1. Introduction

1.1 The Appeal Panel convened on 24th April 2002 to consider appeals against the Institute’s guidance to the NHS on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia.

1.2 The Appeal Panel comprised Professor Sir Michael Rawlins (chair of the Appeal Panel and chair of the Institute), Dr Susanna Lawrence and Mr Roy Luff (non-executive directors of the Institute’s Board), Mrs Jean Gaffin (patient representative) and Dr Michael Carter (industry representative).

1.3 Appeals were lodged by the following appellants:
   • Lundbeck Ltd
   • Janssen-Cilag Ltd

1.4 Both appellants were represented at the appeal hearing.

1.5 The following individuals involved in the appraisal were present and answered questions from the Appeal Panel: Professor David Barnett (chair of the Appraisal Committee), Professor Littlejohns (clinical director of the Institute and executive lead for this appraisal), Dr Carol Longson (Appraisal Programme Director).

1.6 Also present were Dr Sarah Garner, Dr Alec Miners and Tina Eberstein (technical leads), Cathryn Fuller (technology appraisal administrator) and Stephen Hocking (legal advisor).

1.7 Dr Carter informed the Panel and the appellants of three potential conflicts of interest. First, he received a
pension from AstraZeneca who manufactured another atypical antipsychotic which was not the subject of this appeal. Second, he had been responsible, during the late 1980s for the early development of an atypical antipsychotic that was not the subject of an appeal. Third, he was chairman of a company (Metris Therapeutics) that was in receipt of a grant from Johnson and Johnson Development Corporation, part of the Janssen-Cilag organisation. Neither of the appellants objected to Dr Carter's continuing membership of the Appeal Panel. The other members of the Appeal Panel noted Dr Carter's potential interests but did not consider that they precluded him from taking part.

1.8 The three grounds on which the Appeal Panel can hear an appeal are:

1) The Institute has failed to act fairly and in accordance with the Appraisal Procedure set out in the Interim Guidance for Manufacturers and Sponsors.

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

3) The Institute has exceeded its powers.

1.9 Janssen-Cilag had previously written to the Institute requesting that their appeal should be held in the absence of the representatives from Lundbeck. Lundbeck’s representatives, however, indicated at the hearing that they anyway wished to leave immediately after their appeal had been considered and did not therefore plan to hear Janssen-Cilag’s appeal. Under these circumstances the Janssen-Cilag representatives’ agreed to withdraw their request.

Appeal by Lundbeck Ltd

2 Appeal Ground Two: The Institute has prepared guidance which is perverse in the light of the evidence submitted.
2.1 The appellants alleged that the Appraisal Committee had failed to reflect, adequately, the new authorised indication for the product. This had been granted by the European Commission after the Provisional Appraisal Determination (PAD) had been prepared and disseminated. The appellants pointed out that the revised indication was “Sertindole should only be used for patients intolerant to at least one other antipsychotic agent”. The appellants considered that neither Sections 1.3 nor 3.3 of the Final Appraisal Determination (FAD) adequately reflected this since it was implied that sertindole was only recommended in patients intolerant of or unresponsive to typical antipsychotics.

In answer to questions from the Appeal Panel Professor Barnett stated that it was not the intention of the Appraisal Committee for sertindole’s use to be restricted only to those intolerant or unresponsive to typical antipsychotics. He indicated that if, in the interest of clarity, the appellant and the Appeal Panel believed that the FAD would be improved by inserting in parentheses “typical or atypical” in Section 3.3, line 10, after “antipsychotic agents” he would have no objection. The appellants indicated that this would meet their demands.

The Appeal Panel considered that Sections 1.3 and 3.3 of the PAD did not reflect, fully, the recently authorised indication for the product. It agreed that the Appraisal Committee had been perverse in its construction of these Sections of the FAD and it endorsed the proposed wording suggested by Professor Barnett.

The Appeal Panel upheld the appeal on this point.

The Panel recommends that the Institute’s Guidance Executive incorporate the change to Section 3.3 as proposed by Professor Barnett.
Appeal by Janssen-Cilag

3 Appeal Ground One: The Institute has failed to act fairly and in accordance with the Appraisal Procedure set out in the Interim Guidance for Manufacturers and Sponsors.

3.1 The appellants alleged that there had been a substantial change, between the PAD and the FAD. In particular, the FAD no longer distinguished risperidone from other atypical antipsychotics in respect of its favourable effects on relapse rates, and the development of adverse reactions.

The appellants pointed out that they had no opportunity to comment on the changes introduced in the FAD, whilst the manufacturers of other products were able to do so in their responses to the PAD. Moreover, the Institute had provided no reason, to the appellant, for these changes; and the FAD no longer brought to the attention of health professionals the “gold standard” evidence supporting the use of risperidone.

Professor Barnett explained that the purpose of the appraisal had been to delineate the role of atypical antipsychotics, as a class, in the management of schizophrenia. He indicated that the changes made to the PAD resulted from the Appraisal Committee’s consideration of the comments of all stakeholders including patient/carer organisations and relevant professional bodies as well as manufacturers of atypical antipsychotics. The procedure adopted was entirely in accordance with the Institute’s published processes. Professor Littlejohns agreed that the Institute had powers to ask the Appraisal Committee to prepare a new PAD, rather than proceed to a FAD but had not done so on this occasion because the proposed changes were not considered to be sufficiently great. Professor Barnett confirmed that the Appraisal Committee had not, itself, considered this option as necessary.
The Appeal Panel noted that substantial changes had been made to the FAD in respect of its differentiation of risperidone. The Appeal Panel also noted that it was inherent in a consultation process that the final document (the FAD) might differ from the consultation draft (the PAD) as a result of comments made during the consultation exercise. The Panel considered, however, that the changes made did not amount to such a substantive change to the overall guidance about the use of atypical antipsychotics in patients with schizophrenia that it would be unfair to the appellant not to repeat the consultation stage. The Panel also considered that the Institute’s processes had not been unfair: the rights of consultees to appeal against a FAD were part of the formal appraisal process and enshrined in the Institute’s Interim Guidance, and the appellant was able to have its comments on the FAD heard in this way, albeit in the context of an appeal rather than consultation. The appellant had not therefore been treated unfairly and, indeed, had made full use of their opportunity to make representations at an oral hearing.

The Appeal Panel therefore rejected the appeal on this point.

4 Appeal Ground Two: The Institute has prepared guidance which is perverse in the light of the evidence submitted.

4.1 The appellant alleged that the Appraisal Committee’s decision to remove the specific reference to the effect of risperidone on relapse rates, in Section 4.1.3 of the PAD and as described in the clinical trial by Csernansky (2002), was perverse. In view of the Appraisal Committee’s concerns about the short-term nature of many clinical trials of atypical antipsychotics in schizophrenia, the appellant considered that the failure to give special prominence to the “gold standard” Csernansky trial to be perverse.
Professor Barnett explained that the appraisal remit was to give advice on the use of atypical antipsychotics for schizophrenia, as a group, in view of the wide variations in access across England and Wales. The Appraisal Committee had received comments on the PAD from consultees and, taken in the round, considered it appropriate to make the changes noted by the appellants. Professor Barnett also explained that the Appraisal Committee had been presented with unpublished material that manufacturers regarded as “Commercial-in-Confidence”. This included long-term data demonstrating reductions in relapse rates with other atypical antipsychotics. Professor Barnett indicated that whilst the totality of the evidence persuaded the Appraisal Committee of the overall superiority of atypical antipsychotics over typical antipsychotics, it was not able to reliably differentiate between the clinical effectiveness of individual atypical antipsychotics.

Professor Littlejohns reminded the Appeal Panel that a clinical guideline on the management of schizophrenia was currently under development by the Mental Health Collaborating Centre. By the time this was completed, data to support distinctions between atypical antipsychotics (either for relapse rates or for the development of extrapyramidal symptoms) might be available.

The Appeal Panel noted that the papers sent to members were devoid of “Commercial-in-Confidence” data. It also noted, however, that the data in the papers available to Appeal Panel members included studies that claimed to demonstrate reduced relapse rates with other atypical antipsychotics. The Panel accepted that these, and other unpublished data available to the Appraisal Committee, represented the basis upon which the Committee changed the PAD and remove specific references to individual products. The Appeal Panel reminded itself that, for the omission of specific reference to evidence to be perverse, the reference sought would have to be close to essential for any acceptable guidance. Whilst the Appeal Panel
agreed the evidence in question was of good quality it did not agree that it was of such paramount importance. The Appeal Panel did not therefore consider that the Committee had acted perversely in this respect.

The Appeal Panel therefore rejected the appeal on this point.

4.2 The appellant alleged that the Appraisal Committee’s decision to remove the specific references to the effect of risperidone on extrapyramidal symptoms (including tardive dyskinesia), in Section 4.1.4 of the PAD and as described in the clinical trial by Csernansky (2002), was perverse. In particular, the revised wording (FAD Section 4.1.4) “In the long term there may be limited data to support a reduced incidence of EPS with some of the atypicals. Additionally there was little evidence on comparative rates of tardive dyskinesia between the atypicals or between the typicals and atypicals due to the paucity of long-term trial data” was not compatible with the evidence submitted by Janssen-Cilag.

The appellant explained that the Csernansky study showed reductions in extrapyramidal symptoms including tardive dyskinesia. Whilst the change in rates of emergence of tardive dyskinesia did not reach conventional levels of statistical significance a separate meta-analysis conducted by Janssen-Cilag had demonstrated lower rates with risperidone.

Professor Barnett re-iterated the points made in 4.1 above: that the focus of the appraisal was on atypical antipsychotics as a group; that the Appraisal Committee had had access to “Commercial-in-Confidence” data that was unavailable to Janssen-Cilag; that there was, overall, inadequate data to differentiate between atypical antipsychotics; and that the Committee had considered the data in the round.

The Appeal Panel, noting its conclusions in 4.1 above, considered that the Appraisal Committee had given careful attention to the totality of the evidence available
to it. The Panel did not consider that the Appraisal Committee had acted perversely in its revision of the PAD.

The Appeal Panel therefore rejected the appeal on this point.

4.3 The appellant argued that eliminating differences between atypicals was unarguably wrong. It appeared to the appellant that the Appraisal Committee had generalised the findings of in the Csernansky study (including relapse rates, extrapyramidal symptoms, tardive dyskinesia) to all atypicals. This was also unarguably wrong and perverse.

Professor Barnett explained that the Appraisal Committee deliberately avoided generalising the findings with one atypical to the others in the group. The pharmacological heterogeneity of the group would have rendered this wholly inappropriate.

The Appeal Panel considered that the Appraisal Committee had not attempted to generalise findings with one atypical to the group as a whole. It did not regard the Appraisal Committee as having acted perversely.

The Appeal Panel therefore rejected the appeal on this point.

4.4 The appellant alleged that the Appraisal Committee had ignored the views of both Janssen-Cilag and of Dr J Geddes in rejecting the special place of risperidone in the management of schizophrenia.

The Appeal Panel noted that the article by Dr Geddes, provided by the appellant, stated “The preponderance of evidence now supports the use of risperidone as a first-line treatment for patients with schizophrenia…” Whilst the Appellant argued that Geddes was suggesting that risperidone should be preferred over other atypicals because of the perceived better quality of data on relapse rates with risperidone, the Panel felt
that any difference in quality of data was not so striking as to make it perverse not to single out risperidone as a treatment of choice ahead of other atypicals. The Panel considered that the evidence on which Geddes based his comments was fully consistent with the FAD Section 1.2 and that the Appraisal Committee had not been perverse in its review of this matter.

The Appeal Panel therefore rejected the appeal on this point.

4.5 The appellant alleged the Appraisal Committee had acted perversely by recommending in the FAD (Section 1.5) that clozapine should be used in treatment-resistant schizophrenia only after “….a lack of satisfactory clinical improvement despite the sequential use of the recommended doses for 6 to 8 weeks of at least two antipsychotics, typical or atypical”. The appellant claimed that this was in contradiction to the advice given in Sections 1.2 and 1.3 of the FAD; and that it would be more appropriate for this Section to advise that at least one of the antipsychotics used before the use of clozapine should be an atypical one.

Professor Barnett fully accepted the force of the appellant’s argument but explained that the Appraisal Committee had been constrained by the terms of the licensed indication for clozapine “….patients unresponsive to, or intolerant of, conventional neuroleptics”.

The Appeal Panel considered that, at the time clozapine was licensed in the late 1980s it was the only (indeed it was the first) atypical antipsychotic agent available. The wording of the indication was therefore appropriate at the time. With the more recent advent of other atypicals, which lack clozapine’s myelotoxic potential, the Panel considered that it was not necessarily appropriate for two typical antipsychotics to be used before recommending the use of clozapine. Consequently, although sympathising with the position the Appraisal Committee found themselves, in their
The consideration of this matter, the Appeal Panel considered that the Committee had acted perversely.

The Appeal Panel therefore upheld the appeal on this point.

The Appeal Panel recommends that the Guidance Executive revises Section 1.5 as follows: that the words (lines 2 and 3) “within its licensed indications” be deleted; and that the words (line 5) “typical or atypical” be deleted and replaced by “of which at least one should be atypical”.

4.6 The appellant considered that the inclusion of certain statements relating to the side effects of atypical antipsychotics, in Section 3.6 of the FAD, was perverse. First, the phrase “sexual dysfunction which can result from drug-induced hyperprolactinaemia” was perverse because of the absence of good supporting evidence. Second, the phrase alleging that sexual dysfunction was likely to be under reported” was tenuous and inappropriate. Third, there was lack of clarity about other distressing metabolic side effects such as diabetes and glucose dysregulation.

Professor Barnett explained that the side effects mentioned in Section 3.6 were those reported by patients as being of greatest concern to patients themselves. The inclusion of the reference to hyperprolactinaemia as a cause of sexual dysfunction had been included at the suggestion of several professional consultees.

The Appeal Panel noted that the side effects described in Section 3.6 were clearly ascribed to patients themselves. They did not consider that the Appraisal Committee had been perverse in including such information, nor did the Panel consider that the Committee had acted perversely in incorporating the statement about sexual dysfunction and hyperprolactinaemia.
The Appeal Panel therefore rejected the appeal on this point.

4.7 The appellant alleged that the inclusion in the FAD of the evidence summarising the clinical and cost effectiveness of clozapine, yet excluding such information about risperidone, was perverse.

Professor Barnett stated that the Appraisal Committee considered that the unique indications for the use of this product, which was not shared by any other atypical antipsychotic, required particular comment.

The Appeal Panel concurred with this view.

The Appeal Panel therefore rejected the appeal on this point.

4.8 The appellant alleged that the statement (FAD Section 1.4) “It is not recommended that...individuals change from one atypicals...if currently achieving good control of their condition without unacceptable side effects with typical antipsychotics drugs” was perverse in the light of the results of the Csernansky study. This showed that even well-controlled patients, on typical antipsychotics, were at risk of relapse and that this risk could be reduced by changing to risperidone.

Professor Barnett explained that the central feature of the Appraisal Committee’s guidance on the use of antipsychotics was contained within Section 1.1 of the FAD. The Appraisal Committee had not considered it appropriate for the Institute’s guidance, in respect of the management of patients currently taking typical antipsychotics, to go any further than the advice given in Section 1.4.

The Appeal Panel, recognising the uncertainties and difficulties in giving advice about this matter, considered that the Appraisal Committee had acted in a way which it felt was appropriate and in the best interests of patients and their carers. The Panel did not consider that the Appraisal Committee had acted perversely in formulating its advice on this point.
The Appeal Panel therefore rejected the appeal on this point.

5  Findings

5.1 The Appeal Panel upholds the appeal of both the appellants (on the grounds referred to in paragraphs 2.1 and 4.5 above). The Appeal Panel does not consider that it would be appropriate, having regard to the nature of the points successfully appealed, to refer the FAD back to the Appraisal Committee for reconsideration.

5.2 With respect to the appeal by Lundbeck the Panel recommends to the Board that the Guidance Executive revises the Guidance in accordance with its findings in paragraph 2.1 above.

5.3 With respect to the appeal by Janssen-Cilag the Panel recommends to the Board that the Guidance Executive revises the Guidance in accordance with the findings in paragraph 4.5 above.

5.4 Subject to these changes the Panel recommends that the Guidance now be issued to the National Health Service.