CASE AUTH/1944/1/07

DRUG AND THERAPEUTICS BULLETIN/DIRECTOR v PFIZER

Promotion of Exubera

An article entitled 'Exubera: inhaled insulin for diabetes' which appeared in Drug and Therapeutics Bulletin (DTB), January 2007, criticised the promotion of Exubera (inhaled insulin human) by Pfizer. In accordance with established practice the matter was taken up by the Director as a complaint under the Code.

Exubera was indicated for the treatment of adults with type 2 diabetes mellitus not adequately controlled with oral antidiabetic agents and requiring insulin therapy. It was also indicated for the treatment of adults with type 1 diabetes mellitus, in addition to long or intermediate acting subcutaneous insulin, for whom the potential benefits of adding inhaled insulin outweighed the potential safety concerns.

The DTB article stated that despite the promotional claim that Exubera maintained 'long-term glycaemic control', experience of use in routine long-term management of diabetes was limited. The longer-term effects of continual exposure to high levels of insulin powder on the lungs were not known.

The Panel noted that the National Institute for Health and Clinical Excellence (NICE) technology appraisal for inhaled insulins stated that current guidelines recommended a target HbA1c of 6.5-7.5% although it was acknowledged that such targets might not be achieved in all patients. The NICE technology appraisal also stated that treatment with inhaled insulin should only be continued beyond 6 months and in the longer term if there was evidence of a sustained improvement in HbA1c that was judged to be clinically relevant to the individual patient's overall risk of developing long-term complications of diabetes.

Exubera was a new product and its summary of product characteristics (SPC) did not place any limit on the length of treatment with the product.

The Exubera European Public Assessment Report (EPAR) referred to studies that looked at HbA1c referring to HbA1c <8% as acceptable and HbA1c <7% as good.

The Panel noted that no claim relating to routine long-term management of diabetes was made. Claims for 'long-term glycaemic control' were made in various items. Skyler (2004) was cited to support the claims. Skyler (2004) compared the efficacy and safety of a regimen including inhaled insulin with conventional treatment in type 1 and type 2 diabetes over at least two years. The comparator arm was discontinued after two years due to the small number of patients (n=45). Of the 159 patients electing to continue on inhaled insulin 89 patients recorded at least four years of treatment. The mean HbA1c was 8.23% ± 1.21% after 4 years compared with 8.71% ± 1.49% at the start of treatment with inhaled insulin. A graph separated the results for type 1 and type 2 patients on inhaled insulins. Type 2 diabetics (n=57) had a mean HbA1c of around 9% which fell on commencement of treatment to around 7.7% gradually rising to around 8% after 4 years. Type 1 diabetics (n=31) had a mean HbA1c of around 8% which fell to around 7.5% gradually rising to around 8.5%. After 4 years the rate of overall hypoglycaemia decreased in the inhaled insulin group as did the rate of severe hypoglycaemia compared to the rates after 4 weeks of inhaled insulin treatment.

Jovanovic *et al* was a two year study in type 1 diabetics comparing subcutaneous and inhaled insulin. HbA1c started at 7.4% and rose to 7.5% (n=291) for the inhaled insulin group whereas levels fell in the subcutaneous group (7.5% to 7.3%) (n=291). Hypoglycaemic events per patient were essentially comparable in both groups. Severe hypoglycaemic events rates were lower with inhaled insulin, fasting plasma glucose (FPG) declined from 170.1 to 156.8mg/dL with inhaled insulin but rose with subcutaneous insulin (166.9 to 173.5mg/dL) and there was less weight gain with inhaled insulin.

Rosenstock *et al* was a two year study in type 2 diabetics comparing subcutaneous and inhaled insulin. HbA1c started at 7.7% and ended at 7.3% (n=319) for the inhaled insulin group and similarly fell in the subcutaneous group 7.8% to 7.3% (n=316). There were fewer hypoglycaemic events per patient with inhaled insulin. Severe hypoglycaemia event rates were comparable. There were greater FPG reductions (151.2 to 135.6mg/dL) with inhaled insulin than with subcutaneous insulin (148.2 to 147.1mg/dL) and less weight gain with inhaled insulin.

On balance the Panel considered that the two year data, Jovanovic *et al* and Rosenstock *et al*, showed that glycaemic control was maintained; HbA1c levels were similar to current guideline recommendations. Other studies over six months Quattrin *et al*, Skyler *et al* (2005) and Hollander *et al* concluded that inhaled insulin provided glycaemic control comparable to that with a conventional insulin regimen in both type 1 and type 2 diabetics.

The Panel considered that an important factor was the meaning of 'long-term'. In that regard, given the nature of diabetes the Panel did not accept that 6

month data was long enough and so in support of the claims at issue the results of Quattrin *et al*, Skyler et al (2005) and Hollander *et al* were disregarded. With regard to the remaining data the Panel considered that although Skyler (2004) followed patients for four years, patient numbers were very small (31 type 1 diabetics and 57 type 2 diabetics). The Skyler data suggested that after an initial dip in HbA1c levels following the initiation of inhaled insulin, levels rose over time. The more robust studies (Jovanovic *et al* and Rosenstock *et al*) were conducted over two years. The data appeared to show that glycaemic control with inhaled insulin was better in type 2 diabetes than in type 1 although the Panel noted that none of the papers reported statistical significance for any results. Both Skyler (2004) and Jovanovic *et al* reported increases in HbA1c over the course of their studies in type 1 diabetes although the clinical significance of the rise was not stated. Conversely Skyler (2004) and Rosenstock *et al* showed decreases from baseline HbA1c in type 2 diabetics. All studies reported positive results for inhaled insulin with regard to hypoglycaemia/severe hypoglycaemia event rates.

Beneath the heading 'Exubera – maintains long-term glycaemic control', in a detail aid, the data from Skyler (2004) appeared showing the results for type 1 and type 2 diabetes. The Panel considered the claim in the context of the graph. The Panel noted its comments on Skyler (2004) above. The data did not adequately demonstrate that glycaemic control had been maintained. The Panel considered the claim in association with the graph was misleading and not capable of substantiation. Breaches of the Code were ruled.

The detail aid included the claim 'Exubera – insulin to maintain long-term glycaemic control' referenced to Skyler (2004). No details from the study were given with the claim. The Panel did not consider that the Skyler (2004) data on its own was sufficient to substantiate the claim. It was thus misleading to cite Skyler (2004) in this regard and a breach of the Code was ruled. The Panel then considered whether the two year data supported the claim. The Panel noted its comment above regarding the two year data and considered that although there was data to show glycaemic control for two years in both type 1 and type 2 diabetes there appeared to be a possible difference in response between the two. The claim gave no indication of the time period and thus the Panel considered that, taking into account the two year data the unqualified claim was misleading and not capable of substantiation. The Panel ruled breaches of the Code.

Similar rulings were made in relation to advertisements which included the claim 'New Exubera…' 'Maintains long-term glycaemic control' referenced to Skyler (2004) and in relation to a slide set and two mailings.

An article entitled 'Exubera: inhaled insulin for diabetes' which appeared in the Drug and Therapeutics Bulletin (DTB), January 2007, criticised the promotion of Exubera (inhaled insulin human) by Pfizer Limited. In accordance with established practice the matter was taken up by the Director as a complaint under the Code.

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COMPLAINT

The DTB article stated that despite the promotional claim that Exubera maintained 'long-term glycaemic control', experience of use in routine long-term management of diabetes was limited. The longer-term effects of continual exposure to high levels of insulin powder on the lungs were not known.

When writing to Pfizer, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

Pfizer submitted that as Exubera was a new product its use in routine, long-term management of diabetes was limited. Although there were limited data in routine use, there was data supporting long-term glycaemic control. However, there was no claim that Exubera should be used 'routinely'. Clearly the place of Exubera in the individual patient was a clinical decision based on the specific circumstances of the patient. Since its launch, the promotional materials had highlighted to health professionals that Exubera was a new product through the use of language, such as 'new' and 'introducing inhaled insulin' and use of the black triangle. The claim 'Exubera – Maintains long-term glycaemic control' was not synonymous with claiming that Exubera had been used in routine long-term management of diabetes.

Pfizer provided a number of publications that it submitted gave an up-to-date evaluation of the evidence in relation to Exubera and long-term control of HbA1c (six month, two year and four year data):

- Skyler (2004) looked at sustained long-term efficacy and safety of inhaled insulin during 4 years of continuous therapy.

- Jovanovic *et al* (2006) showed sustained efficacy and that inhaled insulin was well tolerated over a 2-year period in patients with type 1 diabetes.

- Rosenstock *et al* (2006) showed sustained efficacy and that inhaled insulin was well tolerated over a 2-year period in patients with type 2 diabetes.

- Quattrin *et al* (2004) compared the efficacy and safety of inhaled insulin with subcutaneous insulin

therapy in patients with type 1 diabetes in a 6-month, randomized, comparative trial.

- Skyler *et al* (2005) looked at the use of inhaled insulin in a basal/bolus insulin regimen in type 1 diabetic patients in a 6-month randomized, comparative trial.

- Hollander *et al* (2004) compared the efficacy and safety of inhaled insulin with subcutaneous insulin therapy in patients with type 2 diabetes in a 6-month, randomized, comparative trial.

Pfizer listed the most recent promotional materials for Exubera containing the claim, 'Exubera – insulin to maintain long-term glycaemic control':

a) Sales aid (EXU608) and electronic version of sales aid (EXU759)

Pfizer submitted this was for use by its speciality field force – the diabetes care team. A page entitled 'Exubera – maintains long-term glycaemic control' was carefully set in context within the sales aid. The flow of information clearly set out indications and contraindications then outlined pharmacodynamic data and clinical efficacy data. Study descriptions were included. The page relating to long-term control of HbA1c with Exubera followed the clinical efficacy data and clearly described the study. The claim appeared twice more through the detail aid.

The electronic version of the sales aid contained the same information and layout as the hardcopy booklet and provided the representatives with an alternative format (other than additional information on dosing which was not relevant to the claim relating to long-term control).

The representatives utilised these two items during sales calls with health professionals. The diabetes care team primarily called on specialists who initiated insulin therapy in diabetes, consultant diabetologists.

b) Advertising

Pfizer submitted recent examples of advertising in healthcare publications: EXU852A (Northern Ireland Medical Review) and EXU854F and EXU853F (Hospital Doctor).

c) Slide set for health professionals (EXU592a2/b2)

Pfizer submitted that this was a comprehensive slide set on Exubera, containing detailed notes. The CD-ROM was distributed via diabetes care team primarily to consultant diabetologists. The representatives did not use/present these slides.

Data on long-term glycaemic control was included within the slide set following extensive information on indications and contraindications for the product and the clinical efficacy data, including primary and secondary endpoints. Within the notes section of the slide there was detailed information for the health professional on the design and results of the study.

d) Mailings to health professionals

Pfizer submitted that the most recent mailings had been sent to GPs and respiratory clinicians in November 2006, copies were provided of EXU772 (GP mailing) and EXU773 (respiratory clinicians mailing).

Pfizer submitted that the promotional materials for Exubera had been pre-vetted by the Medicines and Healthcare products Regulatory Agency (MHRA). From January 2006 to June 2006 all of the promotional materials for Exubera were submitted and reviewed by the MHRA. This included the sales aid, the slide set, advertisements, and mailings. These materials included the claim 'Exubera – maintains long-term glycaemic control'.

In summary, Pfizer submitted that statements made in relation to the use of Exubera in the maintenance of long-term control were supported by the date and had been subject to extensive regulatory review. Pfizer made no claim for 'routine' use of Exubera in diabetes management and it did not, therefore, consider there was a *prima facie* case.

PANEL RULING

The Panel noted that the National Institute for Health and Clinical Excellence (NICE) technology appraisal for inhaled insulins stated that current guidelines recommended a target HbA1c of 6.5-7.5% although it was acknowledged that such targets might not be achieved in all patients. The NICE technology appraisal also stated that treatment with inhaled insulin should only be continued beyond 6 months and in the longer term if there was evidence of a sustained improvement in HbA1c that was judged to be clinically relevant to the individual patient's overall risk of developing long-term complications of diabetes.

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The Panel examined each type of promotional item separately.

a) Exubera sales aids

One page was headed 'Exubera – maintains long-term glycaemic control' beneath which the data from Skyler (2004) appeared showing the results for type 1 and type 2 diabetes. The Panel considered the claim in the context of the graph. The Panel noted its comments on Skyler (2004) above. The data did not adequately demonstrate that glycaemic control had been maintained.

The Panel considered the claim in association with the graph was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled.

Two more pages of the detail aid included the claim 'Exubera – insulin to maintain long-term glycaemic control' referenced to Skyler (2004). No details from the study were given with the claim.

The Panel did not consider that the Skyler (2004) data on its own was sufficient to substantiate the claim. It was thus misleading to cite Skyler (2004) in this regard and a breach of Clause 7.2 was ruled.

The Panel then considered whether the two year data supported the claim. The Panel noted its comment above regarding the two year data and considered that although there was data to show glycaemic control for two years in both type 1 and type 2 diabetes there appeared to be a possible difference in response between the two. The claim gave no indication of the time period and thus the Panel considered that, taking into account the two year data the unqualified claim was misleading and not capable of substantiation. The Panel ruled breaches of Clauses 7.2 and 7.4.

b) Advertisements

The advertisements included the claim 'New Exubera…' 'Maintains long-term glycaemic control' referenced to Skyler 2004.

The Panel did not consider that Skyler (2004) on its own was sufficient to substantiate the claim. It was thus misleading to cite Skyler 2004 in this regard and a breach of Clause 7.2 was ruled.

The Panel then considered whether the two year data supported the claim. The Panel noted its comment above regarding the two year data and considered that although there was data to show glycaemic

control for two years in both type 1 and type 2 diabetes there appeared to be a possible difference in response between the two. The claim gave no indication of the time period and thus the Panel considered that, taking into account the two year data the unqualified claim was misleading and not capable of substantiation. The Panel ruled breaches of Clauses 7.2 and 7.4.

c) Slide set

One slide was headed 'Long-term glycaemic control maintained- 4-year data' beneath which the data from Skyler (2004) appeared. The Panel considered its rulings in (a) above applied here.

d) Mailings

Both mailings included the claim 'Exubera is an insulin to maintain long-term glycaemic control' referenced to Skyler (2004). The Panel considered its rulings in (b) above applied here.

Complaint received **17 January 2007**

Case completed **5 March 2007**