Review proposal of Esketamine for treatment-resistant depression (TA854)

Esketamine for treatment-resistant depression TA854 was published in December 2022.

Proposal / Decision

1. The evidence received does not indicate that an update of the existing recommendations is required at this time.

   The guidance will therefore remain unchanged, in its current form, unless or until NICE becomes aware of substantive information which would make it reconsider.

Rationale

2. The new evidence available for esketamine in treatment-resistant depression does not sufficiently show a relative benefit compared to currently available treatments that is greater than the benefit considered in TA854, therefore the new clinical data supports the current recommendation in TA854.

   There are some issues that may be partially addressed by the new evidence but substantial uncertainty remains for many of the key issues identified in TA854.

   There have been no changes to the marketing authorisation or price of esketamine that would suggest further review.

Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?

3. The company had a confidential discount through a patient access scheme, which would have applied if the technology had been recommended. This has since been withdrawn. There have been no changes to the list price.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

4. There have been no changes to the marketing authorisation for this indication.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

5. There was substantial uncertainty in the original guidance about treatment line and clinical pathway, choice of comparator treatments, internal and external

validity of the clinical evidence, long-term effects of treatment, natural history of the disease, resource use and implementation.

A new poster presentation from Reif et al (2023) at the European Congress of Psychiatry 2023 showed results from the ESCAPE-TRD trial. It concluded that esketamine + selective serotonin reuptake inhibitors (SSRI) increases the proportion of patients in remission compared to quetiapine extended-release + SSRI.

Quetiapine as a third line or more treatment is likely to be a more appropriate comparator than oral antidepressants at second line or more considered in TA854 because it is an augmentation therapy and esketamine is likely to be used later in the treatment pathway (see sections 3.3 to 3.5 of the final guidance). Therefore, this is a more relevant trial design for establishing relative clinical benefit from currently available treatments. However, this trial represents only one augmentation therapy that may be used in clinical practice at this line.

ESCAPE-TRD's primary outcome showed a rate of remission of 28.7% for the esketamine arm vs 18.2% for the quetiapine arm at 8 weeks. However, in TA854, the committee considered that response and remission rates from similar studies should be interpreted with caution (see section 3.14 of the final guidance). ESCAPE-TRD's difference in MADRS scores between the 2 treatment arms (a 60 point scale, assuming that a MADRS score of 12 or less is clinical remission) was 2.8 at 8 weeks, 2.2 at 32 weeks and a mean least squares difference over the entire time period of 2.4. This was in the context of an overall reduction in MADRS score of approximately 20 points on the MADRS scale over the 32 weeks in the quetiapine arm. In TA854, the difference between arms was 4.0 for the full population covered by the marketing authorisation at 4 weeks. The subgroup of people with 3 or more previous treatments was considered the most appropriate subgroup in TA854 and the overall difference in MADRS was higher, but the value was considered confidential by the company and cannot be reported here. In TA854, the results of a network meta-analyses were considered unreliable due to heterogeneity, so an unadjusted analysis with trial results were used (see section 3.6 of the final guidance). Using a naïve comparison of change in MADRS score compared to currently available treatments suggests the benefit of esketamine from ESCAPE-TRD is smaller than the to the benefit of esketamine considered by the committee in TA854. Therefore, this new clinical evidence from ESCAPE-TRD may not provide sufficient information to change the current recommendation at this time.

In TA854, stakeholders also highlighted the high levels of responses to all treatments in clinical trials that do not happen in clinical practice. The

committee also noted concerns about unblinding of treatment and how this may affect results, but ESCAPE-TRD is an open-label study, so results should be interpreted with caution.

The new evidence may contribute some reduction in uncertainty about treatment line (there is more evidence later in the pathway), comparator treatment (quetiapine XR is a relevant comparator) and longer-term effects of the treatment (these results are for up to 32 weeks instead of 4 weeks). However, they do not resolve many of the other substantial uncertainties with the evidence base or modelling concerns.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

6. TA899 – This appraisal was recently terminated. No implications for current guidance.

Equality issues

7. There were some potential equality issues raised in the original guidance:

    - Geographical access may be an equalities consideration because an aspect of the diseases is lack of energy and motivation, and administration would therefore need to be in the community setting. There were also concerns about equity of access in the criminal justice system. Although the committee considered these issues were matters of equity, not equality and could not be addressed in the recommendation.

    - People with lower socio-economic status are more likely to have treatment-resistant depression.

Proposal/decision paper sign off

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