CASE AUTH/2385/2/11

# BAXTER v NOVO NORDISK

## NovoSeven leavepiece

**Baxter complained about the source data used in support of a cost effectiveness claim which appeared in a NovoSeven leavepiece issued by Novo Nordisk. Baxter supplied FEIBA (factor viii inhibitor bypassing activity).**

**Baxter was concerned about the efficacy assumptions which fed into the supporting reference (Knight *et al* 2003) which described an economic model of the different strategies that could be used to treat episodes of bleeding in haemophilia patients with inhibitors. Baxter noted that the NovoSeven efficacy data (92%) fed into Knight *et al* 2003 was from Key *et al* (1998) and the efficacy input into the economic model for FEIBA (79%) was from a 1990 publication. Baxter alleged that Knight *et al* (2003) was out-of-date and did not reflect the efficacy of NovoSeven in clinical practice. In particular Baxter noted two more recent comparative studies (Astermark *et al* 2007 and Young *et al* 2008) failed to show a significant difference between NovoSeven and FEIBA.**

**Baxter submitted that a cost effectiveness claim should be based on current prices and the most up-to-date efficacy data of the products being compared.**

**The detailed response from Novo Nordisk is given below.**

**The Panel noted that the page of the leavepiece at issue was headed 'How can NovoSeven help you cut costs?' and immediately below was the claim 'A systematic review based on 2001 prices found that on-demand treatment with NovoSeven was cost-effective compared to treatment with pd-aPCC' referenced to Knight *et al* (2003). This was followed by the claim 'Now even better value' above text and an accompanying graph which illustrated a 30% increase (FEIBA) and a 5% decrease (NovoSeven) in prices since 2001.**

**The Panel noted that by means of a literature review Knight *et al* (2003) examined the cost-effectiveness of different strategies in the treatment of high-responding haemophilia A patients with inhibitors. The results showed that NovoSeven was the most cost-effective treatment for such patients, on demand or when they bled, compared with treatment with FEIBA. The reason why NovoSeven was the cheapest option despite its higher acquisition cost was due to the difference in success rates of treating minor bleeds at home, 92% for NovoSeven vs 79% for FEIBA. This reduced the need for further treatment doses and hospitalisation costs. The authors noted that the robustness of the assumptions needed further research.**

**The Panel noted that the cost-effective claim in the leavepiece was, in effect, based on an indirect comparison of NovoSeven and FEIBA in which the reported efficacy of the two products was 92% and 79% respectively. The source data were over 10 years old. Two more recent comparisons of NovoSeven and FEIBA (Astermark *et al* and Young *et al*) had suggested that the difference between the two was not so pronounced. A Cochrane review of 2010 (available when the leavepiece was produced) however, noted methodological flaws in these studies and that neither was able to prove the superiority of one treatment over the other. In a meta-analysis of the published efficacy data for NovoSeven and FEIBA, Treur *et al* (2009) noted 'that a typical regimen of NovoSeven is likely to produce significantly higher efficacy levels than typical FEIBA treatment at the 12, 24 and 36 hour time points'. A review of 18 studies by Knight *et al* (2009) stated that overall, higher efficacy and bleed cessation rates were noted for NovoSeven rather than FEIBA. The authors concluded that the wide variations in definitions of efficacy and study methods made comparison of results across studies difficult. Further head-to-head trials should incorporate a standardized measurement for defining efficacy. The Panel thus considered that the claim at issue was not a fair reflection of the totality of the evidence and was thus misleading. A breach of the Code was ruled.**

**Upon appeal by Novo Nordisk the Appeal Board considered that it had to decide whether the results of Knight *et al* (2003), to which the claim at issue was referenced, were robust enough to be relied upon in 2011.**

**The Appeal Board noted that a systematic review of the relevant literature by Knight *et al* (2009) noted the paucity of comparative studies, with only two direct head-to-head trials (Astermark *et al* and Young *et al*). The authors stated that although, overall, the published literature reported higher efficacy for NovoSeven (81-91%) than for FEIBA (64-80%), the measurement of efficacy of the two was open to interpretation due to a wide variety of methods being used to evaluate effectiveness. It was recommended that further head-to-head, randomised, controlled trials should incorporate a validated standard method of efficacy assessment. In that regard the Appeal Board noted, for instance, that the efficacy results from Key *et al* had been reported at 3 hours (92% for NovoSeven) whereas the Treur *et al* meta-analysis reported efficacy at 12, 24 and 36 hours (66%, 88% and 95% respectively for NovoSeven and 39%, 62% and 76% for FEIBA).**

**The Appeal Board noted that although most of the published data consistently reported higher efficacy**

**for NovoSeven than FEIBA, neither of the two direct comparisons as noted by the Cochrane report, were able to prove superiority of one over the other. Treur *et al* stated that their analysis suggested that NovoSeven was more effective than FEIBA; Knight *et al* (2009) stated that future trials should incorporate a validated standard method of efficacy assessment and the Cochrane report stated that there was a need for further well-designed, adequately powered, randomized controlled trials.**

**The Appeal Board noted that haemophilia with inhibitors was an ultra-orphan disease. Patient numbers were extremely limited and so it was difficult to design robust, comparative clinical studies. Nonetheless, reliable cost-efficacy modelling depended upon the input of robust data. In the Appeal Board's view the economic model derived by Knight *et al* (2003) did not accurately reflect all of the current evidence and the widely acknowledged limitations on the data. The Appeal Board upheld the Panel's rulings of a breach of the Code.**

Baxter Healthcare Ltd complained about a leavepiece (ref UK/NV7/0809/0125a) for NovoSeven (eptacog alfa (activated)) produced by Novo Nordisk Ltd. NovoSeven was indicated, *inter alia*, to treat episodes of bleeding in haemophilia patients with inhibitors. The leavepiece was entitled 'Delivering rapid bleeding control to patients. Securing value for you'. The page at issue was headed 'How can NovoSeven help you cut costs?'. Baxter supplied FEIBA (factor viii inhibitor bypassing activity). Inter-company dialogue had failed to resolve the matter.

**COMPLAINT**

Baxter complained about the misleading use of data which reported 92% efficacy of NovoSeven in support of a cost-effectiveness claim. The supporting reference for the claims in the leavepiece, under the heading 'How can NovoSeven help you cut costs?' was Knight *et al* (2003) which described an economic model of the different strategies that could be used to treat bleeding episodes in haemophilia patients with inhibitors, using a Markov decision process. Baxter was concerned about the efficacy assumptions which fed into the model and thus allowed unreasonable claims to be made for the cost of treatment with NovoSeven.

Knight *et al* (2003) cited two previous economic analyses of the use of NovoSeven compared to FEIBA (Odeyemi and Guest 2002a and b), however, all of these publications derived their measure of the efficacy of NovoSeven (2003) (92%) from Key *et al* (1998). By contrast the efficacy rate input into the model by Knight *et al* (2003) for FEIBA was 79% for home treatment derived from Hilgartner *et al* (1990).

Baxter alleged that the use of Knight *et al* (2003) as a measure of efficacy for the health economic assessment of NovoSeven was misleading, and did not promote NovoSeven objectively. This reference was out-of-date and did not reflect the efficacy of NovoSeven in clinical practice.

Baxter noted that two more recent and robust publications directly compared the two products in objective terms. The first, Astermark *et al* (2007), was a randomised, comparative, cross-over study of the two products where each subject served as their own control. Although the primary endpoint of the study to show equivalence was not met, rates of efficacy for the two products were similar at all time points.

The second, Young *et al* (2008), was also a randomised comparison. There were two different dose regimes used for NovoSeven in this study; in terms of pain and mobility (the primary end points) no statistically significant differences were seen between the two products.

Baxter noted that in 2010 the Cochrane Collaboration published a systematic review of bypassing agents. Only Astermark *et al* and Young *et al* met the review criteria in terms of design and quality and were thus included in the formal analysis. Although a formal meta-analysis could not be carried out due to the difficulty of comparing the two studies, the authors concluded that the trials 'did not show superiority of one treatment over the other'.

The cost comparisons made in the leavepiece were based solely on the measures of efficacy used by Knight *et al* (2003) and derived from Key *et al*. Each of the economic analyses had shown NovoSeven to be cheaper than FEIBA in routine use; however this was primarily driven by the disparate efficacy measures used which did not reflect current comparative data, clinical practice or experience. Novo Nordisk updated these economic models with recent prices; however the underlying efficacy assumptions were unchanged.

Baxter noted that Key *et al* was the subject of a warning letter sent to Novo Nordisk by the US Food & Drug Authorisation (FDA) in 2004. The FDA believed the article was substantially flawed and was not robust enough to serve as the basis for promotional claims for NovoSeven, either for safety or efficacy. In particular, the FDA's concerns related to patient enrolment, treatment and monitoring.

Baxter argued that, to be fair, a cost-effectiveness claim should be based on current prices and the most up-to-date efficacy data for the products being compared. On the basis that the efficacy data used by Novo Nordisk was from a single arm study from 1998, when there were good quality randomised comparative studies from 2007 and 2008, Baxter believed that Novo Nordisk had been very selective in its use of evidence to support its claims. This was not balanced, it was misleading and in breach of the Code.

Baxter believed that the promotion of NovoSeven as a less expensive option than FEIBA in this patient

group, and the promotional use of studies based on this specific efficacy claim were both misleading, in breach of Clause 7.3.

Baxter had noted that it had unsuccessfully asked Novo Nordisk to stop using these references in its promotional materials.

**RESPONSE**

Novo Nordisk stated that the leavepiece was produced for the NovoSeven key account managers to use to highlight the importance of rapid bleed control in haemophilia patients with inhibitors. Furthermore, the leavepiece highlighted the costs of treatment and cost effectiveness of NovoSeven in the home treatment setting as the first line of management of mild to moderate bleeds in these patients. Following Baxter's initial complaint, the item was withdrawn from circulation on 8 November 2010.

**Efficacy assumptions in cost-effectiveness modelling**

Novo Nordisk ascertained from Baxter's complaint and from inter-company dialogue, that its main concern was the alleged misleading use of Key *et al*, which reported 92% efficacy for NovoSeven, as the primary source of efficacy data for NovoSeven for cost effectiveness analyses. Baxter claimed this was communicated in its letters to Novo Nordisk, dated 22 October and 22 November 2010. Novo Nordisk noted that neither of these letters included information or any criticism of the use of this reference to support the efficacy of NovoSeven. This was first highlighted when Novo Nordisk asked Baxter to provide an agenda for a teleconference that Baxter requested as part of inter-company dialogue.

Baxter claimed its complaint related a page of the leavepiece which referred to the economic model published by Knight *et al* (2003). This study concluded that on-demand treatment with NovoSeven was cost effective compared with treatment with FEIBA. Novo Nordisk noted that Knight *et al* (2003) was undertaken by the School of Health and Related Research (ScHARR), University of Sheffield, which received funding for the study from the Department of Health. Furthermore, the economic analysis was developed with the input of clinical expert advice and was reviewed by a representative from the National Institute for health and Clinical Excellence (NICE).

Baxter alleged that the efficacy assumption, based on Key *et al*, that fed into the economic model published by Knight *et al* (2003) allowed unreasonable claims to be made for the cost of treatment with NovoSeven. Hence, Baxter believed the use of the Key *et al* as a measure of efficacy for the health economic assessment was misleading and did not promote NovoSeven objectively.

**Justification for use of Key *et al***

Novo Nordisk stated that Knight *et al* (2003) used the results of a systematic review of the economic literature to inform the development of the economic model, with particular reference to the economic models published by Odeyemi and Guest (2002a and b) and Colowick *et al* (2000).

Clinical effectiveness rates for NovoSeven and FEIBA were taken from Odeyemi and Guest (2002a and b). Knight *et al* (2003) stated that the selection of these clinical studies was supported by the results of a clinical effectiveness review reported by Lloyd Jones *et al* (2003).

Cross referencing to the Odeyemi and Guest references, the following justification was given for the selection of Key *et al*: 'This was selected as the basis of the efficacy data following a literature review and was endorsed by the expert panel involved in the development of this analysis'.

These three economic evaluations (Knight *et al* 2003, Odeyemi and Guest 2002a and b) were peer reviewed published studies that used Key *et al* as the source of NovoSeven efficacy data. The use of this study was also validated by expert clinical opinion and was supported by the results of Lloyd Jones *et al*. As a result, Novo Nordisk had no reason to question the validity of using these data as the source of efficacy data for NovoSeven in this analysis. Furthermore, the economic evaluation undertaken by Knight *et al* (2003) included extensive sensitivity analyses which showed that the efficacy of NovoSeven would need to be reduced from 92% to <84% in order for FEIBA to become cheaper.

**Astermark *et al* and Young *et al***

Baxter provided evidence from two comparative studies (Astermark *et al* and Young *et al*) that were published after Knight *et al* (2003). These studies had been subject to a systematic review by the Cochrane Collaboration in 2010. This review compared the results of comparative studies only, of which there were two available, and concluded that the trials did not show superiority of one treatment over the other.

The FENOC study (Astermark *et al*) was a prospective, open-labelled, cross-over, clinical equivalency study. The authors acknowledged that the study lacked statistical power and the primary end point for equivalency at the 6 hour interval was not achieved. Furthermore, in a pre-determined definition of therapeutic equivalence in the study, the two products were not equivalent at any stage of the designated post-infusion time points in a study not powered for superiority.

Baxter proposed that in Young *et al*, there was no statistically significant difference between the two products. However, Baxter had omitted important contextual information about this citation. The

efficacy evaluations in this trial included two methods:

- A subjective global treatment response algorithm for pain assessment and mobility at specific time points (which was not a validated method assessment). Baxter had correctly highlighted that there were no statistically significant differences between NovoSeven and FEIBA and this related only to this pain and mobility assessment.

- The percentage of patients achieving bleed resolution without needing rescue medication within 9 hours of the first administration of the trial product. Novo Nordisk stressed that this efficacy evaluation was more relevant for a health-economic evaluation than the global treatment response algorithm. In this evaluation, the percentage of patients who required additional rescue medication was significantly lower for the NovoSeven 270mcg/kg dose group vs FEIBA (p=0.032) and approached significance (p=0.069) in the multiple dose group (90mcg/kg x 3 doses) vs FEIBA. The efficacy of both NovoSeven treated groups (91.7% efficacy for the NovoSeven 270mcg/kg group and 90.8 % efficacy for the 3 x 90mcg/kg) in this randomised setting were consistent with the efficacy evaluation in the real world clinical practice in Key *et al*.

Ideally there should be a systematic approach to identifying all the relevant data for use in an economic evaluation and Novo Nordisk pointed out the limitations of conducting economic evaluations for rare diseases, where it was recognised that the data were more limited.

**Literature reviews**

Since the economic evaluation by Knight *et al*, there had been three further systematic reviews of the clinical literature (Cochrane review, Knight *et al* (2009) and Treur *et al*).

- Novo Nordisk accepted the Cochrane review concluded that on the basis of the comparative evidence the two published trials did not demonstrate superiority of one product over another. Once again, however Novo Nordisk noted that the inclusion criteria for this review only included comparative trials. Again, Baxter had omitted important contextual information as stated in the conclusion of the Cochrane review. This Cochrane review concluded that more advanced methodologies were required to address the problem of high heterogeneity between studies. The review referred to the Bayesian meta-analysis published by Treur *et al* and concluded that other systematic reviews might help in the choice of the more effective concentrates, by using a Bayesian approach to pool randomised and non randomised evidence.

- Knight *et al* (2009) included data from such trials and concluded that estimates of efficacy from randomised clinical trials using dosing regimes in line with the guidelines were higher for NovoSeven (81-91%) than for FEIBA (64-80%).

- Treur *et al* included data from all published studies using a Bayesian meta-regression and concluded a typical NovoSeven regimen would resolve joint bleeds more effectively than a typical FEIBA regimen. This demonstrated that a typical regimen of NovoSeven (90mcg/kg repeated every 3 hours as necessary) resulted in cumulative bleed resolution of 66%, 88% and 95% after 12, 24 and 36 hours respectively. This compared with 39%, 62% and 76% for a typical FEIBA regimen (75IU/kg repeated every 12 hours if necessary). As far as Novo Nordisk was aware Treur *et al* was the only meta-analysis that combined all of the available clinical evidence for NovoSeven and FEIBA. These figures were statistically significant and also robust in sensitivity analyses. The meta-analysis integrated data from over 2000 joint bleeds and provided more relevant information on treatment efficacy than the results of individual studies. In order to assess the impact of individual studies on the results of the meta-analysis sensitivity analyses were undertaken. When the two direct comparator trials were weighted more heavily in the analysis (Astermark *et al* and Young *et al*), NovoSeven treatment remained significantly more effective than FEIBA.

On this basis, Novo Nordisk believed the efficacy assumptions used in the Knight *et al* (2003) economic model (92% in Key *et al* and 79% in Hilgartner *et al* 1990) appeared to be consistent with the evidence obtained from the available systematic reviews and meta-analysis.

Baxter referred to Novo Nordisk continuing to update these economic models with recent prices. This was in fact presented on a further page of the brochure. Novo Nordisk appreciated that this did not include adequate detail on the assumptions used for the economic evaluation and this had already been resolved with Baxter as part of the inter-company dialogue. Novo Nordisk noted that this economic analysis was intended to update the economic evaluation published by Knight *et al* (2003) to assess the impact of changes in treatment cost since 2001, when the analysis was undertaken. Updating the efficacy data used in the analysis would not permit a comparison with 2001 values. However based on the evidence presented above Novo Nordisk contended that the efficacy assumptions used in the economic evaluation were consistent with the current evidence.

**FDA warning letter (2004) issued to Novo Nordisk in USA**

Baxter also referred to an FDA warning letter sent to Novo Nordisk about the use of Key *et al* in a Spanish language promotional brochure for use in the US. The letter noted that Key *et al* was a home treatment study which reported that 92% of bleeds

were resolved within 24 hours, with a mean 2.3 doses of NovoSeven, administered at a mean of 1.2 hours from the start of the bleed. The FDA concluded that the design of the study did not allow a determination of safety and efficacy for the purpose of product labelling and should therefore not be used to support these specific promotional claims in the US as per guidance of a specific clause of the FDA. Novo Nordisk maintained that this related to a very specific promotional issue in the US, which was not relevant in this case. Nevertheless, the efficacy of 92% of bleed resolution in a specific time frame was consistent with recently published data as demonstrated above.

**Conclusion**

In the concluding two paragraphs of its complaint, Baxter alleged that it believed the promotion of NovoSeven as a less expensive option than FEIBA in this patient group was misleading in breach of Clause 7.3. Baxter concluded by stating that to be fair, a cost effectiveness claim should be based on current prices and the most up to date efficacy data for the products being compared. Novo Nordisk agreed and maintained that the cost effectiveness evidence was consistent with the efficacy data in the published literature for both of these products. Key *et al* remained a seminal paper for NovoSeven and the results of subsequent systematic reviews and meta-analysis supported the assumption of 92% efficacy for NovoSeven. Economic evaluations inevitably required the modelling of cost and efficacy assumptions from a number of disparate sources which had the potential to generate uncertainty in the results. This emphasised the importance of extensive sensitivity analyses to assess the robustness of the model results. The economic evaluation undertaken by Knight *et al* (2003) showed that the efficacy of NovoSeven would need be reduced from 92% to <84% in order for FEIBA to become cheaper.

Based on this evidence Novo Nordisk denied that use of this efficacy assumption for cost effectiveness evaluations was misleading and refuted a breach of Clause 7.3.

**PANEL RULING**

The Panel noted that the page of the leavepiece at issue was headed 'How can NovoSeven help you cut costs?' and immediately below was the claim 'A systematic review based on 2001 prices found that on-demand treatment with NovoSeven was cost-effective compared to treatment with pd-aPCC' referenced to Knight *et al* (2003). This was followed by the claim 'Now even better value' above text and an accompanying graph which illustrated a 30% increase (FEIBA) and a 5% decrease (NovoSeven) in prices since 2001.

The Panel noted that by means of a literature review Knight *et al* (2003) examined the cost-effectiveness of different strategies in the treatment of high-responding haemophilia A patients with inhibitors. The results showed that NovoSeven was the most cost-effective treatment for such patients, on demand or when they bled compared with treatment with FEIBA. The authors noted that the reason why NovoSeven was the cheapest option despite its higher acquisition cost was due to the difference in success rates of treating minor bleeds at home, 92% for NovoSeven (Key *et al*) vs 79% for FEIBA (Hilgartner *et al*). This reduced the need for further treatment doses and hospitalisation costs. The authors also noted that the robustness of the assumptions needed further research.

The Panel noted each party's submission on Key *et al*. The Panel noted that haemostasis was achieved in 92% of evaluable bleeds with NovoSeven. In the intention to treat analysis of all bleed events the authors stated that efficacy outcomes were equivalent to the evaluable bleeds, with an effective response in 88% of treated episodes.

The Panel noted Novo Nordisk's submission that Knight *et al* (2003) had stated that the selection of the studies by Odeyemi and Guest was supported by the results of a clinical effectiveness reviewed reported by Lloyd Jones *et al*. The Panel further noted that Lloyd Jones *et al* was the same group as Knight *et al* (2003).

Astermark *et al* was a prospective, open-label, randomized study designed to test equivalence of FEIBA and NovoSeven in certain joint bleeds. The primary outcome was evaluation 6 hours after treatment. The criterion for declaring the products' equivalence at 6 hours by patient report was not met. The products were equivalent in terms of bleeding cessation at 24 hours; NovoSeven 85.7%, FEIBA 90.5%, p=0.038; and at 48 hours, NovoSeven 92.7% and FEIBA 95.1%, p=0.001. The study authors noted that failure to achieve equivalence, particularly at the 6 hour time point, was probably related to a lack of statistical power. It could not be construed as evidence that one product was different or better. The study authors also noted that in exploratory analysis neither product was superior to the other either in terms of efficacy or ability to stop bleeding at any time point. The study concluded that the products 'appeared to exhibit a similar effect on joint bleeds although the efficacy between the products was rated differently by a substantial proportion of patients'.

Young *et al* evaluated the efficacy and safety of single 270mcg/kg dose NovoSeven vs standard 90mcg/kg dose NovoSeven and FEIBA for controlling joint bleeds in a home treatment setting. Efficacy was assessed by the requirement for additional haemostatics within 9 hours and a novel global response algorithm. The percentage of patients requiring additional haemostatic medication was significantly greater for the FEIBA treatment group than for the single dose 270mcg/kg NovoSeven group. The efficacy difference between the FEIBA and the NovoSeven 3 x 90mcg/kg group approached but did not achieve statistical

significance (p=0.069). No significant differences in treatment for the global response algorithm were discovered although a trend towards a better response with NovoSeven was noted.

The Panel noted that efficacy was rated by the patient in both Young *et al* and Astermark *et al*.

The Panel noted that the leavepiece at issue was dated August 2010. The Cochrane Collaboration report was last assessed as up-to-date on 6 July 2010. It thus appeared that it was available when the leavepiece was produced and used. The Cochrane report stated that Young *et al* and Astermark *et al* qualified for inclusion but the data were not presented in such a way as to allow these to be combined in a meta-analysis. Each study showed methodological flaws and neither was able to prove the superiority of one treatment over the other. The authors stated that based on the available randomized evidence it was not possible to consider one treatment more efficacious or safer than the other. The authors' separate analysis of Young *et al* and Astermark *et al* showed that NovoSeven and FEIBA were, *inter alia*, similar in efficacy. The authors noted that non-randomized evidence could usefully be taken into account and referred to Treur *et al*.

Treur *et al* was also a meta-regression analysis of the published efficacy data of NovoSeven and FEIBA. Seventeen studies were included including Astermark *et al*, Key *et al* and Young *et al*. Pooled efficacy levels for typical NovoSeven and FEIBA regimens were estimated. At 12 hours the efficacy was 66% (NovoSeven) and 39% (FEIBA), at 24 hours 88% NovoSeven and 62% (FEIBA) and at 36 hours 95% (NovoSeven) and 79% FEIBA. The study authors noted that the results suggested 'that a typical regimen of NovoSeven is likely to produce significantly higher efficacy levels than typical FEIBA treatment at the 12, 24 and 36 hour time points'. It was noted that the models' assumption that second or subsequent doses had similar efficacy was arguably unrealistic. However, data for more relevant parameters was not available. Many limitations were discussed including hierarchy of study designs, relevance of outcome data and bleeding sites.

Knight *et al* (2009) reviewed 18 studies to establish, *inter alia*, robust estimates of efficacy and speed of bleed resolution. Overall, whilst noting that comparisons between studies were difficult, the overall efficacy rates from randomized clinical trials were 64-80% for FEIBA and 81-91% for NovoSeven 12 hours after treatment. In the non-randomized trials 65-88% for FEIBA and 90% for NovoSeven treatment. Overall higher efficacy and bleed cessation rates were noted for NovoSeven rather than FEIBA. The authors concluded that the wide variations in definitions of efficacy and study methods make comparison of results across studies difficult. Further head-to-head trials should incorporate a standardized measurement for defining efficacy.

The Panel noted that the cost-effective claim in the leavepiece was, in effect, based on an indirect comparison of NovoSeven and FEIBA in which the reported efficacy of the two products was 92% (Key *et al*) and 79% (Hilgartner *et al*) respectively. The source data were over 10 years old. Two more recent, direct comparisons of the NovoSeven and FEIBA had suggested that the difference between the two was not so pronounced. A Cochrane review of 2010 stated that the trials (Astermark *et al* and Young *et al*) did not show a difference in the effectiveness of the two products. The review by Knight *et al* (2009) referred to the difficulties in comparing data across studies. The Panel thus considered that the claim at issue was not a fair reflection of the totality of the evidence and was thus misleading. A breach of Clause 7.3 was ruled.

During its consideration of this case, the Panel noted that the page of the detail aid at issue featured a graph which showed the percentage price change for FEIBA and NovoSeven in the period 2001 to 2010. In that time the cost of FEIBA had risen by 30% whilst the cost of NovoSeven had decreased by 5%. The graph appeared to show that NovoSeven was 35% less expensive than FEIBA. The Panel was concerned that showing the percentage change in price might give a misleading impression of the absolute differences in acquisition cost and asked that Novo Nordisk be advised of its concerns in this regard.

**APPEAL BY NOVO NORDISK**

Novo Nordisk stated that the leavepiece highlighted the importance of rapid bleeding control in haemophilia patients with inhibitors and the cost effectiveness of NovoSeven in the home treatment setting in the first line management of mild to moderate bleeds.

**Background to complaint**

Novo Nordisk submitted that Knight *et al* (2003) demonstrated the cost effectiveness of NovoSeven vs FEIBA from an NHS perspective using a modelled economic evaluation. Modelled economic evaluations aimed to determine the cost effectiveness of one product over another and were based on a synthesis of the best available evidence at the time and most plausible assumptions that reflected clinical practice. The robustness of the results based on these assumptions was tested using sensitivity analyses, where one or more of the model inputs were altered and the impact on the results assessed. The sensitivity analysis performed on the economic evaluation undertaken by Knight *et al* (2003) showed that the efficacy of NovoSeven would need to be reduced from 92% to less than 84% in order for FEIBA to become cheaper or the efficacy of FEIBA increased from 79% to more than 88%. This demonstrated that the results of Knight *et al* (2003) were robust to changes in the model inputs and NovoSeven remained cost effective compared with FEIBA (table 14 of Knight *et al* 2003).

Novo Nordisk noted that haemophilia with inhibitors was an ultra-orphan disease and it was well recognised that data were more limited than for more common conditions. Over the last 30 years a number of studies for both NovoSeven and FEIBA had been published including two comparative, randomised, controlled trials (RCTs), and several uncontrolled and single arm studies. The Panel had stated that two recent direct comparisons of NovoSeven and FEIBA (Astermark *et al* and Young *et al*) had suggested that the efficacy difference between the two products was not so pronounced as those included in the economic model by Knight *et al* (2003) and stated that these findings had been confirmed by the Cochrane report. In the clinical practice management of haemophilia with inhibitors, treatment regimens were based on individual patient's haemostatic profile and the need to stop bleeding effectively. Treatment was not based on rigid regimens in RCTs and to do so would be unrealistic. For a rare disease such as haemophilia with inhibitors, it was almost impossible to design a single study that would statistically demonstrate the superiority of one product over another as trials were limited by small patient numbers. In the UK, there were just 189 patients with haemophilia with an inhibitor, (UK Haemophilia Centre Doctors' Organisation - Annual Report 2010). In ultra-orphan diseases, it was relevant to consider all of the available evidence, from both RCTs and non RCTs and therefore a meta-analysis of this evidence was recommended to increase the sample size on which the efficacy was based. This was supported by the conclusions of the Cochrane report. The Treur *et al* meta-analysis best reflected the totality of all the clinical evidence, including the two head-to-head trials and the key single arm studies in terms of number of bleeds for both products (Key *et al* and Negrier *et al* 1997).

Novo Nordisk noted that the Panel had stated that the authors of the Cochrane report had noted that non-randomised evidence could usefully be taken into account and referred to Treur *et al*. Treur *et al* was a meta-regression analysis of the published efficacy data of NovoSeven and FEIBA from 1965 up to October 2007. Novo Nordisk noted that in one set of sensitivity analyses, the Treur model was re-estimated after removing, sequentially and then together, two large 'outlier' studies, Key *et al*, which reported on the efficacy of NovoSeven, and Negrier *et al*, which reported on the efficacy of FEIBA, in order to test whether either one or both of these studies could skew the overall efficacy results in either direction. Treur *et al* stated that despite these omissions, the modelled NovoSeven treatment remained significantly more efficacious than modelled FEIBA treatment at 12, 24 and 36 hours. The efficacy results at 36 hours were 95% for NovoSeven and 79% for FEIBA. These were consistent with the efficacy inputs used in Knight *et al* for NovoSeven (92%) and FEIBA (79-88%).

Novo Nordisk noted that the Treur *et al* meta-analysis had systematically identified and meta-analysed all of the available evidence and therefore the results of the analysis reflected the totality of the available evidence. Although this analysis was not available when Knight *et al* (2003) was published the results of this analysis were consistent with the efficacy inputs used in Knight *et al* (2003). The table below summarised the efficacy inputs used in the model by Knight *et al* and the efficacy figures that had since been published for NovoSeven and FEIBA.

Summary of published efficacy rates for NovoSeven and FEIBA

| | | COCHRANE | | | |
|---|---|---|---|---|---|
| | Knight *et al* (2003) | Young *et al* (both measured at 9 hours) | Astermark *et al* (Primary endpoint measured at 6 hours) | Knight *et al* (2009) (Systematic Review) | Treur *et al* + (efficacy modelled inputs measured at 24 and 36 hours) (meta-analysis) |
| NovoSeven | 92% within 3-6 hours | 91% | 79% | 81% - 91% (efficacy measured at 9 hours) | 24 hours: 88% 36 hours: 95% |
| FEIBA | 79% within 36 hours | 63% | 80% | 64% - 80% (efficacy measured at 24 hours) | 24 hours: 62% 36 hours: 76% |

Based on this information Novo Nordisk disagreed with the Panel that the efficacy inputs for the analysis in Knight *et al* did not reflect the totality of the evidence and it maintained that these inputs were consistent with recently published evidence reflective of clinical practice.

Knight *et al* (2003) was an independent economic evaluation and when it was published it considered all of the available evidence. Although new clinical evidence had been published, there had been no new economic evidence for the UK to confirm or refute the conclusions, hence Knight *et al* (2003) remained the most recent publication to compare the cost effectiveness of NovoSeven and FEIBA.

In conclusion Novo Nordisk submitted that the previously submitted evidence supported its claim 'How NovoSeven can help you cut costs' and reflected the totality of evidence in a rare disease area, as the efficacy differences were supported by the results of a recent meta-analysis and were therefore not misleading. The Panel had unfairly focussed on rigid RCT evidence in its ruling and erroneously omitted important contextual information regarding Treur *et al*.

**COMMENTS FROM BAXTER**

Baxter stated that modelled economic evaluations of medicines in clinical practice must be based on robust data. It was clear that Novo Nordisk had been highly selective in its choice of data sources for the comparative efficacy of the two products, and therefore it did not represent the total body of evidence.

According to the NICE guide to the methods of technology appraisal 2008, the most reliable evidence about relative treatment effects was from experimental studies with high internal and external validity. The highest level of evidence was derived from randomised prospective studies, particularly head-to-head studies where comparative efficacy measures could be derived.

Baxter submitted that in its complaint, and in its dialogue with Novo Nordisk, it had repeatedly referred to the only independent, randomised, head-to-head comparison between the two products, namely the FENOC study by Astermark *et al*. This study was one of only two deemed suitable for scrutiny by a subsequent Cochrane review of the two treatments in this patient group. This was the only valid source of comparative efficacy data between the two products.

Although FENOC demonstrated substantial variations in response to treatment between patients, and even between different bleeding episodes in the same patient, what was not demonstrated after repeated data analysis was superiority of one treatment over the other. This conclusion was mirrored in the Cochrane publication.

Economic models put forward by Novo Nordisk repeatedly showed NovoSeven as cost-effective compared with FEIBA, however these models used older, less robust sources of efficacy data, and gave misleading results.

Following the publication of FENOC, Carlsson *et al* (2008) conducted a cost-utility analysis using the efficacy measures reported in the earlier publication. With a few exceptions this model showed that treatment with FEIBA gave a lower average cost per treatment episode than NovoSeven, contrary to all the economic models quoted by Novo Nordisk. Although this study used non-UK prices as part of the evaluation, these were still reflected the price differential in the UK.

Novo Nordisk placed a lot of emphasis on the analysis of literature by Truer *et al*, however there were a number of issues with this publication. The NICE guide stated that in the absence of valid RCT evidence, evidence from studies least open to bias would be considered. Truer *et al* was a Bayesian analysis combining results of 18 studies, 11 of which were observational in design without a control group. Two studies included fewer than 10 patients, which could be considered small even in this ultra-orphan disease. The studies differed in the way in which outcomes were measured, only joint bleeds were considered (compared to total number of bleeds), and they were subject to publication bias. Although sensitivity analysis was carried out the authors did not report the results of the model when only data from randomised, head-to-head studies was included. Bearing all this in mind, in the light of randomised, controlled evidence from FENOC, it was hard for Novo Nordisk to argue that this publication was not open to bias.

Baxter alleged that it was not its intention or objective to claim that FEIBA was either more effective, or more cost-effective, than NovoSeven. It was clear from the evidence from well-designed studies that both products had a role in treatment, and that neither was superior to the other. Baxter's challenge to the promotional claims made by Novo Nordisk rested on this point. Taking the conclusion of the Cochrane publication that the two products were similar in terms of safety and effectiveness, the acquisition cost of each treatment became the determining factor.

Baxter stated that current list prices were £780 per 1000 U for FEIBA and £525.20 for 1mg NovoSeven, comparable to the costs quoted by Carlsson *et al*. Taking the dose regimens from FENOC as the example, the acquisition cost of the two medicines (rounded to the nearest hole vial) for a typical 70kg adult would be approximately £4,680 for FEIBA (85 U/kg, one dose) and £6,827 for NovoSeven (90mcg/kg, two doses 2 hours apart).

This was in line with observational data collected in Italy and published by Gringeri *et al* (2003). This group observed treatment of 52 patients with haemophilia A and inhibitors over an 18-month period and recorded all costs related to their care, and various measures of quality of life. The average monthly cost of care was just under €18,000 per patient; NovoSeven represented approximately half of this cost. Although approximately half the NovoSeven was used to cover surgical procedures, even allowing for this it was illuminating to note the relative contributions to overall treatment costs of FEIBA and NovoSeven in this publication.

Baxter submitted that it was well known that recombinant therapies were expensive – given the widely accepted view that the two products were comparable in terms of efficacy, it was counter-intuitive for Novo Nordisk to claim superior cost-effectiveness for its product. As Novo Nordisk had admitted, the 92% efficacy figure for NovoSeven as used in its economic analysis was derived from Key *et al*. With regard to the appropriateness of this as a source of evidence, Baxter noted that it had been challenged by the FDA as being insufficiently robust as a basis for safety or efficacy claims and, additionally, it reported treatment of patients outside the licensed indication for FEIBA, and reported unlicensed doses of NovoSeven.

Baxter alleged that given that no sub-analysis of the results in haemophilia A patients could be done in this study, it was impossible to establish the true efficacy of NovoSeven in this report. Further, as the exclusion criteria made clear, it was very likely that patients who failed to respond to NovoSeven were not included in the final efficacy analysis, further skewing the results.

As the Panel had noted in its ruling, the claim in question was based on selective use of data, it did not fairly reflect all the evidence and was thus misleading. The appeal by Novo Nordisk had not

changed this, and Baxter was confident that the Panel's ruling was correct.

**APPEAL BOARD RULING**

The Appeal Board noted Novo Nordisk's submission at the appeal, that the leavepiece was to be used by representatives to open a discussion with prescribers about the cost effectiveness of using NovoSeven. The intention was to convince prescribers that NovoSeven was more cost effective than FEIBA.

The Appeal Board noted that although NovoSeven could be used to treat any episode of bleeding, the efficacy data from Key *et al*, which fed into the economic model of Knight *et al* (2003), related only to its use in mild to moderate episodes. The limitation of the data in this regard was not stated on the page in question. The following page of the leavepiece (overleaf) featured a graph headed 'Cost of managing a mild-to-moderate bleeding episode based on current prices' which was the first mention of 'mild to moderate' in the leavepiece in question.

The Appeal Board considered that it had to decide whether the results of Knight *et al* (2003), to which the claim at issue was referenced, were robust enough to be relied upon in 2011. The Appeal Board noted that a systematic review of the relevant literature by Knight *et al* (2009) (6 randomised controlled trials, 11 prospective or retrospective cohort studies and 1 meta-analysis) noted the paucity of comparative studies with only two direct head-to-head trials (Astermark *et al* and Young *et al*). The authors stated that although, overall, the published literature reported higher efficacy for NovoSeven (81-91%) than for FEIBA (64-80%), the measurement of efficacy of the two was open to interpretation due to a wide variety of methods being used to evaluate effectiveness. It was recommended that further head-to-head, randomised, controlled trials should incorporate a validated standard method of efficacy assessment. In that regard the Appeal Board noted, for instance, that the efficacy results from Key *et al* had been reported at 3 hours (92% for NovoSeven) whereas the Treur *et al* meta-analysis reported efficacy at 12, 24 and 36 hours (66%, 88% and 95% respectively for NovoSeven and 39%, 62% and 76% for FEIBA).

The Appeal Board noted that although most of the published data consistently reported higher efficacy for NovoSeven than FEIBA, neither of the two direct comparisons as noted by the Cochrane report, were able to prove superiority of one over the other. Treur *et al* stated that their analysis *suggested* that NovoSeven was more effective than FEIBA; Knight *et al* (2009) stated that future trials should incorporate a validated standard method of efficacy assessment and the Cochrane report stated that there was a need for further well-designed, adequately powered, randomized controlled trials.

The Appeal Board noted that haemophilia with inhibitors was an ultra-orphan disease. Patient numbers were extremely limited and so it was difficult to design robust, comparative clinical studies. Nonetheless, reliable cost-efficacy modelling depended upon the input of robust data. In the Appeal Board's view the economic model derived by Knight *et al* (2003) did not accurately reflect all of the current evidence and the widely acknowledged limitations on the data. The Appeal Board upheld the Panel's rulings of a breach of Clause 7.3. The appeal was thus unsuccessful.

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| **Complaint received** | **11 February 2011** |
| **Case completed** | **11 July 2011** |