CASE AUTH/2053/10/07 *NO BREACH OF THE CODE*

GLAXOSMITHKLINE v ASTRAZENECA

Symbicort leavepiece

GlaxoSmithKline complained about a Symbicort (budesonide/formoterol) leavepiece, issued by AstraZeneca, which explained Symbicort SMART (Symbicort Maintenance and Reliever Therapy in one inhaler) therapy and in that regard contained the statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed*'. The asterisk referred the reader to the summary of product characteristics (SPC) and to the fact that Symbicort 'as needed' was not indicated for prophylactic use prior to exercise. GlaxoSmithKline considered that use of the asterisk acknowledged that there was important information that prescribers needed to know.

The Symbicort SMART regimen was a novel approach to treating asthma and therefore something that prescribers were not familiar with; there was thus a responsibility to provide adequate and visible safety information. The complexity and restrictions of the regimen were glossed over by the simple, unqualified statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed' which implied that there was no upper limit to such a regimen and was inconsistent with the SPC. GlaxoSmithKline alleged that the statement was unbalanced, misleading and did not encourage rational use.

The Panel noted that the statement at issue 'Rx Symbicort 200/6 1 inhalation bd plus as needed' appeared as facsimile handwriting to mimic a prescription. The asterisk referred readers to the SPC and reminded them that Symbicort as needed was not indicated for prophylactic use prior to exercise. Section 4.2 of the SPC (Posology and method of administration) stated that, with regard to maintenance and reliever therapy, patients should take a daily maintenance dose of Symbicort and in addition take Symbicort as needed in response to symptoms.

The Panel considered that the statement accurately reflected the dosage particulars listed in the SPC. It would be unlikely that a prescriber would copy the statement in the leavepiece without seeking further information and advising a patient accordingly. In the Panel's view prescribers would be familiar with the use of medicines such as Symbicort and well aware of the need to act if patients asked for too many repeat prescriptions ie over-used their inhalers. The Panel considered that given the audience to which it was directed, the statement was not unbalanced, misleading or exaggerated as alleged. Further, the Panel did not consider that the statement was such that it did not encourage the rational use of Symbicort. No breach of the Code was ruled.

GlaxoSmithKline UK Ltd complained about a Symbicort (budesonide/formoterol) leavepiece (ref SYMB 07 11774) issued by AstraZeneca UK Limited which explained Symbicort SMART (Symbicort Maintenance And Reliever Therapy in one inhaler) therapy.

COMPLAINT

GlaxoSmithKline noted that the leavepiece contained the statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed*'. The asterisk referred the reader to the summary of product characteristics (SPC) and related to the fact that Symbicort 'as needed' was not indicated for prophylactic use prior to exercise. Its presence acknowledged that there was important information that prescribers needed to know.

GlaxoSmithKline was concerned that the statement was unbalanced, exaggerated and misleading. GlaxoSmithKline considered that there needed to be some qualification within or immediately associated with the statement in accordance with the supplementary information to Clause 7 of the Code.

The Symbicort SMART regimen was a novel approach to treating asthma; the complexity and restrictions of the regimen were glossed over by the simplified statement at issue. Being a novel regimen, it was something that prescribers were not familiar with; hence there was a responsibility to provide adequate and visible safety information.

The leavepiece made no attempt to specify a safe upper limit on the number of 'as-needed' inhalations which was stipulated in the SPC. The following statement was taken directly from section 4.2 of the SPC for the Symbicort 100/6 and 200/6 Turbohaler (GlaxoSmithKline emboldening added for convenience):

- The recommended maintenance dose is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. **Not more than 6 inhalations should be taken on any single occasion.**

- A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. **Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice.** They should be reassessed and their maintenance therapy should be reconsidered.

The unqualified statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed' implied that there was no upper limit to such a regimen and was inconsistent with the SPC.

In inter-company correspondence AstraZeneca had stated that there was no need to include the dosage limits because had this been significant safety information, it would have been included in the 'Special warnings and precautions for use' section of the SPC. GlaxoSmithKline disagreed with this position and believed that the provision of information on any medicines must be conducted ethically and in the context of the prescribers' knowledge of the product/regimen, with patient safety at its core. It was not reasonable to refer to where safety information was placed in the SPC. In fact, section 4.4 'Special warnings and precautions for use' of the Symbicort SPC stated:

- If patients find the treatment ineffective, or exceed the highest recommended dose of Symbicort, medical attention must be sought (see section 4.2 'Posology and method of administration').

In addition, section 4.2 'Posology and method of administration' stated:

- Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Symbicort as-needed inhalations.

GlaxoSmithKline believed that both of the above statements indicated that the limit on the number of 'as-needed' inhalations was considered important enough to be made clear in promotional material to ensure prescribers were aware of appropriate use of the SMART regime.

In inter-company correspondence AstraZeneca had stated that 'Rx Symbicort 200/6 1 inhalation bd plus as needed' was not a claim and therefore further qualification was not required. GlaxoSmithKline disagreed; this statement appeared as an instruction to prescribers, written in a style to mimic a doctor's prescription in a piece of promotional literature. If, as claimed by AstraZeneca, the leavepiece was not intended as comprehensive dosing information but was meant to provide background information to make physicians aware of the significance of over-relying on short acting bronchodilators, then the statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed' mimicking a prescription should not appear at all.

Symbicort maintenance and reliever therapy was a novel approach to the treatment of asthma which prescribers might not be familiar with. It was the responsibility of the pharmaceutical industry to provide clear information in this case regarding the dosage limits to ensure patient safety.

GlaxoSmithKline alleged that the statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed' was unbalanced, misleading and did not encourage the rational use of the medicine, in breach of Clauses 7.2 and 7.10.

RESPONSE

AstraZeneca disagreed that the statement at issue was a claim. The statement was included in the leavepiece because it was essential for prescribers to know how a prescription for Symbicort as maintenance and reliever therapy should be written. A single inhaler used both as maintenance therapy and additionally for the relief of symptoms was a new concept in the management of asthma. The statement 'plus as needed' was agreed in the course of the European Mutual Recognition Process and was stated in section 4.1 of the Symbicort 200/6 SPC. Without clearly telling prescribers how a prescription should be written it was thought that prescriptions might not be correctly understood and in some cases invalid prescriptions such as 'Rx Symbicort SMART …' would have been written.

An asterisk and a footnote which referred to the SPC was included in the leavepiece as 'Symbicort 200/6 1 inhalation bd plus as needed' was the most widely studied dose and considered the usual treatment regimen for the majority of patients. It was not the only licensed dose or strength. Additionally, AstraZeneca indicated to the prescriber that while Symbicort was approved for 'reliever' use it should not be used for regular prophylactic use.

AstraZeneca noted GlaxoSmithKline's comments that 'Rx Symbicort 200/6' implied that there was no upper limit to such a regimen and therefore it was inconsistent with the SPC. Furthermore, GlaxoSmithKline recognised that the asterix was there as an acknowledgement that important information was available which prescribers needed to know.

All medicines had safe upper dosing limits and these were as stated in the SPC, referred to in the leavepiece, together with other important information which prescribers needed to know.

The Medicines and Healthcare products Regulatory Agency (MHRA) was particular about the inclusion of all relevant statements with regard to the safe use of products yet in pre-vetting AstraZeneca's materials it had not commented about the need to present additional information in the leavepiece.

AstraZeneca noted that GlaxoSmithKline had drawn attention to section 4.2 'Posology and method of administration' of the SPC and seemed to suggest that these two sentences should be reproduced in all promotional materials. If the detail of the posology and method of administration section of the SPC had to be reproduced in promotional materials this would have profound implications for the industry in general. AstraZeneca noted the context in which these statements were included in section 4.2 of the SPC.

It was well recognized in asthma management that in periods of poor asthma control patients often overused their 'reliever', bronchodilator, when in fact they needed more maintenance corticosteroid. This section provided the rationale for Symbicort as maintenance and reliever therapy, because when the patient had symptoms their use of Symbicort as a 'reliever'

provided additional corticosteroid helping to bring their asthma back under control.

Furthermore, section 4.4 of the SPC stated that 'If patients find the treatment ineffective, or exceed the highest recommended dose of Symbicort, medical attention must be sought'. This statement was a variation of statements included in similar sections of most asthma therapies. In fact the SPC for GlaxoSmithKline's Seretide stated in the same section: 'Serious asthma-related adverse events and exacerbations may occur during treatment with Seretide. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Seretide. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician'.

AstraZeneca rejected the notion that the full details of the recommended doses of Symbicort, as in the SPC, needed to be listed in promotional materials. In referring to the SPC in the leavepiece, AstraZeneca had responsibly provided clear information as to the correct and judicious use of Symbicort. AstraZeneca recognized its obligations and considered that it had maintained high standards in this and all other materials. AstraZeneca therefore denied that the leavepiece breached the Code as alleged.

PANEL RULING

The Panel noted that the statement at issue 'Rx Symbicort 200/6 1 inhalation bd plus as needed' appeared as facsimile handwriting to mimic a prescription. The asterisk referred readers to the SPC and reminded them that Symbicort as needed was not indicated for prophylactic use prior to exercise. Section 4.2 of the SPC (Posology and method of administration) stated that, with regard to maintenance and reliever therapy, patients should take a daily maintenance dose of Symbicort and in addition take Symbicort as needed in response to symptoms.

The Panel considered that the statement at issue accurately reflected the dosage particulars listed in the SPC. It would be unlikely that a prescriber would copy the statement in the leavepiece without seeking further information and advising a patient accordingly. In the Panel's view prescribers would be familiar with the use of medicines such as Symbicort and well aware of the need to act if patients asked for too many repeat prescriptions ie over-used their inhalers. The Panel considered that given the audience to which it was directed, the statement was not unbalanced, misleading or exaggerated as alleged. No breach of Clause 7.2 was ruled. Further, the Panel did not consider that the statement was such that it did not encourage the rational use of Symbicort. No breach of Clause 7.10 was ruled.

Complaint received	**1 October 2007**
Case completed	**20 November 2007**