CASE AUTH/3402/10/20

COMPLAINANT v SANOFI

Out of date prescribing information and inaccurate information for Dupixent

A complainant who described him/herself as a health professional, alleged that material on the product website for Dupixent (dupilumab) was inaccurate. Dupixent was marketed by Sanofi and indicated for the treatment of atopic dermatitis in certain patients. It was also indicated for the maintenance treatment of severe asthma in certain patients.

The complainant alleged that a document which referred to Dupixent and the National Institute for Health and Care Excellence (NICE) technology appraisal guidance included outdated prescribing information. The complainant further alleged that a guide to Dupixent for health professionals included outdated information in that it stated that the safety and efficacy of Dupixent had not been established in asthma whereas the Dupixent summary of product characteristics (SPC) stated that it was licensed for asthma. The use of outdated prescribing information or misleading information about a medicine could seriously harm patients by having clinicians making wrong treatment decisions.

The detailed response from Sanofi is given below.

The Panel noted that according to the Dupixent 200mg and 300mg SPCs (last revised 22 December 2020 and 9 December, respectively), Dupixent was indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who were candidates for systemic therapy and the treatment of severe atopic dermatitis in children 6 to 11 years old who were candidates for systemic therapy. The medicine was also indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide who were inadequately controlled with high dose inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment; the Panel noted that this indication was very specific and contrary to the complainant's view that the medicine was 'licensed for asthma'.

The Panel noted that the SPC included, in Section 4.4 Special warnings and precautions for use, that dupilumab should not be used to treat acute asthma symptoms or acute exacerbations. Dupilumab should not be used to treat acute bronchospasm or status asthmaticus. Systemic, topical, or inhaled corticosteroids should not be discontinued abruptly upon initiation of therapy with dupilumab. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician.

The Panel noted that the guide for health professionals in question related to information and resources regarding the use of Dupixent in atopic dermatitis. The document provided by the complainant stated on a page headed 'Additional considerations with

Dupixent', beneath the heading 'Comorbid Asthma', that the safety and efficacy of Dupixent had not been established in the treatment of asthma. Patients with comorbid asthma should not adjust or stop their asthma treatments without consultation with their prescribing doctor. Patients with comorbid asthma should be monitored carefully following discontinuation of Dupixent.

The Panel noted that Section 4.4 of the Dupixent SPC, Special warnings and precautions for use, stated beneath the heading 'Atopic dermatitis patients with comorbid asthma' that 'Patients on dupilumab for moderate-to-severe atopic dermatitis who also have comorbid asthma should not adjust or stop their asthma treatments without consultation with their physicians. Patients with comorbid asthma should be monitored carefully following discontinuation of dupilumab.'. The Panel noted that there was no mention in the SPC of the efficacy or safety of Dupixent in the treatment of asthma not being established other than in children with severe asthma below the age of 12 years in Section 4.2.

The Panel further noted that Section 5.1, Pharmacodynamic properties, discussed the clinical efficacy and safety in asthma and referred to three randomised, double-blind, placebo-controlled, parallel-group, multi-centre studies of 24 to 52 weeks in treatment duration which enrolled a total of 2,888 patients (12 years of age and older) which were included in the asthma development program.

The Panel noted that the statement 'Safety and efficacy of Dupixent have not been established in the treatment of asthma' was included in the October 2017 prescribing information provided by Sanofi which was created before the asthma indication for Dupixent was approved and added to the SPC in May 2019. The August 2019, December 2019 and July 2020 prescribing information for Dupixent provided by Sanofi did not include this statement.

On the evidence before it the Panel considered that the general statement in the health professional guide that the safety and efficacy of Dupixent had not been established in the treatment of asthma was misleading and inconsistent with the particulars listed in the SPC; breaches of the Code were ruled. The Panel considered that Sanofi had failed to maintain high standards in that regard and a further breach of the Code was ruled.

The Panel noted that the health professional guide was clear in that it promoted the moderate to severe atopic dermatitis indication of Dupixent. Whilst noting that the misleading statement might result in confusion amongst health professionals who were aware of Dupixent's other indication, as add-on maintenance treatment for severe asthma in certain patients 12 years and older, the Panel did not consider that the matter within the particular circumstances of this case warranted a ruling of a breach of Clause 2, a sign of particular censure and reserved for such use. No breach was ruled.

With regards to the document which referred to Dupixent and the NICE technology appraisal guidance, the Panel noted Sanofi's submission that the current prescribing information was dated July 2020 whereas the material in question included a previous version dated October 2017. The prescribing information was thus out of date and the Panel therefore ruled a breach of the Code as acknowledged by Sanofi.

The Panel noted from the documentation provided by Sanofi that there had been a number of updates to the Dupixent SPC and subsequent prescribing information since October 2017 including, amongst other things, the addition of angioedema and anaphylactic reactions as side effects of unknown frequency in June 2020, and whilst included in the current July 2020 prescribing information, were omitted from the October 2017 prescribing information which was included on Sanofi's Dupixent NICE technology appraisal guidance document when the complaint was received (October 2020).

The Panel noted that according to documentation provided by Sanofi the prescribing information had been updated at least twice before the July 2020 version - August 2019 and December 2019. The Panel was concerned that the October 2017 prescribing information on Sanofi's Dupixent NICE technology appraisal guidance document had not been identified and updated on any of these occasions. The Panel considered that Sanofi had failed to maintain high standards and a breach of the Code was ruled.

The Panel considered that these failures brought discredit upon and reduced confidence in the pharmaceutical industry. It was crucial that health professionals and others could rely upon the industry for up-to-date and accurate information about their medicines. A breach of Clause 2 was ruled.

A complainant who described him/herself as a health professional complained about the promotion of Dupixent (dupilumab) by Sanofi. Dupixent was indicated for the treatment of atopic dermatitis in certain patients. It was also indicated for the maintenance treatment of severe asthma in certain patients.

COMPLAINT

The complainant alleged that information on the Dupixent website (www.dupixent.co.uk) was inaccurate and in that regard referred to two documents. The complainant alleged that a Sanofi document which referred to Dupixent and the National Institute for Health and Care Excellence (NICE) technology appraisal guidance included outdated prescribing information. The second document was a guide to Dupixent for health professionals which the complainant alleged included outdated information. The complainant referred to a section headed 'Comorbid Asthma' on page 3 in which it was stated that the safety and efficacy of Dupixent had not been established in asthma. However, section 4.1 of the Dupixent summary of product characteristics (SPC) showed that Dupixent was licensed for asthma. The complainant stated that the use of outdated prescribing information or misleading information about a medicine could seriously harm patients by having clinicians making wrong treatment decisions.

When writing to Sanofi, the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2 and 9.1 of the Code.

RESPONSE

Sanofi explained that the guide for health professionals (ref MAT-GB-2001250 (v1.0)) was entitled 'Helping patients achieve long-term disease control in moderate-to-severe atopic dermatitis A guide to Dupixent (dupilumab) for healthcare professionals.' It was a downloadable resource on the dupixent.co.uk website which contained information and resources for health professionals about atopic dermatitis (AD) and Dupixent. The page in question was headed

'Additional Considerations With Dupixent' and featured various sections in a boxed area. The section in question was:

> 'Comorbid Asthma
>
> Safety and efficacy of Dupixent have not been established in the treatment of asthma. Patients with comorbid asthma should not adjust or stop their asthma treatment without consultation with their prescribing doctor. Patients with comorbid asthma should be monitored carefully following discontinuation of Dupixent.'

Sanofi noted that the indication for Dupixent was very specific and related to a clear subsection of patients as stated in Section 4.1 of the Dupixent SPC (Therapeutic indications) which stated:

> 'Asthma
>
> Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.'

Furthermore, Section 4.4, Special Precautions and Warnings included:

> 'Atopic dermatitis or CRSwNP [chronic rhinosinusitis with nasal polyposis] patients with comorbid asthma
>
> Patients on dupilumab for moderate-to-severe atopic dermatitis or severe CRSwNP who also have co-morbid asthma should not adjust or stop their asthma treatments without consultation with their physicians. Patients with comorbid asthma should be monitored carefully following discontinuation of dupilumab.'

Sanofi submitted that that statement (as the SPC was a combined document with all indications) was ostensibly the same as the section highlighted above that appeared in the item in question.

In reference to the allegation regarding the licensed indication, Sanofi submitted that it had been very diligent so as to not attempt to broaden the licenced indication which was specific to 'severe asthma, with various criteria' and had been responsible in stating that the safety and efficacy of Dupixent had not been established in the treatment of what would be a broader indication - 'asthma'. In addition, the statement above was clearly in a section headed 'Comorbid Asthma' and was followed by statements about management/ monitoring of patients with comorbid asthma, strictly in line with Sanofi's licence.

Sanofi denied any breach of Clauses 3.2 ,7.2, 9.1 or 2 in respect of this aspect of the complaint.

Sanofi explained that the document which referred to the NICE technology appraisal guidance, 'NICE Technology Appraisal Guidance TA534 Dupilimab for treating moderate to severe atopic dermatitis', (ref SAGB.DUP.18.06.0858(1)), was a further downloadable resource from the Dupixent website. As noted by the complainant the item contained prescribing information with an October 2017 date of revision; the current prescribing information had a date of preparation of July 2020.

Sanofi stated that it had the following process in place to update prescribing information following an SPC change as per its standard operating procedure:

- The regulatory team, in conjunction with the appropriate medical lead, determined if an SPC change should result in a change to the prescribing information.
- New prescribing information was approved and archived on the accessible regulatory SharePoint and onto the electronic approval system library.
- The superseded prescribing information was marked not for use after the new prescribing information approval date.
- All brand leads were advised of the new prescribing information and the date for all materials with superseded prescribing information to be withdrawn.
- A list was drawn up of all materials containing the superseded prescribing information.
- At that point all materials containing the out of date prescribing information were withdrawn.
- New materials were then certified for use with the current updated prescribing information.

Sanofi stated that it had carried out a full investigation of the approval of the website and the NICE technology appraisal guidance in question, having immediately closed access to the 'Resources' page on the website pending the outcome of the investigation.

During the investigation Sanofi further noted that the item in question was due for reapproval in early August 2020. During the period from end March to November 2020 across the whole of Sanofi and Sanofi Genzyme there was a transitioning of a multitude of relevant materials from the Zinc system/platform, due to its pending withdrawal from use, onto the new review and approval system, Veeva PromoMats platform. It was decided that any materials not transitioned by final shutdown of Zinc were to be considered withdrawn and only materials approved on PromoMats were effective and 'live'. The job bag originator for the item 'NICE Technology Appraisal Guidance TA534' had not re-approved the item as he/she considered it was not required for the appropriate teams for which it was first made available. When the website was being transitioned to PromoMats the document had still been 'live', so it was not noticed by the website originator/review team that it was not certified/approved when the webpage was certified (MAT-GB-2001592 (v1.0)) in mid-August 2020. The result of that was that the 'NICE Technology Appraisal Guidance TA534' material had not been certified on PromoMats when it appeared on the website. Sanofi therefore self-declared a breach of Clause 14.1 of the Code in addition to a breach of Clause 7.2 in respect of the incorrect prescribing information.

Sanofi submitted that it had various robust processes and SOPs which covered the development and approval of prescribing information when there was a significant SPC change; the development, approval and withdrawal of materials and recorded training for all relevant members of staff involved in these activities. Sanofi had no other explanation except for human error for the breaches noted above. Sanofi therefore denied breaches of Clauses 9.1 and 2.

PANEL RULING

The Panel noted that according to the Dupixent 200mg and 300mg SPCs (last revised 22 December 2020 and 9 December, respectively), accessed via the electronic medicines compendium (eMC) link provided by Sanofi with its response, Dupixent was indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who were candidates for systemic therapy and the treatment of severe atopic dermatitis in children 6 to 11 years old who were candidates for systemic therapy.

The Panel noted that according to the SPCs Dupixent was also indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide who were inadequately controlled with high dose inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment; the Panel noted that this indication was very specific and contrary to the complainant's view that the medicine was 'licensed for asthma'.

The Panel noted that Section 4.4, Special warnings and precautions for use, stated that dupilumab should not be used to treat acute asthma symptoms or acute exacerbations. Dupilumab should not be used to treat acute bronchospasm or status asthmaticus. Systemic, topical, or inhaled corticosteroids should not be discontinued abruptly upon initiation of therapy with dupilumab. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose might be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

The Panel noted that the guide for health professionals related to information and resources about Dupixent and atopic dermatitis. The document provided by the complainant stated on a page headed 'Additional considerations with Dupixent', beneath the heading 'Comorbid Asthma', that the safety and efficacy of Dupixent had not been established in the treatment of asthma. Patients with comorbid asthma should not adjust or stop their asthma treatments without consultation with their prescribing doctor. Patients with comorbid asthma should be monitored carefully following discontinuation of Dupixent.

The Panel noted that Section 4.4 of the Dupixent SPC, Special warnings and precautions for use, stated beneath the heading 'Atopic dermatitis patients with comorbid asthma' that 'Patients on dupilumab for moderate-to-severe atopic dermatitis who also have comorbid asthma should not adjust or stop their asthma treatments without consultation with their physicians. Patients with comorbid asthma should be monitored carefully following discontinuation of dupilumab.'. The Panel noted that there was no mention in the SPC of the efficacy or safety of Dupixent in the treatment of asthma not being established other than in children with severe asthma below the age of 12 years in Section 4.2.

The Panel further noted that Section 5.1, Pharmacodynamic properties, discussed the clinical efficacy and safety in asthma and referred to three randomised, double-blind, placebo-controlled, parallel-group, multi-centre studies (DRI12544, QUEST, and VENTURE) of 24 to 52 weeks in treatment duration which enrolled a total of 2,888 patients (12 years of age and older) which were included in the asthma development program.

The Panel noted that the statement 'Safety and efficacy of Dupixent have not been established in the treatment of asthma' was included in the October 2017 prescribing information provided by Sanofi which was created before the asthma indication for Dupixent was approved and added to the SPC in May 2019. The August 2019, December 2019 and July 2020 prescribing information for Dupixent provided by Sanofi did not include that statement.

On the evidence before it, the Panel considered that the general statement in the health professional guide, that the safety and efficacy of Dupixent had not been established in the treatment of asthma was misleading and inconsistent with the particulars listed in the SPC; a breach of Clauses 7.2 and 3.2 was ruled. The Panel considered that Sanofi had failed to maintain high standards in that regard and a breach of Clause 9.1 was ruled.

The Panel noted that the health professional guide was clear in that it promoted the moderate to severe atopic dermatitis indication of Dupixent. Whilst noting that the misleading statement might result in confusion amongst health professionals who were aware of Dupixent's other indication, as add-on maintenance treatment for severe asthma in certain patients 12 years and older, the Panel did not consider that the matter within the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and was reserved for such use. No breach of Clause 2 was ruled.

With regards to the Sanofi document referring to Dupixent and the NICE technology appraisal guidance, the Panel noted Sanofi's submission that the current prescribing information was dated July 2020 whereas the material in question included a previous version of the prescribing information, dated October 2017. The prescribing information was thus out of date and the Panel therefore ruled a breach of Clause 7.2 as acknowledged by Sanofi.

The Panel noted from the documentation provided by Sanofi (including track changed copies of its SPCs) that there had been a number of updates to the Dupixent SPC and subsequent prescribing information since October 2017 including, amongst other things, the addition of angioedema and anaphylactic reactions as side effects of unknown frequency in June 2020 and whilst included in the current July 2020 prescribing information, were omitted from the October 2017 prescribing information which was included on Sanofi's Dupixent NICE technology appraisal guidance document when the complaint was received (October 2020).

The Panel noted that according to documentation provided by Sanofi the prescribing information had been updated at least twice before the July 2020 version - August 2019 and December 2019. The Panel was concerned that the October 2017 prescribing information on Sanofi's Dupixent NICE technology appraisal guidance document had not been identified and updated on any of these occasions. The Panel considered that Sanofi had failed to maintain high standards and a breach of Clause 9.1 was ruled. The Panel considered that these failures brought discredit upon and reduced confidence in the pharmaceutical industry. It was crucial that health professionals and others could rely completely upon the industry for up to date and accurate information about their medicines. A breach of Clause 2 was ruled.

The Panel noted Sanofi's explanation regarding the reason for the error and the company's voluntary admission that the material had not been certified which was taken up in Case AUTH/3447/12/20.

Complaint received 21 October 2020

Case completed **29 March 2021**