ACD Consultees and Commentators

Vorioxetine for treating major depressive disorder (583)

Response from the Cochrane Depression, Anxiety and Neurosis Review Group (CCDAN)

We would like to make some comments about the clinical efficacy part of the document. We have not commented on the cost-effectiveness analysis.

General comments

The company submitted evidence for the second line population only, so there is little overlap with our Cochrane review. NICE have taken account of previous reviews, one of which has a set of studies similar to our Cochrane review - we identified an additional study comparing vortioxetine with venlafaxine, and two studies with duloxetine. This evidence was not submitted by the company.

The other review considered by NICE is an indirect comparison meta-analysis (http://www.ncbi.nlm.nih.gov/pubmed/25249164) sponsored by the company.

1. The appropriateness of agomelatine as comparator in a non-inferiority trial

In light of our Cochrane review, we think the choice of agomelatine in a non-inferiority trial in the submission is questionable, and we have some concerns about the company submission with respect their justification for this. Their submission reads:

"Agomelatine: although not widely used within the UK it is recognised as an efficacious and well-tolerated antidepressant that has a mode of action distinct from the SSRIs and SNRIs87. The most recent NICE surveillance review for CG90101 identified two meta-analyses31,102, "which indicate that agomelatine is at least as efficacious as escitalopram, fluoxetine, sertraline, venlafaxine and paroxetine in reducing depression scores for response and remission in patients with depression and severe depression". (Page 47)

and

"Although agomelatine is seldom used within the NHS, a recent independent meta-analysis found it to be effective164. Also, it is commonly prescribed in other European countries and fulfils the criteria for a "better tolerated, newer generation" antidepressant within the NICE treatment pathway, according to expert clinical advisors consulted by Lundbeck" (page 65)

Our Cochrane review shows, that paroxetine may be better than agomelatine. The effect was not significant, but the SMD effect size is similar to the one from our comparison of agomelatine vs.

placebo. Furthermore, in the light of the liver problems with agomelatine, the assertion that agomelatine is "better tolerated" seems not to be justified. In our agomelatine review, we conclude that the efficacy and clinical utility of agomelatine is rather low.

The poor efficacy and tolerability data for agomelatine makes it a very surprising choice of drug to provide a fair test in a non-inferiority trial in the submission, and we would question the company submission in relation to the appropriateness of this drug.

2. Concerns about the adequacy of the network meta-analysis.

We recognize that the ERG partly acknowledge the weaknesses in the network, but we feel that the extent of the limitations and the impact of these is insufficiently clear. Vortioxetine is only linked to the network via one study Kasper (2013). The interpretation of the network data should be much more cautious.

The consultation document states:
"The ERG stated that it was questionable whether Kasper et al. (2013) was suitable for inclusion in the indirect treatment comparison. It stated that it was unclear whether the population consisted entirely of patients receiving second-line treatment, or whether it also included those who had been treated for a previous depressive episode in the last 12 months but were starting first-line treatment for a current major depressive episode." (page 20, point 3.26)

The York ERG report reads:
"It was unclear whether all such patients were genuinely switching patients, or whether they had been treated for a prior depressive episode. The ERG considers that the patients are likely to be a mix of these cases, and therefore the eligibility of these two trials for an indirect treatment comparison of switch populations is questionable." (page 60.)

The company submission reads in their limitations:
"For instance, Kasper (2013) provides the data for agomelatine vs. sertraline and placebo (Kasper 2010, Olié and Kasper 2007, respectively). In this publication, a post-hoc analysis was undertaken which provided the data for the "previously treated" population. This population was defined as patients receiving any antidepressant treatment within the previous 12-month period. This criterion may have allowed patients who were not necessarily switching antidepressants within the current episode to be included in the study. Therefore the population in Kasper 2013 may be slightly wider than those of the other trials. A conclusion on the impact on the estimates of relative effects cannot be drawn. In such a post-hoc analysis, randomisation is not strictly preserved, but expert health economists and statisticians considered this to be a theoretical rather than practical consideration and therefore did not expect it to be an effect modifier." (page 137)

These statements require clarification, and a more detailed examination of the studies referred to yields greater clarity and a potentially different interpretation.

The subgroup included from the two agomelatine trials (Kasper 2010 and Olie & Kasper 2007) had some antidepressant treatment in the last 12 month, but do not refer to non-response anywhere in their inclusion criteria. In fact, Kasper 2010 (which is the main comparison) excluded patients with "previous depression resistance to antidepressants" (Kasper 2010,

page 111) and Olie & Kasper excluded “previous resistance to antidepressants (defined as the failure to respond to two different prior antidepressant medications prescribed for >=4 wk during the current depressive episode)” (page 663). In addition, both trials used wash-out periods, which lasted up to 5 weeks if the patients were treated with fluoxetine or trazodone in the Kasper 2010 study.

We would NOT regard this as a switching population. Switching would have been the exception rather than the rule in this group of patients. According to Star*D there is a decline in the response rates in every treatment step (as noted in the company submission), so the agomelatine response rates seem to be clearly overestimated for second line treatment. This is of major importance, because vortioxetine is only linked to the network via the Kasper study (see page 116 in the company submission). We would therefore question the validity of the entire network.

Lastly, the evidence for agomelatine as a second line treatment in treatment resistant depression is weak. To our knowledge, the only trial of agomelatine in treatment resistant depression was a pilot study by Servier (CL3-027), which remained unpublished.

3. Clinically important outcome

We do not agree with their clinical expert, that “The clinical expert explained that a reduction in 1 item of the MADRS by 2 or more points would generally be considered clinically meaningful”. (page 36) We recognize this is of minor importance, as the Committee agreed that Remission and relapse preventions are more useful to judge clinical efficacy.

4. Error

On page 20 (see 3.26) the document states that the Rosso trial was the only trial that compared vortioxetine with duloxetine, but the trial compared duloxetine and bupropion.