NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Appeal Hearing

Febuxostat for the management of hyperuricaemia in patients with gout.

Introduction

1. An Appeal Panel was convened on 29th October 2008 to consider an appeal against the Institute's Final Appraisal Determination (FAD) to the NHS, on the use of febuxostat for the management of hyperuricaemia in patients with gout.

2. The Appeal Panel ("the Panel") consisted of Mr. Jonathan Tross (non-executive director of the Institute and chair of the Panel), Mr. Mark Taylor (non-executive director and Vice Chair of the Institute), Mr. Bob Osborne (lay representative), Dr Frank McKenna (NHS representative) and Dr Kate Lloyd (industry representative). Mr. Bob Osborne stated that he had suffered an incidence of gout flares in his 20s and had since continued to be prescribed allopurinol. The Chair noted this but did not see it as calling into question his objectivity. No objection was raised. All other members stated they had no interest to declare in respect of the appeal under consideration. Mr. Stephen Hocking (Beachcroft) was in attendance as a legal adviser to the Panel.

3. The Panel considered an appeal submitted by Ipsen Limited. Ipsen was represented by Dr Robin Kingswell, Mr Steve Hill, Dr Mireille Bonnemarie, Mr Stephen Beard and Dr Ilse Vanvlaenderen and in this decision is referred to as "the Company".

4. In addition the following individuals involved in the appraisal were present and available to answer questions from the Panel: Professor David Barnett (chair of the Appraisal Committee), Professor John Cairns (member of the Appraisal Committee), Professor Michael Doherty (Professor of Rheumatology), Dr Meindert Boysen (Associate Director of the Institute) and. Dr Helen Cheung (Technical Advisor)

5. There are three grounds on which an appeal can be lodged:

1. Ground 1.The Institute has failed to act fairly and in accordance with the published procedures as set out in the Institute's Guide to the Technology Appraisal Process;
2. Ground 2. The Institute has prepared guidance that is perverse in light of the evidence submitted;
3. Ground 3. The Institute has exceeded its legal powers.

6. The chair of the Appeals Committee (Mr. Mark Taylor), in preliminary correspondence, had confirmed that the appellant had potentially valid grounds of appeal in relation to the first two grounds. Three points of appeal (appeal points 1-3) were admitted under Ground 1, two points of appeal (appeal points 5-7) were admitted under Ground 2. One appeal point (appeal point 4) under Ground 1 was not admitted. The company did not submit an appeal under Ground 3. The company had proposed an alternative wording to the FAD recommendation in its statement of appeal.

7. The Final Appraisal Determination ("the FAD") considered at this Appeal provides guidance on the use of febuxostat for the management of hyperuricaemia in patients with gout. The FAD had been prepared under the Single Technology Appraisal Process.

8. Following introductory remarks from the Company and from Professor Barnett for the Appraisal Committee, the Panel considered each ground in turn.

Ground 1. The Institute has failed to act fairly and in accordance with its published procedures.

9. The Company raised three points of appeal. Points one and two were taken together.

> Appeal point 1. The institute has acted unfairly by failing to act in accordance with the provisions of its appraisal procedures concerning selection of comparators.
> Appeal point 2. The Institute has acted unfairly given that there is no clinical evidence to support NICE in its decision to reject allopurinol fixed-dose 300mg (the acknowledged standard of care) in favour of titrated dosing.

10. On appeal points 1 and 2, Dr Kingswell for the Company argued further that the Guide to the Single Technology Appraisal Process (STA) states that the health effects and cost effectiveness of a technology under review should be compared with 'current standard treatment in the NHS in England and Wales'. The current standard treatment in all but 2% of cases of gout treated with the current standard technology, allopurinol, involves doses of 300mg or less per day. However, the Committee guidance had been based on titrated dosing with allopurinol up to 900mg per day. This had not been referenced in the final scope for the appraisal, and is not reflective of current practice. Further, there is little evidence of safety and efficacy at higher doses or from formal randomized control trial evidence of the benefits of titrated dosing above the standard 300mg level on serum uric acid (sUA) concentration levels or gout symptoms. The case for use of titrated dosing up to 900mg is based on consensus clinical judgement and the historic licensing indications for allopurinol rather than an objective evidence base or current practice. The Company, in making its manufacturers statement, which in their view reasonably compared febuxostat to the current standard practice, had been disadvantaged by the reliance on titrated dosing of allopurinol as the basis for the Committee's recommendation, which it had not been given to understand would be the case.

11. Professor David Barnett on behalf of the Appraisal Committee said that the Company's argument on points 1 and 2 was based on a misreading of the scope. The Guide to the Methods of Technology Appraisal in terms of comparators states that 'best alternative care is the essential comparator…' rather than just current practice, although he acknowledged that the Guide did refer to considering routine UK care as well. It was right to look at best practice rather than sub optimal use. The indications for allopurinol covered three levels of dosage; 100-200mg for mild hyperuricaemia, 300-600mg for moderately severe hyperuricaemia, and 700-900mg for severe hyperuricaemia. The company would have been aware of this. During the appraisal it was not clear whether the coverage of the licence for febuxostat would extend beyond treatment of moderately severe and severe hyperuricaemia. It was reasonable to take account of professional guidelines in the public domain such as the BSR and EULAR guidelines. Professor Doherty commented that treatment was complex: many people do not receive treatment at all; there is evidence on the dose related response in reducing serum uric acid concentration levels in the EULAR guideline which supports the view that titrating to 900mg would deliver a better response than 300 mg fixed dose; that titration reflects best professional practice rather then current practice mainly in the general practice context; allopurinol was a long established treatment with a clear safety and efficacy record. Dr Boysen said that the issue of titrated dosing had been raised

in advance of the issue of the Appraisal Consultation Document in the clarificatory letter of 15 February 2008.

12. The Panel considered the points made and reviewed the full documentation on the use of comparators. It concluded that it was not unfair to take account of best practice recommendations as well as actual current practice. It considered that the best practice identified by the committee was or should be widely known whether or not it was widely followed, as it was set out, e.g., in clinical guidelines and the allopurinol SPC. It noted that the scope referred to 'allopurinol' rather than restriction to set levels of dosage. Under the circumstances the Panel felt the Institute was not at fault if the Company had initially assumed that allopurinol 300 mg would be the only comparator in play. In any case the company had been alerted to the issue of titration during the appraisal and had had the opportunity to make comments. The panel also noted that the comparison used for the analysis of ICER per QALY in paragraph 4.12 was based on evidence on fixed dose allopurinol, rather than on assumptions of benefits at titrated dosage above the 300mg level, although it was clear that the possibility that titration may deliver greater benefits had played a material role in the committee's reasoning.

13. For all of these reasons the Panel rejected the appeal on these points.

> Appeal point 3. The Institute has acted unfairly by effectively reducing the scope of the appraisal by focusing the review on gout flares rather than the management of hyperuricaemia as outlined in the scope.

14. On appeal point 3, the Company argued that the committee had focused solely on the avoidance of gout flares rather then the well established longer term benefits in terms of quality of life of reducing serum uric acid concentrations (sUA) through hyperuricaemia management. They had therefore in effect unfairly redefined the scope of the appraisal to the 'management of flares in gout' narrowing the scope of the appraisal to the exclusion of consideration of other issues covered in the full scope.

15. On appeal point 3, Professor Barnett for the Committee said that it had taken account of the full benefits both in terms of avoidance of gout flares and the avoidance of long term symptoms from deposits of urate crystals. The Committee had accepted that it was reasonable to assume some relationship between serum uric acid concentrations levels above the recommended

threshold and adverse symptoms, but said there was no evidence to support the view that this relationship was linear. Paragraph 4.12 of the FAD reflected a sensitivity analysis of the ICER per QALY of febuxostat and was not a denial of the wider quality of life benefits.

16. The panel was satisfied that the Committee in the FAD had taken account of the full range of outcomes covered by the final scope (gout flares, serum urate levels, reduction in tophus areas, adverse effects of treatment, and health-related quality of life. The panel did not feel that the committee's approach could be characterized as a de facto change in scope. The Committee had not, therefore, departed from the procedures normally used by the Institute and had not acted unfairly.

17. The Panel therefore dismissed the appeal on this point.

Ground 2. The Institute has prepared guidance which is perverse in the light of the evidence submitted.

18. The Company raised three points of appeal. Points five and six were taken together

> Appeal point 5. The decision by the NICE Appraisal Committee to disregard the wider health-related quality of life (HRQoL) impacts of gout, through symptoms that are strongly related with raised sUA levels is a perverse one in the light of evidence submitted.
> Appeal point 6. NICE and the ERG have inappropriately questioned the use of the sUA level as an appropriate surrogate clinical endpoint.

19. On behalf of the Company on appeal points 5 and 6, Dr Kingswell and colleagues reiterated that the Committee had perversely ignored some of the utility gains associated with treatment of hyperuricaemia by producing recommendations which were completely driven by gout flare avoidance. That ignored the disbenefits of other chronic symptoms associated with raised sUA levels independent of the flare effects. The Company referred to an IMS study which had investigated the assumption that more adverse symptoms occurred with increasing serum uric acid concentration levels in patients with clinical gout. The measured results showed benefits on a wide range of QOL indicators. Reducing sUA levels is a well accepted surrogate clinical endpoint. The Company contended that, by not fully accepting its use, the Committee was unreasonably ignoring the well established professional framework for managing gout.

20. On appeal points 5 and 6 on behalf of the Committee Professor Barnett, Professor Doherty and Professor Cairns explained that the Committee had accepted that it was plausible that high serum uric acid concentration levels caused more problems for patients. However, the problem was establishing the precise relationship given the uncertainty arising from factors such as co-morbidity and the wide range of responses on QOL measures. As a result, while accepting the existence of a relationship between high sUA levels and symptoms, there were doubts about the robustness of the association, leading in particular to doubts about an assumption of a linear relationship. Nor was it possible to establish whether the superior reduction effects of the use of febuxostat against the most prescribed dosage of allopurinol (i.e. 300mg or less) would also have been achieved against a titrated dosage of allopurinol. The conclusions reached by the Committee had reflected the utility gains from treatment to reduce serum uric acid concentration below the recommended threshold level within the uncertainties of the evidence.

21. The Panel considered the points made, mindful of the fact that the remit of the Appeal Panel is not to revisit the issues and evidence considered in the course of the appraisal or substitute its judgement for that of the Appraisal Committee. Rather it is to consider whether the Committee had acted reasonably in reaching its conclusions. The Panel noted that the Committee had not ignored the issue of utility gain from treatment to lower serum uric acid concentration levels. The available evidence had been considered and reflected in the conclusions to the extent that the Committee considered reasonable given the uncertainties about the robustness of aspects of the evidence. The panel felt this approach was reasonable and accordingly rejected the appeal on this point.

> Appeal point 7. The NICE Appraisal Committee and the ETG have ignored the clear evidence of clinical effect in specific patient subgroups where allopurinol does not provide an adequate control of sUA, or where allopurinol is not an appropriate therapy. This decision denies these sub groups an effective and safe treatment in a progressive severe disease of gout in the clear absence of other approved treatments

22. On appeal point 7 the Company argued that the Committee had excluded a number of groups from their recommendation on use of febuxostat. These covered: patients uncontrolled with a dose of allopurinol up to 300mg per day; patients with an sUA level higher than the threshold level where a significant reduction n in sUA levels is required; patients with renal impairment

where an alternative and effective licensed treatment is required; and patients with existing tophi where a significant reduction in sUA levels is required to fully dissolve large pools of crystal urate. They re-iterated their suggested wording amendments as set out in their appeal statement

23. On point 7, the Appraisal Committee had amended and extended the recommendation in the FAD compared to the ACD, which had shown its response on groups for whom allopurinol, including at higher titrated levels, was contraindicated or who were intolerant of allopurinol. Limited first line use was therefore recommended. The committee stated that the refusal to recommend febuxostat as a second line treatment was deliberate. In the committee's view, there was no evidence to support the view that patients, controlled to whatever degree on a properly titrated dose of allopurinol, would be better controlled if switched to febuxostat. In each case it might be expected that xanthine oxidase would be maximally inhibited and there was no evidence to support the view that any further improvement in clinical outcome would be expected.

24. The panel noted that the Committee had amended its recommendation between the ACD and FAD to include recommended use of febuxostat for people who are intolerant of allopurinol or for whom allopurinol is contra-indicated. They did not consider that Committee had acted unreasonably in the way they had considered and reflected the evidence in their conclusions, or in setting the parameters for the final recommendation.

25. The Panel therefore dismissed the appeal on these points

Conclusion and effect of the Appeal Panel's decision

26. The Panel dismissed the appeal on both grounds submitted. There is no possibility of further appeal within the Institute against this decision of the Panel. However, the decision of the Panel may be challenged by an interested party through an application to the High Court for permission to apply for judicial review. Any such application must be made promptly and in any event within three months of this decision or the issuing of the Guidance.