CASE AUTH/2369/11/10

ABBOTT HEALTHCARE v GENUS

Promotion of APO-go

Abbott Healthcare complained about the promotion of APO-go (apomorphine pen injection system) by Genus. APO-go was indicated for use in patients with Parkinson's disease with disabling motor fluctuations despite treatment with levodopa and/or other dopamine agonists. Abbott Healthcare supplied Duodopa (levodopa/carbidopa) for the treatment of advanced Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia.

The detailed response from Genus is given below.

Abbott Healthcare alleged that the patient booklets Introduction to APO-go Pen and Introduction to APO-go Pump were disguised promotion. Much of the information presented was on the medicine and not the devices as the titles implied and there was prominent use of the brand name and logo.

Genus had argued that the booklets were for patients identified as suitable for APO-go. Abbott Healthcare believed that just because a patient was on a medicine did not mean a company could switch from providing educational information to promotional information without it being disguised promotion.

Despite inter-company dialogue Abbott Healthcare still had issues with the following claims:

- **'APO-go is a highly effective anti-parkinsonian medication'.**

'Highly effective' was a hanging comparison. It was not clear what APO-go was highly effective compared to? Was it oral medication, generic apomorphine etc?

- **'NO! APO-go therapy is not a last option in Pd [Parkinson's disease]; patients can use APO-go Pen therapy in combination with their oral medication or with an APO-go Pump for many years'.**

- **'Nausea doesn't affect everyone, is very temporary'.**

Abbott Healthcare appreciated that adverse events did not affect every patient, however if a product [sic] was listed as common, ie might affect less than one in every 100 patients, and domperidone had to be used at initiation of therapy it was misrepresentative to state such a claim especially when the audience were patients not health professionals.

- **'Nodule formation is usually not a significant problem'.**

Not consistent with summary of product characteristics (SPC).

Abbott Healthcare alleged that the booklets failed to meet high standards, lacked safety data, side effect profile and contraindications etc which could prejudice patient safety and therefore brought discredit to the industry (breach of Clause 2).

The Panel noted that Genus had not categorically stated what the target audience was for the booklets. The company had variously stated that they were for those identified as 'being APO-go patients' and for those identified as 'being suitable for APO-go therapy'. It was thus unclear as to whether the booklets were intended for those already receiving APO-go therapy or for those considering starting such therapy. The Panel examined the content of the booklets and noted that the pen booklet referred to patients who were already using the APO-go pump but needed a boost at various times of the day. Both booklets, however, 'introduced' patients to APO-go and listed the benefits of therapy and gave detailed information about the challenge test. In the Panel's view the booklets were most likely to be given to patients who were being considered for APO-go therapy but for whom the prescribing decision could not be made until the results of the challenge test were known. In the Panel's view the booklets were designed to influence a patient's decision as to whether to start APO-go therapy should the challenge test be successful.

The Panel considered that companies could prepare material about a product for patients who might be prescribed that product but it was very important that such material met all the relevant requirements of the Code. The Code prohibited the promotion of a prescription only medicine to the public. It permitted the provision of factual information presented in a balanced way. Such material must not raise unfounded hopes of successful treatment or be misleading about the safety of a product. In addition, the Code required that statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a prescription only medicine.

In relation to the Introduction to APO-go Pen booklet, the Panel did not consider that the claim that 'APO-go is a highly effective anti-parkinsonism medication' was a hanging comparison as alleged. No comparison was made or implied and thus the Panel ruled no breach.

The Panel noted the vague allegation with regard to the claim 'No! APO-go therapy is not the last

option in Pd; patients can use APO-go Pen therapy in combination with their oral medication or with an APO-go Pump for many years'. The Panel did not consider that the claim in itself constituted advertising a prescription medicine to the public. It was factual and balanced. The Panel did not consider that the complainant had proven this allegation on the balance of probabilities and thus ruled no breach.

The Panel noted that under the heading 'What are the possible side effects of APO-go Pen therapy' it was stated that 'APO-go Pen can cause nausea and vomiting as well as low blood pressure. Nausea doesn't affect everyone, is very temporary and usually only occurs when APO-go Pen therapy is first initiated. Domperidone (Motilium), an anti-sickness medication, is always used with APO-go initiation to avoid nausea'. The APO-go pen SPC stated that patients must be established on domperidone for at least two days prior to initiation of therapy. Once treatment had been established domperidone therapy might be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension. The Panel thus did not consider that with regard to the incidence and duration of nausea, the booklet fairly reflected the information in the SPC and was misleading in that regard. Breaches of the Code were ruled.

The Panel noted that under the same heading it was stated that 'Nodule formation occurs in some APO-go patients' and was 'usually not a significant problem, but occasionally if severe, can lead to erratic absorption of the drug and may affect the therapeutic outcome'. The APO-go pen SPC stated that most patients experienced injection site reactions, particularly with continuous use, including subcutaneous nodules. The Panel thus did not consider that to state that nodule formation only occurred in some patients accurately reflected the data in the SPC and was thus misleading in that regard. Breaches of the Code were ruled.

In relation to the Introduction to APO-go Pump booklet, the Panel considered that its last three rulings above applied. Its ruling about the claim 'APO-go is a highly effective anti-parkinsonian medication …' did not apply as this claim did not appear in the Introduction to APO-go Pump booklet.

The Panel considered that both booklets would influence patients regarding APO-go therapy. On balance the Panel considered that the booklets constituted advertising a prescription only medicine to the public and a breach of the Code was ruled. The Panel noted that the introduction to both booklets stated that APO-go had '… a similar effect to the gold standard treatment, levodopa'. The Panel considered that to describe a medicine as a model of excellence did not meet the requirements of the Code; information about APO-go had not been presented in a balanced way. It also noted its rulings of breaches above which it considered meant that the booklets were not factual and were misleading. A breach of the Code was ruled.

The Panel considered that as promotion of a prescription only medicine to the public was not allowed such promotion could not be disguised. No breach was ruled in that regard.

The Panel did not consider that the content of the booklets was misleading given their titles. They both contained information relevant to the medicine and its method of administration. The booklets were not comprehensive in relation to side effects. Only nausea and skin nodules were mentioned. There were other side effects listed in the SPC that were not included in the section headed 'What are the possible side effects of APO-go [Pen/continuous infusion] therapy?'. This was not balanced and was misleading with respect to the safety of the medicine. Breaches of the Code were ruled. The use of the brand name was not misleading. No breach was ruled in that regard.

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

In relation to the Skin Management Guide, Abbott Healthcare stated that this patient literature was still available despite issues raised regarding Code breaches. In particular, Abbott Healthcare had issue with a claim that skin nodules were more likely to be caused with poor skin care.

The SPC stated 'most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis'. These were listed as very common ie less than one in ten patients. This was not reflected in this leaflet.

The Panel noted that the document at issue was a four page, A4 leaflet entitled 'APO-go skin management'. The first paragraph, headed 'What are skin nodules?', explained that a side effect of APO-go therapy could be redness, tenderness, itching and the development of nodules and/or hardening of the skin at the injection site. A section 'What causes them?' followed and referred to a local inflammatory reaction which varied greatly between individuals and which '… sometimes occurs in response to the medication or the needle and is more likely with poor skin care'. The next two pages headed 'What can I/my carer do to help minimise or prevent these skin reactions?' included information regarding hygiene, choosing an injection site and needle siting. The final page referred to treatment of existing nodules/hardened skin areas and included the statement that 'skin nodules although common, present no significant problems in the majority and shouldn't stop treatment'.

The SPC stated general disorders and administrative site conditions were very common

(≥1/10). Most patients experienced injection site reactions particularly with continuous use. These might include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) might also occur.

The Panel considered that the purpose of the leaflet in question was to explain to patients what skin nodules were, how they were caused, encourage patients and carers to follow good hygiene practices, to give advice about siting needles etc and to explain what could be done if skin nodules developed. The Panel considered that the leaflet was clear that APO-go therapy was associated with the development of skin nodules in response to the medication or to the needle and was more likely with poor skin care. The Panel considered that Abbott Healthcare's allegation was vague; no details had been provided as to why the claim was alleged to be in breach of the Code. The Panel thus did not consider that Abbott Healthcare had proven its complaint on the balance of probabilities. The Panel did not consider that the booklet was misleading about the cause of skin nodules as alleged. It did not state that these were wholly due to poor skin hygiene. No breach of the Code was ruled in this regard.

The Panel considered that the booklet was misleading about the incidence of injection site reactions. The leaflet stated that skin nodules were common whereas the SPC stated that injection site reactions were very common and experienced by most patients. A breach of the Code was ruled.

Abbott Healthcare Products Ltd complained about the promotion of APO-go (apomorphine pen injection system) by Genus Pharmaceuticals Ltd. APO-go was indicated for use in patients with Parkinson's disease with disabling motor fluctuations despite treatment with levodopa and/or other dopamine agonists. Inter-company dialogue had left certain matters unresolved. Abbott Healthcare supplied Duodopa (levodopa/carbidopa) for the treatment of advanced Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia.

1 Introduction to APO-go Pen (APO-0210-669) and Introduction to APO-go Pump (APO-0110-640) patient booklets

COMPLAINT

Abbott Healthcare alleged that the booklets were disguised promotion. Much of the information presented was on the medicine and not the devices as the titles implied, in breach of Clause 7.2, and there was prominent use of the brand name and logo.

Genus had argued that the booklets were for patients identified as suitable for APO-go. Abbott Healthcare believed that just because a patient was on a medicine did not mean a company could switch from providing educational information to promotional information without it being disguised promotion.

Despite inter-company dialogue Abbott Healthcare still had issues with the following claims:

- 'APO-go is a highly effective anti-parkinsonian medication'. (Breach of Clause 7.2).

  'Highly effective' was a hanging comparison. It was not clear what APO-go was highly effective compared to? Was it oral medication, generic apomorphine etc?

- 'NO! APO-go therapy is not a last option in Pd [Parkinson's disease]; patients can use APO-go Pen therapy in combination with their oral medication or with an APO-go Pump for many years'. (Breach of Clause 22).

- 'Nausea doesn't affect everyone, is very temporary'. (Breach of Clauses 7.2 and 7.9).

  Abbott Healthcare appreciated that adverse events did not affect every patient, however if a product [sic] was listed as common ie might affect less than one in every 100 patients and domperidone had to be used at initiation of therapy it was misrepresentative to state such a claim especially when the audience were patients not health professionals.

- 'Nodule formation is usually not a significant problem'. (Breach of Clauses 7.2 and 7.9).

  Not consistent with summary of product characteristics (SPC).

Although the booklets were for patients identified as suitable for APO-go, claims must not be written with promotional intent. Abbott Healthcare believed that the booklets failed to meet the high standards set by the industry (breach of Clause 9.1), lacked safety data, side effect profile and contraindications etc (breach of Clause 7.9) which could prejudice patient safety and therefore brought discredit to the industry (breach of Clause 2).

Abbott Healthcare alleged breaches of Clauses 2, 7.2, 7.9, 9.1, 12.1 and 22 and asked that the booklets and claims at issue be withdrawn.

RESPONSE

Genus did not consider that the booklets were in breach of the Code; they were not for the public, they were for those identified as being APO-go patients. The booklets informed patients about the medicine their health professional had recommended and so encouraged concordance, and thus tied in with the recent NHS White Paper theme of informed patients and 'no decision about me, without me'.

With regard to Abbott Healthcare's ongoing

misunderstanding around the 'device vs drug' issue, Genus had explained several times that due to the unique nature of APO-go and the fact that it was administered subcutaneously, referring to the pen and pump was entirely acceptable as they were each integral to the product.

The APO-go pen was a registered medicinal product.

The APO-go pump referred to the continuous infusion, and the medicine and device were fundamentally linked: neither could be used alone. Genus' branded pump could only be used with the peripherals that were supplied with the pre-filled syringe or APO-go ampoules.

Therefore, Genus did not believe that the booklets were disguised promotion, or that it had 'switched' from providing educational information. The booklets were entirely clear.

In relation to the four claims at issue, Genus stated that its response was the same as previously submitted to Abbott Healthcare.

- 'Highly effective'. This claim was factual, did not use any superlatives and was not 'disguised promotion' as these pieces were for patients already identified as APO-go patients. This was not a hanging comparison as it was not stated that APO-go was highly effective compared with anything. Several products could be highly effective in the same context.

- 'NO! APO-go is not a last option ...'. The booklets were for patients identified as suitable for APO-go, and this claim, which was fact (the National Institute for Health and Clinical Excellence (NICE) Guidelines algorithm was provided) was to reassure patients that by having APO-go therapy they had not exhausted their Parkinson's disease management options. The claim that patients could be on APO-go for many years was also factual, and so Genus did not believe there was an issue with this claim. This provided balanced and fair information to help educate. There was no need, or intention, to promote as these patients had already been chosen for APO-go. Again, this coincided with the 2010 NHS White Paper surrounding informed patients, and Genus did not consider there was a breach of the Code.

- 'Nausea doesn't affect everyone ...'. Genus submitted that this claim, in context of the full paragraph from which it had been taken, was not misrepresentative. The preceding sentence and following details put the claim in a clear context: 'APO-go [PEN/continuous infusion] can cause nausea and vomiting as well as low blood pressure. Nausea doesn't affect everyone, is very temporary and usually only occurs when APO-go [PEN/continuous infusion] therapy is first initiated. Domperidone (Motilium), an anti-sickness medication, is always used with APO-go initiation to avoid nausea.' Therefore, Genus submitted this was an accurate declaration. Not all patients were affected by nausea, especially those who had already been on dopaminergic therapies. The use of domperidone was a prophylactic measure as it was not known which patients would be affected, and so represented good clinical practice. Genus did not agree this was in breach of Clause 7.9 as the statement reflected available evidence and was capable of substantiation by clinical experience.

- 'Nodule formation is usually not a significant problem'. Genus submitted that the context in which the above claim appeared in both booklets was balanced and fair: 'Nodule formation occurs in some APO-go patients. Although apomorphine is rapidly absorbed from subcutaneous tissue, in some instances when the muscle underneath isn't active enough, it can pool in the skin causing nodules to form. Nodule formation is usually not a significant problem, but occasionally, if severe, can lead to erratic absorption of the drug and may affect the therapeutic outcome. Any nodule formation can be improved with strict rotation of the injection site used and improved skin hygiene'. Genus stated 'not usually a significant problem' and by doing so conceded that there was a problem, but one that could be managed. In context this was perfectly balanced and was based on available evidence and clinical experience. Genus (formerly Britannia) had almost 20 years' experience in Parkinson's management with APO-go.

PANEL RULING

The Panel noted that Genus had not categorically stated what the target audience was for the booklets. The company had variously stated that they were for those identified as 'being APO-go patients' and for those identified as 'being suitable for APO-go therapy'. It was thus unclear as to whether the booklets were intended for those already receiving APO-go therapy or for those considering starting such therapy. The Panel examined the content of the booklets and noted that the pen booklet referred at one point to patients who were already using the APO-go pump but needed a boost at various times of the day. Both booklets, however, 'introduced' patients to APO-go and listed the benefits of therapy and a quarter of each book (2 to 3 pages) gave detailed information about the challenge test. In the Panel's view the booklets were most likely to be given to patients who were being considered for APO-go therapy but for whom the prescribing decision could not be made until the results of the challenge test were known. In the Panel's view the booklets were designed to influence a patient's decision as to whether to start APO-go therapy should the

challenge test be successful.

The Panel considered that companies could prepare material about a product for patients who might be prescribed that product but it was very important that such material met all the relevant requirements of the Code, particularly Clauses 22.1 and 22.2. Clause 22.1 prohibited the promotion of a prescription only medicine to the public. Clause 22.2 permitted the provision of factual information presented in a balanced way to the public either directly or indirectly. Such material must not raise unfounded hopes of successful treatment or be misleading about the safety of a product. In addition, Clause 22.2 required that statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a prescription only medicine.

Introduction to APO-go Pen booklet

The Panel did not consider that the claim that 'APO-go is a highly effective anti-parkinsonism medication' on page 2, was a hanging comparison as alleged. No comparison was made or implied and thus the Panel ruled no breach of Clause 7.2.

The Panel noted the vague allegation of a breach of Clause 22 with regard to the claim 'No! APO-go therapy is not the last option in Pd; patients can use APO-go Pen therapy in combination with their oral medication or with an APO-go Pump for many years' on page 6. The Panel did not consider that the claim in itself constituted advertising a prescription medicine to the public as prohibited by Clause 22.1. Nor did it fail to meet the requirements of Clause 22.2. It was factual and balanced. The Panel did not consider that the complainant had proven this allegation on the balance of probabilities and thus with regard to this specific claim ruled no breach of Clause 22.

The Panel noted that under the heading 'What are the possible side effects of APO-go Pen therapy' it was stated that 'APO-go Pen can cause nausea and vomiting as well as low blood pressure. Nausea doesn't affect everyone, is very temporary and usually only occurs when APO-go Pen therapy is first initiated. Domperidone (Motilium), an anti-sickness medication, is always used with APO-go initiation to avoid nausea'. The APO-go pen SPC stated that patients must be established on domperidone for at least two days prior to initiation of therapy. Once treatment had been established domperidone therapy might be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension. The Panel thus did not consider that with regard to the incidence and duration of nausea, the booklet fairly reflected the information in the SPC and was misleading in that regard. Breaches of Clauses 7.2 and 7.9 were ruled.

The Panel noted that under the same heading it was stated that 'Nodule formation occurs in some APO-go patients' and was 'usually not a significant problem, but occasionally if severe, can lead to erratic absorption of the drug and may affect the therapeutic outcome'. The APO-go pen SPC stated that most patients experienced injection site reactions, particularly with continuous use, including subcutaneous nodules. The Panel thus did not consider that to state that nodule formation only occurred in some patients accurately reflected the data in the SPC and was thus misleading in that regard. Breaches of Clauses 7.2 and 7.9 were ruled.

Introduction to APO-go Pump booklet

The Panel considered that its last three rulings above applied to the Introduction to APO-go Pump booklet. Its ruling about the claim 'APO-go is a highly effective anti-parkinsonian medication …' did not apply as this claim did not appear in the Introduction to APO-go Pump booklet.

Both booklets

The Panel noted the general allegation of a breach of Clause 22. It first considered the requirements of Clause 22.1. The Panel considered that the booklets would influence patients regarding APO-go therapy. On balance the Panel considered that the booklets constituted advertising a prescription only medicine to the public and a breach of Clause 22.1 was ruled. Turning now to Clause 22.2, the Panel noted that the introduction to both booklets stated that APO-go had '… a similar effect to the gold standard treatment, levodopa'. The Panel considered that to describe a medicine as a model of excellence did not meet the requirements of Clause 22.2; information about APO-go had not been presented in a balanced way. It also noted its rulings of breaches above which it considered meant that the booklets were not factual and were misleading. A breach of Clause 22.2 was ruled.

With regard to the alleged breach of Clause 12.1, the Panel considered that as promotion of a prescription only medicine to the public was not allowed such promotion could not be disguised. No breach of Clause 12.1 was ruled. The matter at issue was better dealt with under Clause 22 of the Code.

The Panel did not consider that the content of the booklets was misleading given their titles. They both contained information relevant to the medicine and its method of administration. The booklets were not comprehensive in relation to side effects. Only nausea and skin nodules were mentioned. There were other side effects listed in the SPC that were not included in the section headed 'What are the possible side effects of APO-go [Pen/continuous infusion] therapy?'. This was not balanced and was misleading with respect to the safety of the medicine. Breaches of Clauses 7.2 and 7.9 were ruled. The use of the brand name was not misleading. No breach of Clause 7.2 was ruled.

The Panel did not consider that high standards had been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of Clause 2 which

was used as a particular sign of censure and reserved for such use.

2 Skin management guide (APO-0110-654)

COMPLAINT

Abbott Healthcare stated that this patient literature was still available despite issues raised regarding Code breaches. In particular, Abbott Healthcare had issue with a claim that skin nodules were more likely to be caused with poor skin care. (Breach of Clause 7.9).

The SPC stated 'most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis'. These were listed as very common ie less than one in ten patients. This was not reflected in this leaflet.

Clause in breach: 7.9.

RESPONSE

Genus noted that Clause 7.9 stated that 'Information and claims about side-effects must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product has no side-effects, toxic hazards or risks of addiction or dependence. The word "safe" must not be used without qualification'. Genus denied that the claim at issue was in breach of Clause 7.9 and submitted that it reflected available evidence, such as Todd *et al* (2008) which listed hygiene as the top key consideration for siting infusions and for best practice to prevent and manage nodule formation. Genus also referred to a 2010 BMJ insert 'Role of apomorphine in the management of Parkinson's disease' which stated that nodules could be minimised by more frequent change of infusion needles, attention to hygiene upon needle insertion and local ultrasound physiotherapy.

PANEL RULING

The Panel noted that the document at issue was a four page, A4 leaflet entitled 'APO-go skin management'. The first paragraph, headed 'What are skin nodules?', explained that a side effect of APO-go therapy could be redness, tenderness, itching and the development of nodules and/or hardening of the skin at the injection site. A section 'What causes them?' followed and referred to a local inflammatory reaction which varied greatly between individuals and which '… sometimes occurs in response to the medication or the needle and is more likely with poor skin care'. The next two pages headed 'What can I/my carer do to help minimise or prevent these skin reactions?' included information regarding hygiene, choosing an injection site and needle siting. The final page referred to treatment of existing nodules/hardened skin areas and included the statement that 'skin nodules although common, present no significant problems in the majority and shouldn't stop treatment'.

The SPC stated general disorders and administrative site conditions were very common (≥1/10). Most patients experienced injection site reactions particularly with continuous use. These might include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) might also occur.

The Panel considered that the purpose of the leaflet in question was to explain to patients what skin nodules were, how they were caused, encourage patients and carers to follow good hygiene practices, to give advice about siting needles etc and to explain what could be done if skin nodules developed. The Panel considered that the leaflet was clear that APO-go therapy was associated with the development of skin nodules in response to the medication or to the needle and was more likely with poor skin care. The Panel considered that Abbott Healthcare's allegation was vague; no details had been provided as to why the claim was alleged to be in breach of the Code. The Panel thus did not consider that Abbott Healthcare had proven its complaint on the balance of probabilities. The Panel did not consider that the booklet was misleading about the cause of skin nodules as alleged. It did not state that these were wholly due to poor skin hygiene. No breach of Clause 7.9 was ruled in this regard.

The Panel considered that the booklet was misleading about the incidence of injection site reactions. The leaflet stated that skin nodules were common whereas the SPC stated that injection site reactions were very common and experienced by most patients. A breach of Clause 7.9 was ruled.

Complaint received **11 November 2010**

Case completed **14 March 2011**