanced way, and not made for the purpose of encouraging members of the public to ask their doctors or other prescribers to prescribe a specific prescription only medicine. Sufficient reference information was provided on the patient and general public area of the website via internal and external links, including to the patient information leaflet (which would also be provided to the patient in hard copy within the package of the prescribed medicine collected at the pharmacy). Napp had included reference information divided into 5 sections: (i) 'What is type 2 diabetes?', (ii) 'What is Invokana?', (iii) 'What else do you need to know about Invokana?', (iv) 'What potential side-effects should you be aware of?' and (v) 'Useful contacts & support'. The three sections about Invokana (ii, iii, & iv) made no promotional claims and Napp refuted the complainant's assertion that the information provided promoted to the public. The information was accurate, balanced, fair, objective and unambiguous and based on an up-to-date evaluation of all the evidence and reflected that evidence clearly. There was sufficient information provided to qualify as reference information so that a patient or member of the public would not need to access the health professionals' section of the website.

Napp submitted that as per Clause 7.2, the information did not mislead directly or by implication, by distortion, exaggeration or undue emphasis. Further, as per Clause 7.4, the information was capable of substantiation as reflected by the SPC.

As per Clause 7.9, there was information provided about adverse reactions to reflect available evidence by the (1) internal and (2) external patient information leaflet links to the electronic medicines compendium (eMC). Napp had reflected section 4 of the patient information leaflet (Possible side effects) within the patients' and general public's section of the website: iv) 'What potential side-effects should you be aware of?'. Within the references section an external (eMC website) Invokana patient information leaflet link was provided, last updated in March 2019, which included Fournier's gangrene.

Napp refuted breaches of Clauses 26.1, 28.1, 7.2, 7.4 and 7.9. The company had maintained high standards, not brought discredit upon or reduced confidence in the pharmaceutical industry, and thus it denied breaches of Clauses 9.1 and Clause 2.

With regard to the prescribing information, and as per Clause 4.1, Napp had provided a clear and legible link to the prescribing information on the first page of the health professional side of the Invokana website as identified by the complainant. Furthermore, as per Clause 4.2, Napp had provided a succinct statement of common and serious adverse reactions, precautions and contra-indications, including specifically necrotising fasciitis (Fournier's gangrene). The prescribing information (dated January 2019) began with a sentence, in bold text, asking the reader to: 'Please refer to the Summary of Product Characteristics (SPC) before prescribing'. At the bottom of page 1 of the prescribing information, within 'Special warnings and precautions', was 'Necrotising fasciitis of the perineum (Fournier's gangrene)**:** post-marketing cases reported with SGLT2 inhibitors. Rare but serious, patients should seek medical attention if experiencing symptoms including pain, tenderness, erythema, genital/perineal swelling, fever, malaise. If Fournier's gangrene suspected, Invokana should be discontinued, and prompt treatment instituted'.

Napp stated that reference 1 within the 'About Invokana' section of the health professionals' website was to the Invokana SPC via an external link to the eMC. Clicking on this link directed a health professional viewing the website to the up-to-date SPC (last updated 12 March 2019). Fournier's gangrene was included in Section 4.4 (Special warnings and precautions for use).

The complainant also stated that: 'This omission is also present in the safety section of the web-site'. Due to an oversight Napp has not provided updated information on Fournier's gangrene within the Safety and Tolerability section of the health professional section of the website. However, on the website Napp had provided the updated prescribing information, and an external link to the Invokana SPC on the eMC website. Furthermore, all UK health professionals were sent a letter. Taken together Napp considered that it had provided clear information about Fournier's gangrene to health professionals.

Napp therefore disagreed with the complainant that it had omitted information within the prescribing information provided, and therefore refuted breaches of Clauses 4.1 and 4.2. Napp had also provided an external link to the up-to-date Invokana SPC. As per Clause 7.2, the information did not mislead directly or by implication, by distortion, exaggeration or undue emphasis. As per Clause 7.4 the information could be substantiated as reflected by the SPC.

Napp submitted that it had therefore maintained high standards, not brought discredit upon or reduced confidence in the pharmaceutical industry, and thus had not breached Clauses 9.1 or Clause 2.

Communication of safety information to health professionals, Napp representatives and medical science liaisons (MSLs)

In late 2018 the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) published a signal assessment report on a possible association between Fournier's gangrene and the use of SGLT2i class of medicines, which included canagliflozin (Invokana). A letter was sent to all UK health professionals in January 2019 from all UK pharmaceuticals companies which marketed SGLT2i medicines, including Napp. The prescribing information was updated in January 2019 in readiness for updates to the SPC and patient information leaflet in March. In March there was a company recall of all materials affected by the updates. The updated prescribing information was included in the safety section of the main sales aid and in the five leavepieces used by the Invokana representatives. As per Clause 7.2 the information and updates of the materials did not mislead directly or by implication, by distortion, exaggeration or undue emphasis. As per Clause 7.4, the information could be substantiated as reflected by the SPC.

In addition, Napp medical information prepared a briefing document which was certified and emailed to all representatives who promoted Invokana. The representatives had to confirm that they had read the briefing and destroyed any existing copies of the Invokana (and Vokanamet) SPCs and were told how to obtain updated copies by use of a 'yes' voting button as part of the email.

Furthermore, a briefing document and slide deck about the EMA PRAC assessment of possible Fournier's gangrene and the letter which had been sent to all health professionals was also sent to the field-based MSLs. The communications described above, along with the attachments demonstrated that Napp took patient safety very seriously.

Napp therefore refuted breaches of Clauses 4.1, 4.2, 7.2, 7.4 and 7.9. Napp had maintained high standards, not brought discredit upon or reduced confidence in the pharmaceutical industry, and thus submitted that it had not breached Clauses 9.1 or 2.

Finally, Napp noted that the complainant had stated that the missing text on Fournier's gangrene was very different to gangrene of the extremities. Napp was unclear about the precise meaning of that sentence and could not comment further, as it had already responded to the complaint about missing text within the prescribing information.

In summary, Napp stated that it had provided a comprehensive response to the complaint and explained how it had maintained high standards (Clause 9.1) and made clear why it refuted breaches of Clauses 4.1, 4.2, 7.2, 7.4, 7.9, 26.1 and 28.1. Napp had not brought discredit upon, or reduced confidence in, the pharmaceutical industry, and it considered that it had held high standards as per Clause 2 as demonstrated in its response by its due diligence regarding patient safety.

PANEL RULING

The Panel noted that Clause 26.1 prohibited the advertising of prescription only medicines to the public. Clause 26.2 permitted information to be supplied directly or indirectly to the public but such information had to be factual and presented in a balanced way. The Panel also noted the reference to a library resource in the supplementary information to Clause 26.2. The Panel noted that Clause 28 covered the Internet and other digital platforms, its supplementary information, Access, stated that unless access to promotional material about prescription only medicines was limited to health professionals and other relevant decision makers, a pharmaceutical company website or a company sponsored website must provide information for the public as well as promotion to health professionals with the sections for each target audience clearly separated and the intended audience identified. This was to avoid the public needing to access material for health professionals unless they chose to. The Panel noted that Clause 28.1 and its supplementary information did not mention material for patients who had been prescribed a specific medicine. The Panel noted that companies could provide information about a specific medicine to patients for whom the prescribing decision had already been made provided that such information complied with the relevant requirements of the Code.

The Panel noted that the landing page of the Invokana website stated 'The content of this website has been developed by Napp Pharmaceuticals Ltd for health professionals, patients who have been prescribed Invokana, or members of the public'. It then asked the reader to select 'I confirm I am a UK healthcare professional' which was followed by 'Please take me to the Invokana health professional website' or 'I am a patient or a member of the general public' which was followed by 'Please take me to the Invokana patient information pages'.

The Panel noted that the opening page of the section of the website that was displayed after the reader selected that they were a patient or a member of the general public stated 'Welcome to this website which aims to provide you with more information about your condition and the medicine your doctor or nurse has prescribed. It is also very important that you read the Patient Information Leaflet for Invokana'. The Panel noted that this section of the website included five sections including: (1) What is type 2 diabetes? which included general information on type 2 diabetes and self-care tips following a diagnosis of type 2 diabetes; (2) What is Invokana? which included information on how Invokana worked and how it should be taken; (3) What else you need to know about Invokana?; (4) What potential side effects should you be aware of?; and (5)

Useful contacts and support. In the Panel's view, the supplementary information to Clause 28.1 was referring to the separation of promotional material intended for health professionals and/or other relevant decision makers from material intended for the general public. The Panel noted that whilst the section providing promotional information to health professionals was clearly labelled and was separated from the section containing information for patients/members of the public, it was clear that the latter was aimed specifically at patients who had been prescribed Invokana and there was thus no information for the general public as required by Clause 28.1 and a breach was ruled.

With regard to the information for patients and the public, the Panel noted that under the heading of 'What else do you need to know about Invokana?', it was stated that although the medicine was not for weight management nor for the management of high blood pressure, Invokana might result in some weight loss when first taken (2 – 4kg) and that it could also lower blood pressure. The Panel considered that such claims for the product effectively promoted Invokana to the public and a breach of Clause 26.1 was ruled.

The Panel noted that prescribing information, the components of which were listed in Clause 4.2, must be up-to-date and satisfy the requirements of Clause 4.2 which included providing a succinct statement of, amongst other things, common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement, and giving in an abbreviated form the substance of the relevant information in the SPC. Failure to provide the required information in the prescribing information would be a breach of Clause 4.1. The Panel noted that the prescribing information dated January 2019, which was available on the website when the complaint was submitted, included necrotising fasciitis of the perineum (Fournier's gangrene) in the special warnings and precautions section. The Panel therefore ruled no breach of Clause 4.1.

The Panel noted the complainant's allegation that Fournier's gangrene was not listed in the safety section of the Invokana website. The Panel noted that this allegation appeared to be in relation to the health professional section of the website and the Panel therefore only made rulings in this regard.

The Panel noted that Clause 7.9 required that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience. The Panel noted Napp's submission that, although an oversight meant that updated information on Fournier's gangrene was not included within the Safety and Tolerability section of the health professional section of the website, the updated prescribing information and a link to the Invokana SPC on the eMC website containing such information was provided. The Panel noted that Fournier's gangrene was a rare but serious and potentially life-threatening infection that required urgent medical attention. The Panel further noted that marketing authorisation holders of products containing SGLT2 inhibitors were specifically required to notify health professionals with regards to this condition. In the Panel's view, it should therefore have been included in the safety and tolerability section rather than relying on its inclusion in other documents (the SPC and the prescribing information) to which the reader was referred. The Panel noted that it was an established principle under the Code that material had to be capable of standing alone. Failure to specifically refer to Fournier's gangrene within the Safety and Tolerability section of the website was misleading and meant that the information given did not reflect available evidence. Breaches of Clauses 7.2 and 7.9 were ruled. As no information had been given,

there could be no breach of Clause 7.4 which required any information, claim or comparison to be capable of substantiation. No breach of Clause 7.4 was ruled.

Although noting the complainant's view that mention of Fournier's gangrene should be on all other materials and communicated to representatives, the Panel considered that he/she had made a comment in that regard and not a complaint; the complainant had not alleged that mention of Fournier's gangrene was not on all other materials and had not been communicated to representatives. The Panel made no rulings in that regard.

The Panel noted its comments and rulings above and considered that Napp had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its rulings and comments above but decided, on balance, that the circumstances of this case did not merit a ruling of a breach of Clause 2. No breach was ruled.

Complaint received **28 October 2019**

Case completed **25 September 2020**