CASE AUTH/2793/9/15

CLINICAL PHARMACIST v ASTRAZENECA

Identifying patients suitable for Forxiga treatment and failing to provide an accurate response to the Panel

A clinical pharmacist complained about an AstraZeneca leavepiece about how to create a clinical system search to identify patients suitable for treatment with Forxiga (dapagliflozin).

Forxiga was indicated in adults with type 2 diabetes to improve glycaemic control as monotherapy when diet and exercise alone did not provide adequate glycaemic control in patients for whom use of metformin was considered inappropriate due to intolerance. It was also indicated in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, did not provide adequate glycaemic control.

The leavepiece was entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. The front page included 'FORXIGA is not indicated for weight loss and is not recommended for use in patients with an [eGFR] < 60 mL/min/1.73m2. FORXIGA is not licensed for use with thiazolidinedione or GLP-1 agonists'.

The complainant alleged that the search instructions were potentially misleading and could easily identify patients who would not be suitable for treatment. The instructions showed how to add criteria for body mass index (BMI), glomerular filtration rate (GFR) and glycosylated haemoglobin (HbA1c). In all cases a clinical code was added with a qualifying value. However, no time restriction was added to qualify these values. The complainant explained the flaw. Patients were supposed to have an uncontrolled HbA1c to be suitable for treatment so those with an HbA1c above 58 should be identified. However, the value should also be the most recently recorded. A patient with an HbA1c of 48 now who had previously had an HbA1c of 63 should not be included in the final search. However, by applying the instruction as specified they would be included for consideration.

The complainant alleged that whilst he/she hoped that a clinical review would subsequently deem the patient as inappropriate for treatment, the search instructions could be construed as misleading by including such patients. By creating a sub-optimal search the usual high standards demonstrated by the pharmaceutical industry had not been maintained.

The detailed response from AstraZeneca is given below.

The Panel noted that the search was described in 9 steps: Setup initial search; Add Age Range to Search; Add Read Code to Search; Add Medication to Search; Add BMI to Search; Add HbA1c to search; Add GFR to search; Save and Run Report; and Build Report Output. Each step included detailed instructions and some included screenshot examples.

The Panel noted the order of the search criteria, age, read code, and medication were followed by BMI before selecting HbA1c and GFR. The report was then run (Step 8). Step 9, Build Report Output, instructed users to add BMI (22K) and value ≥ 25 before adding columns for HbA1c and GFR but unlike BMI no values were listed for these two criteria at this step in the description in the leavepiece. In the example screenshot of the completed report which appeared below step 9, the column of BMI values was fully populated for each identified patient and appeared before the HbA1c column. Neither the HbA1c nor GFR columns were fully populated. The Panel noted AstraZeneca's submission that the example report was generated using dummy patients in a test system and a report generated using real-life data in a live system would only include patient records that met all the search criteria and would have all the data values populated. The Panel considered that this was not clear from the leavepiece and was compounded by the screenshot heading 'The completed report should resemble this screenshot'. The Panel accepted AstraZeneca's submission regarding the responsibility of prescribers to make clinically reasoned prescribing decisions but considered that it was important that both the instructions and information on the nature and interpretation of the data retrieved was abundantly clear and otherwise complied with the Code. In this regard the Panel was concerned that nowhere in the leavepiece was there any mention of carrying out a clinical review nor was it referred to in the verbal briefing to the diabetes sales leadership team. In the Panel's view, the leavepiece implied that following the 9 step guide would generate a list of uncontrolled patients with a BMI≥ 25 who were suitable for Forxiga. This would include patients who currently had an HbA1c value of less than 58 but who previously had a value of more than 58 being identified as 'uncontrolled'. This impression was compounded by the title '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. In the Panel's view it might lead to controlled patients (based on HbA1c) being identified as uncontrolled and being prescribed Forxiga. The Panel considered that the leavepiece was misleading and a breach was ruled.

Whilst the Panel noted that BMI was relevant to this therapeutic area, the emphasis on BMI in the title, search criteria and the example completed report screenshot which omitted HbA1c values and the failure to refer to the need to carry out a clinical review meant that Forxiga had been promoted for some patients based solely on their weight.

Forxiga was not indicated for weight loss. A breach was ruled.

The Panel however did not consider that the instructions were misleading on the narrow point that no time restrictions were included in the search criteria for BMI, GFR and HbA1c as alleged. No breach was ruled.

The Panel considered that high standards had not been maintained and a breach was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure.

Following notification of the outcome of the case, the complainant noted that, in its response, AstraZeneca had provided inaccurate information about how EMIS could be searched. AstraZeneca initially responded that the information, which it could not validate, was provided by an agency; the agency had confirmed its understanding of the search capabilities of the EMIS system. The complainant was informed and subsequently provided further and better particulars which were provided to AstraZeneca. The company subsequently accepted that the information it had provided was incorrect.

Detailed comments from the complainant and AstraZeneca are given below.

Following receipt of the additional information from both parties the Authority asked AstraZeneca to respond including in relation to a possible report under Paragraph 8.2 of the Constitution and Procedure.

The original Panel reconvened and considered the matter in relation to Paragraph 8.2 of the Constitution and Procedure. The Panel noted that AstraZeneca had provided the requisite undertaking.

The Panel considered that AstraZeneca had not paid sufficient attention to a number of aspects of the production, certification and use of the leavepiece in question. Although the company had been let down by its agency, which had knowingly provided it with an inaccurate response on one point, its governance of the agency had been extremely poor and AstraZeneca had not undertaken sufficient checks when certifying the material and responding to the complaint. The Panel noted that even a brief perusal of the EMIS website, which it had undertaken on conclusion of this case, revealed the comment that 'Emis web allows you to extract and report on their latest blood pressure reading'. Further, the recent material provided by the complainant indicated, contrary to AstraZeneca's earlier response, that the latest readings could be extracted. This was now not disputed by AstraZeneca.

The Panel noted that AstraZeneca had initially submitted that at the WebEx and teleconference on 20 and 26 May a copy of the leavepiece was shown and certain points were explained verbally. The Panel had raised concerns regarding the lack of any written briefing. However, it subsequently transpired that slides had indeed been shown and then distributed to at least one sales manager. The Panel was concerned that one slide described Forxiga as 'The metformin …' and that it was 'to be habitually prescribed as the first choice add-in across the pathway for T2D patients who would benefit from HbA1c control and Weight Loss'. Forxiga was not so licensed. The Panel noted that these claims had not been the subject of complaint. The Panel was also concerned that the final slide stated that each team was to agree how it should be used locally. In the Panel's view this should have come to light in AstraZeneca's enquiries before it responded to a question from the Panel regarding representatives' briefing material. The Panel was concerned that this material had not been before it when it considered the complaint and it was extremely concerned that the material was not certified.

The Panel was also concerned about the certification process in relation to the leavepiece. It was difficult to see how the leavepiece could have been certified unless the signatories had been able to satisfy themselves that when used on the EMIS web system the instructions and output complied with the Code. This had not been done.

The Panel was extremely disappointed by the conduct of AstraZeneca as outlined above. Self-regulation relied, *inter alia*, upon the provision of complete and accurate information to the Panel. It noted the steps undertaken by AstraZeneca to address the issues raised but, nonetheless, considered that the circumstances warranted reporting the company to the Appeal Board under Paragraph 8.2 for it to consider in relation to Paragraphs 11.3 and 11.4 of the Constitution and Procedure.

The Appeal Board noted the Panel's comments above about AstraZeneca's failings with regard to the production, certification and use of the leavepiece in question.

The Appeal Board noted AstraZeneca had limited expertise with regard to the EMIS Web clinical system and in that regard had relied upon its agency which had let it down. Nonetheless the company's failings went way beyond merely relying on the agency's expertise. The company had demonstrated extremely poor governance in this matter. This was not acceptable. The Appeal Board did not understand why representatives had not received a detailed briefing given the complexity of the EMIS system. AstraZeneca had taken full responsibility for its failings and had acted to ensure that such failings did not reoccur. Nonetheless, the Appeal Board considered that it was fundamental for effective self-regulation for companies to provide accurate information to the Panel and for failing to do so and for exercising poor governance it publicly reprimanded AstraZeneca in accordance with Paragraph 11.3 of the Constitution and Procedure.

The Appeal Board noted the Panel's rulings and in particular its view that instructions given in the leavepiece might lead to controlled patients (based on HbA1c) being identified as uncontrolled and being prescribed Forxiga. This raised issues of patient safety. This was unacceptable. Consequently the Appeal Board decided, in accordance with Paragraph 11.3 of the Constitution

and Procedure, to require AstraZeneca to issue a corrective statement to all recipients of the leavepiece to clarify the position. [The corrective statement appears at the end of the report].

A clinical pharmacist complained about instructions produced by AstraZeneca UK Limited about how to create an EMIS Web clinical system search to identify patients suitable for treatment with Forxiga (dapagliflozin) (ref 716.131.011).

Forxiga was indicated in adults aged 18 years and older with type 2 diabetes to improve glycaemic control as monotherapy when diet and exercise alone did not provide adequate glycaemic control in patients for whom use of metformin was considered inappropriate due to intolerance. It was also indicated in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, did not provide adequate glycaemic control.

The item was a leavepiece entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. Above this on the front page was a container with a tap releasing sugar. Below the title was a description in smaller bold text of where the prescribing information and adverse event reporting could be found followed by 'FORXIGA is not indicated for weight loss and is not recommended for use in patients with an [eGFR] < 60 mL/min/1.73m2. FORXIGA is not licensed for use with thiazolidinedione or GLP-1 agonists'. The leavepiece gave detailed instructions for the search including six search criteria.

COMPLAINT

The complainant alleged that the search instructions were potentially misleading and could easily identify patients who would not be suitable for treatment. The instructions showed how to add criteria for body mass index (BMI), glomerular filtration rate (GFR) and glycosylated haemoglobin (HbA1c). In all cases a clinical code was added with a qualifying value. However, no time restriction was added to qualify these values.

The complainant explained the flaw as follows: patients were supposed to have an uncontrolled HbA1c to be suitable for treatment so those with an HbA1c above 58 should be identified. However, the value should also be the most recent recorded on the system. This meant a patient with an HbA1c of 48 now who had previously had an HbA1c of 63 should not be included in the final search. However, by applying the instruction as specified they would be included for consideration.

The complainant alleged that whilst he/she hoped that a clinical review would subsequently deem the patient as inappropriate for treatment, the search instructions could be construed as misleading by including such patients. By creating a sub-optimal search the usual high standards demonstrated by the pharmaceutical industry had not been maintained.

The complainant hoped that the instructions would be withdrawn from circulation and, if desired, replaced with some that were more robust and accurate.

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

RESPONSE

AstraZeneca explained that the Forxiga EMIS search instructions included in the leavepiece were intended to be used by health professionals who used the EMIS Web clinical system. The EMIS Web clinical system allowed primary, secondary and community health professionals to view and contribute to a patient's electronic healthcare record.

The Forxiga EMIS search instructions were intended to enable health professionals to identify type 2 diabetics who were uncontrolled and overweight and who might be suitable for Forxiga treatment. The instructions guided the selection of patients with records held in the EMIS Web system which fulfilled the following criteria:

- Patients aged ≥18 years and ≤75 years

  Forxiga was indicated for patients aged 18 years and over. Section 4.4 of the summary of product characteristics (SPC) stated that therapeutic experience in patients 75 years and older was limited and Forxiga was not recommended for patients in this population. Therefore, patients with a recorded age of 18 - 75 were included within the search results.

- Patients identified as having type 2 diabetes

  Forxiga was indicated for the treatment of type 2 diabetes. Therefore, patients with a recorded diagnosis of type 2 diabetes were included in the search results.

- Patients not prescribed a loop diuretic in the last 3 months

  Forxiga was not recommended for use in patients on loop diuretics (Section 4.4 of the SPC). Therefore, patients with a recorded prescription for a loop diuretic in the last 3 months were excluded from the search results.

- Patients with a body mass index (BMI) of ≥25 kg/m2

  Treatment with Forxiga was not limited to those who were overweight or those with a particular BMI. However, given its known effect in reducing body weight (Section 5.1 of the SPC) it had the potential to particularly benefit patients in whom weight loss would be valuable. Patients with a BMI > 25 kg/m2 were defined as being overweight and as such might benefit from weight loss. Therefore, patients with a record indicating a BMI > 25 kg/m2 were included in the search results.

- Patients with glycosylated haemoglobin (HbA1c) ≥58mmol/mol

Forxiga was indicated for patients with type 2 diabetes mellitus to improve glycaemic control. No specific HbA1c values were stated in the SPC. Guidelines indicated that there was no single figure that defined adequate glycaemic control. Rather, HbA1c goals should be individually tailored. The decision as to what HbA1c threshold should trigger the decision to modify a patient's treatment was a matter of clinical judgement tailored to the needs of each patient.

The 58mmol/mol criterion was selected on the basis of the value specified for treatment intensification in the National Institute of Health and Care Excellence's (NICE) Draft Guidelines for the Management of Type 2 Diabetes and was consistent with the value set in the Quality and Outcomes Framework (QOF) diabetes indicators. Therefore, patients with a recorded HbA1c >58mmol/mol were included in the search results.

- Patients with a recorded eGFR ≥ 60ml/min/1.73 m2

  Forxiga was not recommended for use in patients with moderate to severe renal impairment (patients with CrCl (Creatine clearance) < 60ml/min or eGFR (estimated Glomerular Filtration Rate) < 60ml/min/1.73 m2), (Section 4.4 of the SPC). Therefore, patients with a recorded eGFR value ≥ 60 ml/min/1.73 m2 were included in the search results.

AstraZeneca submitted that no timeframe was specified for the selection criteria, with the exception of the loop diuretic exclusion. If a timeframe had been specified then patients currently uncontrolled and overweight might not be included in the search results. For example, if a 3 month timeframe had been specified for the HbA1c value then patients with no HbA1c value recorded within the last 3 months, who might potentially still be uncontrolled, would not be included. Not imposing a time restriction also recognised the importance of considering a patient's blood glucose and weight control over time, rather than looking at a single point in time. Importantly, the list generated would include the dates on which measurements were recorded.

Once the search criteria had been built the instructions then continued to describe how to produce the patient list. Health professionals were then to identify patients that might be suitable for Forxiga treatment after further clinical evaluation. Patients appearing on the list might not be suitable for treatment with Forxiga for any number of reasons such as allergy to an ingredient. To further support such clinical decision making the leavepiece provided information on important situations in which Forxiga should not be prescribed. Prescribing information, as well as adverse event information, was also included.

In line with standard UK clinical practice, and as specified in the General Medical Council's Good Medical Practice, AstraZeneca expected doctors and other health professionals to 'prescribe medicines only when they had adequate knowledge of the patient's health and were satisfied that the medicine or treatment served the patient's needs'.

In AstraZeneca's view no health professional would ever prescribe solely on the contents of a computer generated list. Rather, they would always use clinical judgement and consider the patient's current health status when making prescribing decisions.

AstraZeneca stated that the instructions did not suggest that Forxiga was indicated or should be prescribed for all patients that appeared in the search results. Rather, the instructions clearly stated in the title that patients identified '**may** be suitable for treatment with dapagliflozin' (emphasis added). As detailed above the search criteria were designed to reflect the Forxiga SPC, along with values appearing in the NICE guidelines and QOF indicators for type 2 diabetes.

AstraZeneca submitted that Forxiga had been promoted in accordance with particulars in the SPC and denied a breach of Clause 3.2.

AstraZeneca stated that its intention in assembling the list of instructions was to provide health professionals who used the EMIS Web system, a way to generate a list of patients who might be suitable for treatment with Forxiga. AstraZeneca firmly believed that health professionals would not prescribe solely on the basis of a computer generated list but rather would consider individual patient's needs and reach clinically-reasoned prescribing decisions.

As such, AstraZeneca submitted that the leavepiece was not misleading and that Forxiga had been promoted in a transparent manner that encouraged rational prescribing and in accordance with its SPC. Consequently, AstraZeneca denied a breach of Clause 7.2.

AstraZeneca submitted that its intention with this leavepiece, as explained above, was in line with the letter and spirit of the Code. AstraZeneca believed that this would be appreciated by the majority of health professionals who saw the material. High standards had been maintained and AstraZeneca denied a breach of Clause 9.1.

For the reasons detailed above, AstraZeneca also denied a breach of Clause 2.

In conclusion AstraZeneca reiterated that its intention with the leavepiece was to provide a tool to support health professionals who wished to identify patients who might be suitable for treatment with Forxiga. Such a tool could not, and should not, be a substitute for a clinician's professional judgment which would consider the individual patients' needs to fully inform a prescribing decision.

In response to a request for further information AstraZeneca stated that the Diabetes Sales Leadership Team (heads of regional business, regional sales managers, and regional account managers) was briefed on the use of the leavepiece on 20 and 26 May 2015 via a WebEx and teleconference. A copy of the leavepiece was shown and the following points were explained verbally:

- The leavepiece was to be offered to healthcare professionals who had an interest in identifying

their diabetic patients who might be suitable for treatment with Forxiga
- Representatives could only provide the leavepiece and must not be involved in any other way beyond provision of the leavepiece
- The leavepiece was available for representatives to order via the usual internal process.

The leadership team was instructed to cascade this information to their sales teams in their upcoming meetings. Consequently there was no written briefing material.

With regard to the search criteria and screenshot, AstraZeneca submitted that EMIS Web was a clinical system that allowed health professionals to record and use information to support patient care. A component of EMIS Web's functionality was the ability to perform searches and reports from the patient database. Practices would commonly run reports from their clinical system to assist in identifying patients for review.

All six search criteria stated in the leavepiece must be fulfilled in order for a patient's details to appear in the list generated. The report generated was not affected by the order of the search criteria. The example report on page 5 of the leavepiece was included at the end of the step-by-step guide to indicate that a report should now be available for extraction and the report should resemble the example. The example report was generated using dummy patients in a test system. AstraZeneca consulted with the agency that produced the step-by-step guide which confirmed that a report generated using real-life data in a live system would only include patient records that met all the search criteria and would have all the data values populated.

With regard to applying a date range for the search, AstraZeneca stated that the agency that produced the step-by-step instructions confirmed that it was not possible to perform a search for only the latest HbA1c value on the EMIS Web clinical system.

Applying a date range for the search criteria was possible, however as stated previously this had certain limitations. For example, if a 3 month timeframe had been specified for the HbA1c value then patients with a latest HbA1c of 58mmol/mol or greater but not recorded within the last three months would not be included in the report. Also, applying a date range would not prevent patients with an HbA1c of less than 58mmol/mol being included in the report if they had a historical HbA1c of 58mmol/mol or greater also recorded in that timeframe.

Therefore, no date range was specified and patients who had ever had an HbA1c value of greater than or equal to 58mmol/mol and satisfied all the additional criteria would be included in the report even if their most recent HbA1c reading was less than 58mmol/mol. Not imposing a time restriction also recognised the importance of considering a patient's HbA1c over time. The report included the dates on which the measurements were recorded.

AstraZeneca submitted that an example might help to illustrate why the history might be clinically useful:

Patient John Smith had the following HbA1c history:

John Smith	Date	HbA1c (mmol/mol)
	December 2014	62
	June 2014	60
	December 2013	64
	June 2013	67
	December 2012	65

Such a history of hyperglycaemia would appear in the report and might prompt the clinician to undertake a detailed case review. Upon review it might, for example, become apparent that:

a) the patient had not had a more recent HbA1c value record – they might therefore warrant re-testing and further follow up
b) There was a more recent HbA1c value of 56mmol/mol available. This might prompt the HCP to carefully evaluate the patient's individual case based on the totality of data and make a clinical decision as to further management.

PANEL RULING

The Panel noted that the leavepiece was entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. The leavepiece then described the EMIS Web search in 9 steps as follows:

1 Setup initial search
2 Add Age Range to Search
3 Add Read Code to Search
4 Add Medication to Search
5 Add BMI to Search
6 Add HbA1c to search
7 Add GFR to search
8 Save and Run Report
9 Build Report Output.

Each step included detailed instructions and some included screenshot examples.

The Panel noted that the complainant was particularly concerned that no time restriction was added to qualify BMI, GFR and HbA1c values which were used as search criteria. In the complainant's view the HbA1c value should be that most recently recorded on the system. The complainant explained that patients were supposed to have an uncontrolled HbA1c to be suitable for treatment so those with an HbA1c above 58 should be identified. By applying the instruction as specified, a patient with an HbA1c of 48 now who had previously had an HbA1c of 63 would be included for consideration when they should not be and the search instructions could be construed as misleading by including such patients.

The Panel noted the order of the search criteria, age, read code, and medication were followed by BMI before selecting HbA1c and GFR. The report was then run (Step 8). Step 9, Build Report Output, instructed users to add BMI (22K) and value ≥ 25 before adding columns for HbA1c and GFR but unlike BMI no

values were listed for these two criteria at this step in the description in the leavepiece. In the example screenshot of the completed report which appeared below step 9, the column of BMI values was fully populated for each identified patient and appeared before the HbA1c column. Neither the HbA1c nor GFR columns were fully populated. The Panel noted AstraZeneca's submission that the example report was generated using dummy patients in a test system and the agency that produced the step-by-step guide confirmed that a report generated using real-life data in a live system would only include patient records that met all the search criteria and would have all the data values populated. The Panel considered that this was not clear from the leavepiece and was compounded by the screenshot heading 'The completed report should resemble this screenshot'. The Panel accepted AstraZeneca's submission regarding the responsibility of prescribers but considered that it was important that both the instructions and information on the nature and interpretation of the data retrieved was abundantly clear and otherwise complied with the Code. In this regard the Panel was concerned that nowhere in the leavepiece was there any mention of carrying out a clinical review nor was it referred to in the verbal briefing to the diabetes sales leadership team. In the Panel's view, the leavepiece implied that following the 9 step guide would generate a list of uncontrolled patients with a BMI≥ 25 who were suitable for Forxiga. This would include patients who currently had an HbA1c value of less than 58 but who previously had a value of more than 58 being identified as 'uncontrolled'. This impression was compounded by the title '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions'. In the Panel's view it might lead to controlled patients (based on HbA1c) being identified as uncontrolled and being prescribed Forxiga. The Panel considered that the leavepiece was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that Clause 3.2 stated that promotion of a medicine must be in accordance with its marketing authorization and must not be inconsistent with the SPC. The Panel noted its comments above about the identification of patients. Whilst the Panel noted that BMI was relevant to this therapeutic area, the emphasis on BMI in the title, search criteria and the example completed report screenshot which omitted HbA1c values and the failure to refer to the need to carry out a clinical review meant that Forxiga had been promoted for some patients based solely on their weight. Forxiga was not indicated for weight loss. A breach of Clause 3.2 was ruled.

The Panel however did not consider that the instructions were misleading on the narrow point that no time restrictions were included in the search criteria for BMI, GFR and HbA1c as alleged. No breach of Clause 7.2 was ruled.

The Panel considered that the arrangements were such that high standards had not been maintained; a breach of Clause 9.1 was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure; no breach of Clause 2 was ruled.

During its consideration of this case the Panel was concerned that only in response to a question from the Panel did AstraZeneca confirm that the example completed report screenshot did not represent the real-life situation as implied by the leavepiece. In the Panel's view this should have been addressed prior to certification. The Panel was further concerned about the lack of written briefing material and the limited verbal briefing that was to be cascaded by the leadership team to their sales teams. In the absence of any written briefing, the Panel queried whether all sales teams would have received the same message and whether there was a process for ensuring that all sales teams had been briefed on the leavepiece before it became available for order. The Panel requested that AstraZeneca's attention be drawn to these concerns.

The above report was published in December 2015 and subsequently in the February Code of Practice Review 2016. Further information from the complainant was considered as in the addendum below.

CASE AUTH/2793/9/15 – ADDENDUM

FURTHER INFORMATION FROM THE COMPLAINANT FOLLOWING NOTIFICATION OF THE PANEL'S RULING

The complainant did not appeal but queried AstraZeneca's statement that the agency which produced the instructions confirmed that it was not possible to search for only the latest HbA1c. Whilst not disputing the validity of the statement from AstraZeneca, the complainant challenged the overall assertion as being patently false.

The complainant explained that the quality and outcomes framework (QOF) for the GP contract was constructed to check for the most recent values for, *inter alia*, blood pressure and HbA1c so clearly it was possible. Further it was easily possible to construct such searches within EMIS Web and examples were provided.

The complainant's comments were provided to AstraZeneca which was asked for detailed comments.

COMMENTS FROM ASTRAZENECA

AstraZeneca stated that it had commissioned a reputable agency to develop the material in question. Upon receiving the complaint AstraZeneca conducted a full investigation and asked its agency for detailed information. The agency informed AstraZeneca that it was not possible to search for only the latest HbA1c value on the EMIS Web clinical system. Recognising the importance of this point, AstraZeneca sought further explicit confirmation and the agency validated its understanding by contacting an EMIS website user. The agency's response was provided. AstraZeneca stated that it did not have access to the EMIS Web clinical system and thus could not validate the information. AstraZeneca submitted it had provided this information to the PMCPA in good faith.

As per its undertaking, the material in question had been withdrawn. AstraZeneca would no longer use

the agency to produce such material. AstraZeneca would forward the complainant's comments to the agency.

AstraZeneca's comments were sent to the complainant.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that it seemed that the agency engaged by AstraZeneca discussed searches with an EMIS website practice manager. In AstraZeneca's response three points were made about searches, date criteria and limiting reporting to certain values. The complainant submitted that each was false.

1 'You can only apply a date range to the search. You cannot ask for only the latest in any of the value criteria'.

The complainant stated it was possible to search on data and to request EMIS to look at only the latest value. It was also possible to look for the earliest value, the highest and the lowest with or without a date restriction. Examples were provided.

2 'You can only apply a date range to the report feature. You cannot ask only for the latest value'.

The complainant stated that searches in EMIS identified the patient. Reports allowed the creation of formatted information about the patients within a search group for easier viewing or export. Documents from EMIS about how to create searches and reports were provided. In the document on reports, under the heading 'Create a list report', step 8 mentioned that users could 'use the Feature Builder screen to add the required criteria; this is the same method as adding a rule to a search'. The searches documented under the 'Add a rule' section clearly described how a rule was created and could be restricted to give the latest values, again using the 'latest blood pressure more than 120/80' type of example.

3 'In answer to the specific question – it is not possible to ask EMIS Web system to return only the latest value in the output report'.

The complainant interpreted this point as being the same as point 2 above.

The complainant also provided a copy of how to create another search from the EMIS support website that further demonstrated restrictions could be made in reporting the latest values in searches and reports. Additionally there were three screenshots of a clinical system from the QOF searches. The basis of QOF was to pay GPs based on performance. For example, a practice must get a certain proportion of patients with diabetes to an HbA1c controlled value of 59 or less. The criteria for QOF established that the value must be within the year of QOF (so that last 12 months when the search runs for a final time on 31 March and that the most recent value is 59 or lower). The practice would not get paid should the patients have an HbA1c of below 59 at the start of the year but above 59 come the end of the year – so the search looked for the latest value within the year timeframe.

The complainant provided three screengrabs showing the search process for a patient with an HbA1c below the target in the last 12 months, one for a patient where the HbA1c was measured but was not at target and the final screengrab was of the actual result – on the same date – for the patient who failed to make the QOF criteria.

The complainant submitted that in summary, limiting a search by date and clinical value was possible within EMIS Web – QOF could not exist without that capability. Those unfamiliar with EMIS Web and GP clinical system might find some of the above difficult to follow and understand but the assertion that searches and reports could not return only the latest results was false.

FURTHER PMCPA CONSIDERATION

Following receipt of the additional information from both parties the Authority decided that the original Panel should reconvene to consider this matter in relation to Paragraph 8 of the Constitution and Procedure. AstraZeneca was so informed, provided with the complainant's further comments and asked to respond.

COMMENTS FROM ASTRAZENECA

AstraZeneca stated that it had recently consulted another agency experienced with EMIS Web, which confirmed that it was possible, using in-built report building functionality, to have the system return information for patients' *latest HbA1c readings*. AstraZeneca therefore acknowledged that, contrary to the information in its original response, the statement made by the complainant was correct.

AstraZeneca and the marketing company president were extremely disappointed and recognised that providing a full and frank disclosure to the PMCPA formed the basis of self-regulation. AstraZeneca conducted a full investigation into the circumstances that led to its failing to provide such a response in this case and was committed to addressing the errors that occurred.

As noted in its first response to the complainant's query, AstraZeneca provided its understanding of the limits of the search functionality in EMIS Web in good faith and considered that it had been badly let down by the agency. In addition, AstraZeneca acknowledged that there had been several failings on its part that contributed to the development of misleading search instructions in the leavepiece and the provision of inaccurate information to the Panel. These failings, and the steps taken to address them, were detailed below.

Development of the leavepiece and first investigation

AstraZeneca initially engaged the services of the agency that generated the search instructions in the leavepiece, in September 2011. Since then AstraZeneca had worked with the agency on many occasions and developed a trusting relationship with a master services agreement in place. Due diligence was conducted in 2011 and, since then, had

been repeated multiple times. Such due diligence had covered, *inter alia*, confidentiality, data privacy, anti-bribery and corruption and good promotional practice. AstraZeneca selected the agency to work on this project (which included instructions for three other clinical systems) as it was considered to have strong technical expertise in the relevant clinical systems and had produced similar materials for another pharmaceutical company. AstraZeneca stated that the agency's proposal was accepted over another from a competing agency based on its overall strength. AstraZeneca was unable to provide this proposal as both AstraZeneca's and the agency's copies were in the possession of employees that had since left the respective organisations.

After an initial scoping meeting, AstraZeneca agreed a project plan for the agency to develop a set of simple, precise and step-wise instructions that would make using general practice clinical systems conduct a review of patients with type 2 diabetes a quick and effective process. It was agreed that instructions for, *inter alia*, the EMIS Web system, would be generated for inclusion in a leavepiece specific to that system. The agency agreed to test the instructions both internally and externally. This testing was to involve assessment from a 'usability and clinical perspective using in-house access to live prescribing systems and long-standing relationships with clinical sites throughout the UK'. AstraZeneca considered it particularly important that the agency conducted thorough testing on its behalf given that it was unable to do so itself; AstraZeneca did not have access to the EMIS Web clinical system or patient data required for comprehensive testing. Also, as noted in the business requirements document, the final report was required to show, *inter alia*, the latest HbA1c result. However, the instructions produced for EMIS Web, unlike the instructions for other systems, did not search on the latest HbA1c result.

After receiving the complaint and during the course of its first investigation, AstraZeneca asked the agency whether it was possible to search for latest values in EMIS Web. The agency responded:

> 'I have just spoken to an EMIS Web site and asked the specific question around the reporting and search criteria. Here are the responses from the practice manager of this site:
>
> - You can only apply a date range to the search. You cannot ask for only the latest in any of the value criteria
> - You can only apply a date range to the report feature. You cannot ask for only the latest value
> - In answer to the specific question – it is not possible to ask EMIS Web system to only return the latest value in the report output.'

AstraZeneca took this to mean that it was not possible to conduct a search for the latest HbA1c value.

Second Investigation

In an interview conducted during AstraZeneca's second investigation, the agency stated that this email relayed the comments of a practice manager, and did not reflect its own understanding of EMIS Web search functionality. The agency did not previously mention this, or correct the information in the email from the practice manager, even though it had now admitted that it knew the information was inaccurate at the time and that a search for the latest HbA1c value was possible.

If the agency, which AstraZeneca contracted as technical experts on the EMIS Web system, had during the first investigation correctly stated that searching for the latest HbA1c value was possible in EMIS Web, AstraZeneca would have put this information into its initial response to the PMCPA. It was absolutely not its intention to provide inaccurate information.

As part of its second investigation AstraZeneca identified two further failings:

1 To gain comfort with the technical aspects of the search instructions and aid its review, AstraZeneca asked that the agency to walk it through the search instructions and create a 'plain English' version. This version was referred to as 'process report'. Given that the signatories could not themselves test the instructions, the Works Agreement and Business Requirements Document made clear that the agency was to conduct user testing (internal and external). The agency confirmed in an email of 13 April 2015 that the set of instructions had been tested externally. AstraZeneca placed a high degree of trust in the agency and understood that this testing had taken place in a robust manner.

   AstraZeneca had now discovered that the agency subjected the search instructions to testing at only one practice site. Further, AstraZeneca discovered that the focus of the agency's testing was to assess ease of use rather than to verify accuracy. Despite the agency's failure to thoroughly test the instructions, AstraZeneca acknowledged that its signatories had not inquired into the nature and scope of testing performed by the agency. Given the information discovered during the second investigation, the signatories now regretted that they trusted the agency with respect to the search requirements.

2 Contrary to the information provided to the Panel in its original response, AstraZeneca had now learned that a slide deck was sent to at least one member of the sales leadership team. As part of its first investigation AstraZeneca interviewed those responsible for creation of the leavepiece, both of whom recalled there not being any form of written briefing document. In its second investigation, AstraZeneca extended interviews to other staff who had worked with the marketing team on this project. A manager produced slides outlining the project for a WebEx on 20 and 26 of May and later emailed these to at least one other manager. The slides had not been certified which was a significant failure to follow the standard operating procedure (SOP) on the Approval of Materials/Activities for Certification and Examination which stated that 'Representative

training materials used to instruct representatives about a medicine or how the product should be promoted' should be certified.

AstraZeneca acknowledged that the circumstances leading up to the approval of the leavepiece were wholly unacceptable, and that its first investigation into this complaint was inadequate. It reiterated its commitment to addressing these issues to ensure that such mistakes were never repeated.

It was never AstraZeneca's intention to provide inaccurate information to the Panel, but this was nonetheless what had happened. The UK marketing company president personally apologised to the Panel for AstraZeneca's conduct. AstraZeneca took full responsibility for the agency's actions as well as of those involved in the development, approval and certification of the leavepiece. The senior management team was fully committed to addressing the contributing factors and improving processes and controls to ensure this did not recur.

Actions taken to ensure such failings do not recur

Since receiving the Panel's ruling, AstraZeneca had taken a number of actions including briefing and training staff. Details were provided.

Conclusion

In summary, AstraZeneca provided its understanding of the limits of the search functionality in EMIS Web in good faith and considered that it had been badly let down by the agency that confirmed this understanding. AstraZeneca acknowledged that there had been several failings on its part; one with certification that contributed to the development of the misleading search instructions in the leavepiece and subsequently one with the initial investigation that led to the provision of inaccurate information to the Panel.

AstraZeneca had a robust compliance framework to help prevent, detect and respond to risks and incidents effectively. This framework included, *inter alia*, elements relating to monitoring, training, standard setting, risk identification and assessment and reporting. It would be happy to provide additional information regarding its comprehensive compliance programme to demonstrate its commitment to ensuring issues like this did not recur.

FURTHER CONSIDERATION BY THE PANEL

The Panel noted that it was considering this matter in relation to Paragraph 8.2 of the Constitution and Procedure which provided that the Panel might report to the Appeal Board any company whose conduct in relation to the Code, or in relation to a particular case before it, or because it repeatedly breached the Code such that it raised concerns about the company's procedures, warranted consideration by the Appeal Board. Such a report to the Appeal Board might be made notwithstanding the fact that a company had provided an undertaking requested by the Panel. The Panel noted that AstraZeneca had provided the requisite undertaking.

The Panel noted its rulings of breaches of Clauses 7.2 and 3.2 and no breach of Clauses 2 and 7.2. It noted that in deciding whether to report a company under Paragraph 8.2 of the Constitution and Procedure it was not limited to matters which were before the Panel during its consideration of a case.

The Panel considered that AstraZeneca had not paid sufficient attention to a number of aspects of the production, certification and use of the leavepiece in question. Although the company had been let down by its agency, which had knowingly provided it with an inaccurate response on one point, its governance of the agency had been extremely poor and AstraZeneca had not undertaken sufficient checks when certifying the material and when responding to the complaint. The Panel noted that even a brief perusal of the EMIS website, which it had undertaken on conclusion of this case, revealed the comment that 'Emis web allows you to extract and report on their latest blood pressure reading'. Further, the recent material provided by the complainant indicated, contrary to AstraZeneca's earlier response, that the latest readings could be extracted. This was now not disputed by AstraZeneca.

The Panel noted that AstraZeneca had initially submitted that at the WebEx and teleconference on 20 and 26 May a copy of the leavepiece was shown and certain points were explained verbally. The Panel had raised concerns regarding the lack of any written briefing. However, it had subsequently transpired that slides had indeed been shown and then distributed to at least one sales manager. The Panel was concerned that the second slide described Forxiga as 'The metformin …' and that it was 'to be habitually prescribed as the first choice add-in across the pathway for T2D patients who would benefit from HbA1c control and Weight Loss'. Forxiga was not so licensed. The Panel noted that these claims had not been the subject of complaint. The Panel was also concerned that the final slide stated that each team was to agree how it should be used locally. In the Panel's view this should have come to light in AstraZeneca's enquiries before it responded to a question from the Panel regarding representatives' briefing material. The Panel was concerned that this material had not been before the Panel when it considered the complaint. In addition, the Panel was extremely concerned that the material was not certified. It was not clear why the material had not been certified.

The Panel was also concerned about the certification process in relation to the leavepiece in question. It was difficult to see how the material could have been certified unless the signatories had been able to satisfy themselves that when used on the EMIS web system the instructions and output complied with the Code. This had not been done. According to AstraZeneca, testing by its agency was to include in-house access to live prescribing systems. It was unclear why AstraZeneca considered it could not, at the very least, be present during in-house testing to question the agency which could be done without AstraZeneca having sight or access to the actual prescribing system. AstraZeneca subsequently confirmed that the agency had tested the material externally. It was thus unclear whether

in-house testing had ever taken place. AstraZeneca acknowledged its failure to inquire into the nature and scope of the agency's testing. The Panel considered that, in addition, AstraZeneca had not adequately instructed the agency in this regard at the outset so as to ensure such testing went beyond ease of access.

The Panel noted the due diligence summary provided by AstraZeneca and the issues raised therein.

The Panel was extremely disappointed by AstraZeneca's conduct as outlined above. Self-regulation relied, *inter alia*, upon the provision of complete and accurate information to the Panel. It noted the steps undertaken by AstraZeneca to address some of the issues raised but, nonetheless, considered that the circumstances warranted reporting the company to the Appeal Board under Paragraph 8.2 for it to consider the matter in relation to Paragraphs 11.3 and 11.4 of the Constitution and Procedure.

COMMENTS FROM ASTRAZENECA ON THE REPORT

At the consideration of the report AstraZeneca submitted that it took full responsibility for the failings in this case and was fully committed to addressing them. It acknowledged that this was a very serious matter. AstraZeneca had already implemented a number of actions to prevent this happening again. Further actions and resource were being implemented to support this. These actions had the full support of the senior leaders both in the UK marketing company and at a global level. AstraZeneca was committed to continual improvement of compliance activities and standards. 'We do the right thing' was one of the company's five core values.

Completed activities included: staff briefed on details of this case at Quarterly Code Review; enhanced due diligence on third party vendors regarding familiarity with the Code and its requirements; suspension of all work with the agency involved and notice to terminate given; trained signatories and originators on failings in this case; updated local working structure on handling Code of Practice complaints; revised approval SOP to be more explicit regarding briefing documents and ensure signatories had all the required information.

Planned activities included: refresher training with signatory revalidation programme to be introduced; third party job bag audits; active review of the current approval system with the goal of replacing it; training for all brand teams on regulatory obligations and responsibilities, properly briefing and managing agencies and support materials and where to seek help; training to new brand team members as part of induction programme; annual refresh training for all marketing staff (as part of wider programme); develop an agency handbook to explain AstraZeneca's expectations; Compliance Assurance Task Force established with a wide ranging remit, initiated by country president, led by the medical director with cross functional representation; 'Right Thing Right Way' initiative; further dedicated resource to support compliance to include a compliance training manager and SOP co-ordinator.

APPEAL BOARD CONSIDERATION

The Appeal Board noted the Panel's rulings and comments about AstraZeneca's failings with regard to the production, certification and use of the leavepiece in question.

The Appeal Board noted AstraZeneca had limited expertise with regard to the EMIS Web clinical system and relied upon the knowledge of its agency which had let it down. Nonetheless the company's failings went beyond merely relying on the agency's expertise. In the Appeal Board's view the company had demonstrated extremely poor governance in this matter. This was not acceptable. The Appeal Board did not understand why representatives had not received a detailed briefing given the complexity of the EMIS system. The Appeal Board noted that AstraZeneca had taken full responsibility for its failings in this case and had already undertaken, or was due to undertake, a number of measures to ensure that such failings did not reoccur. Nonetheless, the Appeal Board considered that it was fundamental for effective self-regulation for companies to provide accurate information to the Panel and for failing to do so and for exercising poor governance it publicly reprimanded AstraZeneca in accordance with Paragraph 11.3 of the Constitution and Procedure.

The Appeal Board noted the Panel's rulings and in particular its view that instructions given in the leavepiece might lead to controlled patients (based on HbA1c) being identified as uncontrolled and being prescribed Forxiga. This raised issues of patient safety. This was unacceptable. Consequently the Appeal Board decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require AstraZeneca to issue a corrective statement to all recipients of the leavepiece to clarify the position. The corrective statement should refer to the case report. Under Paragraph 11.3 details of the proposed content and mode and timing of dissemination of the corrective statement must be provided to the Appeal Board for approval prior to use. [The corrective statement appears at the end of the report].

Complaint received	**10 September 2015**
Undertaking received	**16 November 2015**
Appeal Board consideration	**7 March 2016**
Panel reconvened	**24 February 2016**
Corrective statement issued	**15 June 2016**
Case completed	**17 March 2016**
Updated case report including addendum published	**15 June 2016**

On 15 June 2016, AstraZeneca sent the following corrective statement to recipients of the leavepiece at issue.

'Dear Healthcare Professional,

Corrective Statement

Case AUTH/2793/9/15: Identifying patients suitable for Forxiga treatment

I am writing to you as I understand that your Practice uses the EMIS Web Clinical System.

AstraZeneca produced a leavepiece entitled '9 step guide to identify your uncontrolled and overweight patients with type 2 diabetes (T2D) who may be suitable for treatment with dapagliflozin EMIS Web Instructions' (ref 716.131.011). AstraZeneca markets Forxiga®▼ (dapagliflozin) which is indicated to improve glycaemic control in certain type 2 diabetic patients. You may have been provided with a copy of the leavepiece sometime between 19 May 2015 and 13 November 2015.

Following a complaint under the Association of the British Pharmaceutical Industry (ABPI) Code of Practice for the Pharmaceutical Industry, the Code of Practice Panel ruled that the leavepiece was misleading, it was inconsistent with the Forxiga summary of product characteristics as following the 9 step guide could lead to patients being identified as suitable for Forxiga treatment based solely on their weight and not on HbA1c levels. Forxiga is not indicated for weight loss. The Panel considered that high standards had not been maintained. Subsequently the complainant brought to light that AstraZeneca had provided inaccurate information. As a result of this and other governance issues that subsequently emerged, the Panel reported AstraZeneca to the Code of Practice Appeal Board. The Appeal Board was concerned that use of the leavepiece might lead to the inappropriate prescription of Forxiga, and it considered that it was important that recipients of the leavepiece should be made aware of this. As a result AstraZeneca has been required to issue this corrective statement and to refer to the published report for the case which contains full details.

AstraZeneca takes its responsibilities under the ABPI Code seriously and is disappointed at these failings. As an organisation we will take all steps needed to ensure this is not repeated.

Best regards,'